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# THE LIVER WEEK

*Towards Precision Medicine in Practice and Research of Hepatology*

June 27-29, 2024 | Walkerhill, Seoul, Korea

The Korean Association for the Study of the Liver

THE KOREAN ASSOCIATION OF HBP SURGERY

THE KOREAN LIVER CANCER ASSOCIATION

The Korean Liver Transplantation Society

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June 27-29, 2024 | Walkerhill, Seoul, Korea

THE LIVER WEEK 2024

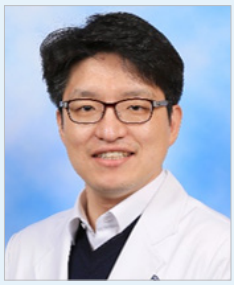
DAY 1: June 27 (Thu)

# PG Course 1

## Viral Hepatitis

**Chairs:**

**Chul Ju Han** (Korea Cancer Center Hospital)
**Hyung Joon Kim** (Chung-Ang Univ.)



**Jun Yong Park**

*Yonsei University*

## Self Introduction

| | |
|---|---|
| 1992-1998 | Yonsei University College of Medicine, Seoul, Korea |
| 2000-2002 | Master Degree, Graduate School, Yonsei University |
| 2007-2013 | Ph.D. Course of Medical Science, Graduate School, Yonsei University College of Medicine |
| 2018- | Professor, Department of Internal Medicine, Yonsei University College of Medicine, |

Jun Yong Park is a Professor of the Division of Gastroenterology as well as a physician of Internal Medicine at the Yonsei University College of Medicine, Korea, since 2009. In his role, he mainly researches on acute/chronic liver disease, viral hepatitis, liver cirrhosis and hepatocellular carcinoma, and treats relevant patients at Severance Hospital.

# Recent Strategies for Hepatitis B Virus Treatment: When and for Whom?

**Jun Yong Park** *Yonsei University*

Chronic hepatitis B (CHB) patients with the grey zone phenotype present a challenge for treatment decisions. Defined by variable HBeAg status, HBV DNA, and ALT levels, these patients fall outside established treatment criteria. The prevalence of this phenotype varies from 28% to 51%, depending on the specific criteria used for diagnosis. Notably, the prevalence is significantly higher among HBeAg negative compared to HBeAg positive CHB patients, with estimates around 80% versus 20% respectively. Importantly, the prevalence of the grey zone phenotype appears to be independent of age, gender, and race. Historically, a conservative approach withheld antiviral therapy in such cases. However, the high efficacy and safety profile of antiviral therapy along with the uncertainty surrounding fluctuating hepatitis in grey zone patients, is leading to a shift towards considering treatment initiation even in these cases. Risk stratification remains desirable for grey zone patients. This could involve lowering the HBV DNA threshold for treatment initiation, utilizing liver fibrosis markers like FibroScan, or exploring specific immune response markers to predict disease progression. Ongoing research is crucial to refine these methods and identify optimal treatment strategies for this population. It's important to remember that even within the grey zone, individual factors might influence treatment benefit. Shared decision-making involving patients in the process is crucial, considering their risk profile, preferences, and potential side effects of antiviral therapy. Beyond preventing disease progression, treating grey zone patients might offer additional benefits like reducing mother-to-child and blood-borne transmission. The cost-effectiveness of such treatment approaches, especially with newer medications, remains a topic of debate.

**Nae-Yun Heo**

*Inje University*

## Self Introduction

Prof. Nae-Yun Heo graduated from Pusan National University College of Medicine for Bachelor's degree in 2001. Then, He got the Mater's and Doctor's degree in University of Ulsan College of Medicine. Also, He had a resident training in Internal Medicine and fellowship in the Department of Gastroenterology in Asan Medical Center, Seoul, Korea. He is affiliated to Inje University Haeundae Paik Hospital since 2011. He is deeply interested in the hepatology including acute and chronic viral hepatitis, liver cirrhosis, hepatocellular carcinoma, and liver abscess

## Research Interests

- Chronic viral hepatitis (HBV, HCV)
- Liver cirrhosis
- Hepatocellular carcinoma
- Liver abscess

## Representative Publications

1. Efficacy and safety of biphenyl dimethyl dicarboxylate and ursodeoxycholic acid combination in chronic hepatitis related to metabolic syndrome components. Korean J Gastroenterol 2021;77:179-189
2. Current status of amebic liver abscess in Korea comparing with pyogenic liver abscess. Korean J Gastroenterol 2020;76:28-36
3. Hepatitis E virus: epidemiology, diagnosis, and management. Korean J Gastroenterol 2019;74:130-136
4. Long-term patient and graft survival of kidney transplant recipients with hepatitis C virus infection in the United States. Transplantation 2018;102:454-460
5. The prevalence of colonic neoplasm in cryptogenic pyogenic liver abscess: a prospectively enrolled cross-sectional study. Korean J Gastroenterol 2016;68:195-201

# Novel Anti-HBV Drugs Close to the Practice

**Nae-Yun Heo** *Inje University*

## Introduction

Hepatitis B virus (HBV) is a partially double stranded DNA virus in hepadnaviridae which induces chronic hepatitis B (CHB) in 90% among the patients infected via vertical transmission. With introduction of antiviral therapies such as interferon (IFN) and nucleos(t)ide analogue (NA), the prognosis of CHB has been improved by preventing the progression of hepatic fibrosis, and reducing the risk of hepatocellular carcinoma. However, the most popular antiviral agent, NA could suppress the replication of HBV effectively, but could not remove the virus in the nucleus of hepatocyte. Therefore, many patients should take the drug for a long-term to maintain viral suppression, and have waited for novel anti-HBV drugs which induce the cure of CHB. In this lecture, I will review the new therapeutic targets of HBV and the current perspective of new drugs on investigation.

## Life cycle of HBV and novel drug targets

HBV virions enter the hepatocyte cytoplasm through a specific interaction with sodium taurocholate cotransporting polypeptide (NTCP) on the membrane of hepatocyte. Then, HBV DNA enters the nucleus after the inner nucleocapsid of HBV is disassembled by the nuclear pore complex. In nucleus, HBV DNA is converted from relaxed circular DNA (rcDNA) to covalently closed circular DNA (cccDNA). cccDNA is a template for pregenomic RNA (pgRNA), preS1 messenger RNA (mRNA), preS2 mRNA, and X mRNA. Some pgRNA is translated into core protein and the polymerase. In cytoplasm, another pgRNA, together with the polymerase, and HBcAg, forms a capsid. Inside the capsid, pgRNA is reversely transcribed into rcDNA. PreS1 mRNA, and preS2 mRNA are used to synthesize surface protein. Newly formed HBV necleocapsids form HBV virions through assembly with surface proteins, and are then released out of hepatocyte. These sequence of each process including 1) Entry to hepatocyte, 2) cccDNA formation, 3) Transcription and translation of HBV gene, 4) Capsid assembly, and 5) Reverse transcription of RNA to DNA, and 6) Enveloping by surface protein and release out of hepatocyte could be therapeutic target.

Another important condition for the persistence of chronic HBV infection is immune escape of the virus. HBsAg may lead to dysregulation of innate and adaptive host immunity through interacting with either the immune or non-immune cells causing impairment of the immune system. Thus, immunomodulato-

ry therapies focused on the restoration of impaired immune responses have been investigated.

## Goal of anti-HBV treatments

Complete cure means not only undetectable HBsAg in serum, but also eradication of intrahepatic HBV DNA such as cccDNA and integrated DNA in host gene. The ideal goal of anti-HBV treatment is complete cure, but new approaches to treating CHB aim for a functional cure, defined as sustained HBV DNA suppression and loss of HBsAg levels with or without the detection of anti-HBs after cessation of treatment. Functional cure is rarely achieved by long-term treatment of NA, and occurs in up to 10% of patients after pegylated interferon. Although new biomarkers such as serum HBV RNA and HBcrAg which is correlated with cccDNA level has been introduced, it is difficult to confirm complete cure without liver biopsy. Therefore, functional cure is realistic therapeutic goal compared with complete cure in current clinical trials.

## Novel anti-HBV drugs on investigation

### *1) Direct acting antiviral agents*

#### a. HBV entry inhibitors

Bulevirtide (Myrclucex B) is a myristoylated polypeptide that contains the pre-S1 region of large

HBsAg protein that can bind to NTCP and block entry of HBV and HDV. Most studies of bulevirtide have focused on chronic HDV infection where 24 weeks of bulevirtide monotherapy has been shown to result in ≥2 log reductions in HDV RNA levels in 46-77% patients at the end of treatment. Decline in HBsAg level by ≥1 log was rarely observed during bulevirtide monotherapy, but was more common with a combination of bulevirtide and PEG-IFN $\alpha$ though HBsAg clearance remained a rare event.

#### b. Agents targeting cccDNA

CRISPR/Cas-9 is a kind of gene-editing enzyme which directly targets and reduces the viral cccDNA reservoir. It destroys the intrahepatic HBV genome and reduces HBsAg levels in preclinical phase study.

#### c. Capsid assembly modulator

Capsid assembly modulators (CAM) primarily prevent encapsidation of pgRNA, resulting in empty capsids devod of rcDNA. In treatment naïve patients, HBV DNA and HBV RNA declines were greater in vebicorvir plus ETV compared to ETV monotherapy.

#### d. Agents targeting viral transcripts

RNA interference (RNAi) through small-interfering RNA (siRNA) and anti-sense oligonucleotide (ASO) are new strategies for CHB treatment. A recent study of a triple combination regimen using NA with JNJ-

3989 (siRNA) and/or JNJ-6379 (CAM) reported the rate of HBsAg <10 IU/mL 19% in NA plus siRNA. Triple combination of NA plus VIR-2218 (siRNA) plus PEG-IFN resulted in a more-profound HBsAg reduction compared to VIR-2218 monotherapy. ASOs inhibit viral protein translation and reduce the production of virions and subviral particles. Bepirovirsen is an X-trigger ASO, which was shown to induce mean HBsAg reductions of 1.5-2.0 log10IU/mL in treatment-naïve or virally suppressed CHB patients.

**e. HBsAg release inhibitors**

Nucleic acid polymers (NAPs) inhibit the assembly and release of HBV subviral particles from the hepatocyte, resulting in significant serum HBsAg declines. In a small study, 39% patients who received REP-2139 or REP-2165 plus TDF and PEG-IFN underwent HBsAg seroconveresion.

### *2) Immunomodulation agents*

**a. Therapeutic vaccination**

The concept of therapeutic vaccines is the introduction of modified HBV antigens that will interact with antigen-presenting cells. The antigen-presenting cells stimulate HBV-specific T-cells to produce antiviral cytokines such as IFN-$\gamma$. GS-4774, a yeast-based T cell vaccine, was the first HBV therapeutic vaccine to study in humans, but there was no significant decline in HBsAg by week 48.

**b. Checkpoint inhibitors**

T cells of patients with CHB overexpress inhibitory receptors such as CTLA-4 and PD-1. Checkpoint inhibitors may recover the exhausted T cells and restore their activity. A single phase 1 study showed the safety of nivolumab in combination with a therapeutic vaccine. In this small study, one patient who received nivolumab achieved a functional cure.

**c. TLR agonists**

TLRs are the first line of defense against invading pathogens. They are accountable for detecting self and non-self-antigens, stimulating the maturation of dendritic cells, and initiating antigen-specific adaptive immune responses.

## Conclusions

To eliminate the intrahepatic HBV virions and its genomes such as cccDNA and pgRNA, several direct-acting antiviral agents and immune modulators with finite treatment duration have been studied. However, the efficacy and safety of novel drugs did not show satisfactory outcomes yet. Therefore, it is eager to find out the effective combination of novels drugs with different mechanism including HBV replication inhibition, HBsAg reduction, and immune stimulation to reach functional cure among ongoing clinical trials.

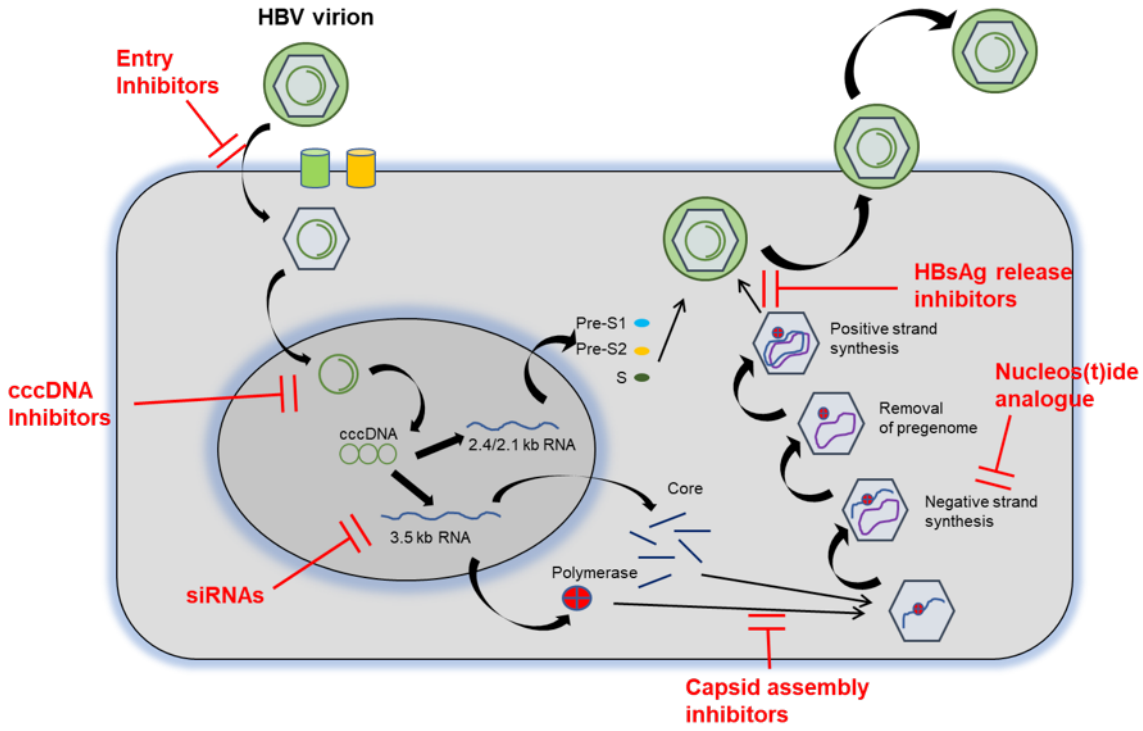



**Figure 1.** Life cycle of HBV and therapeutic targets

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*The Catholic University of Korea*


## Self Introduction

Prof. Jung Hyun Kwon is a Professor of the Department of Internal Medicine, The Catholic University of Korea and is currently holding a position of Chief of Hepatobiliary Center of Incheon Saint Mary's hospital, simultaneously.

Prof. Kwon graduated from The Catholic University of Korea, College of Medicine with his medical degree in 2000 and completed her internship and residency at the Department of Internal medicine, at Seoul Saint Mary's Hospital, The Catholic University of Korea.

Since 2010, Prof. Kwon has been taking a number of roles, including treasurer and informatics committee director of the Korean Association of the Study of the Liver (2019-2023) and currently as treasurer director of the Korean Liver cancer study group (2023-present).

## Research Interests

- Viral hepatitis B natural course
- Viral hepatitis C elimination
- HCC risk factor

## Representative Publications


1. Soon Kyu Lee, Soon Woo Nam, Jeong Won Jang and Jung Hyun Kwon*. Long-Term HBsAg Titer Kinetics with Entecavir/Tenofovir: Implications for Predicting Functional Cure and Low Levels. Diagnostics 2024, 14, 495.
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4. Jina Kim 1, Jason Chia-Hsien Cheng 2, Taek-Keun Nam 3, Jin Hee Kim 4, Byoung Kuk Jang 5, Wen-Yen Huang 6, Hiroshi Aikata 7, Myungsoo Kim 8, Jung Hyun Kwon 9, Jinbo Yue 10, Victor Ho Fun Lee 11, Zhaochong Zeng 12, Jinsil Seong 1. Efficacy of Liver-Directed Combined Radiotherapy in Locally Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis. Cancers (Basel).
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# Treatment of Chronic Hepatitis C in Difficult-to-Treat Patients with Various Comorbidities

**Jung Hyun Kwon** *The Catholic University of Korea*

## Introduction

Chronic Hepatitis C (HCV) remains a significant global health challenge, particularly in patients with co-existing conditions that complicate treatment. Difficult-to-treat HCV patients are typically characterized by the presence of advanced liver disease or Hepatocellular carcinoma, or multiple comorbid conditions, resulting in low sustained virological rate (SVR). Understanding these complexities is crucial for optimizing therapeutic outcomes and improving patient quality of life.

## Challenges in Treating Difficult-to-Treat Patients

### *Decompensated Cirrhosis:*

- Clinical trial data demonstrate that in the population of persons with decompensated cirrhosis, most patients receiving direct-acting antiviral (DAA) therapy experience improvement in clinical and biochemical indicators of liver disease between baseline and posttreatment week 12, including patients with CTP class C cirrhosis.[1] Predictors of improvement or decline have not been clearly identified, although patients with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than antiviral treatment. Patients with decompensated cirrhosis have severely impaired liver function, limiting treatment options. In decompensated cirrhosis, agents without protease inhibitor are effective but requires careful monitoring to prevent further liver deterioration such as [Epclusa (sofosbuvir/velpatasvir) or Harvoni (sofosbuvir/ledipasvir) or Sofosbuvir] plus ribavirin. Liver transplantation may be necessary, and pre-transplant antiviral therapy can help improve post-transplant outcomes. The timing of liver transplantation depends on the overall health and liver function of the patient, typically considered after HCV treatment.

**Hepatocellular Carcinoma (HCC):** Managing HCV in HCC patients involves complex decision-making processes. Real-world data comparing DAA response rates demonstrate that patients with cirrhosis and hepatocellular carcinoma (HCC) have lower SVR rates than cirrhotic patients without HCC. The treatment approach varies based on the stage of HCC. In Korea, for patients with HCV-related HCC, there is a restriction regarding insurance coverage for HCV treatment. Specifically, HCV treatment could be cov-

ered by insurance at least three months after achieving complete remission (CR) following anticancer therapy. This restriction can lead to additional delays in treatment, potentially missing the optimal timing for anti HCV therapy. Consequently, healthcare providers must carefully plan anti-cancer or anti-HCV treatment schedules, considering this insurance coverage limitation, to optimize patient outcomes and manage overall health effectively. Early-stage HCC is often treated with surgical resection or radiofrequency ablation (RFA), and antiviral treatment can be integrated before or after these procedures. For advanced HCC, initial cancer treatment is crucial for tumor control, followed by antiviral therapy to protect liver function and eradicate HCV.

**Post-transplant HCV treatment:** HCV recurrence post-transplant is a critical issue. Antiviral therapy is essential to manage and prevent recurrence. In a recent US study, the optimal timing of DAA therapy appears to be 0 to 3 months after LT for HCV-associated HCC, given increased rates of SVR and improved RFS compared to pre-LT, and and ≥3 months post-LT. Delayed administration after transplant should be avoided.[2] Use of DAAs Post-Transplant: Epclusa and Mavyret are commonly used post-transplant to manage HCV recurrence. These regimens have shown high efficacy in achieving SVR and improving post-transplant liver function.

***Retreatment of Persons in Whom Prior Therapy Has Failed:***

- Daclatasvir-Based Treatment Failures: In Korea, many patients have experienced failure with daclatasvir/asunaprevir for GT 1 due to past health insurance coverage issues. Sofosbuvir/velpatasvir/voxilaprevir (Vosevi) shows high sustained virologic response (SVR) rates in these patients. For instance, Vosevi achieves SVR12 rates above 95% in daclatasvir/asunaprevir treatment failures, and similar efficacy in patients failing Sofosbuvir/velpatasvir (Epclusa) and Glecaprevir/Pibrentasvir (Mavyret).[3]
  - Sofosbuvir-Based treatment failures: In Korea, small number of patients have experienced failure with sofosbuvir/ledipasvir for GT 1 and sosfosbuvir plus ribavirin for GT 2. Mavyret and Vosevi could be achieved SVR in these patients.
  - Glecaprevir/Pibrentasvir Treatment Failures: Recommendations include the use of Vosevi as an effective alternative, especially in patients who have failed previous regimens due to historical health insurance coverage issues.
  - Sofosbuvir/velpatasvir/voxilaprevir after DAA Failure: Recent studies highlight that despite high SVR rates, certain factors negatively impact the treatment response to Vosevi. HCV genotype 3, advanced liver disease, and HCC onset were identified as independent negative predictors of treatment response. However, resistance-associated substitutions and rare genotypes did not significantly impact SVR rates following re-treatment with Vosevi.[4]

## Conclusion

Managing HCV in patients with various comorbidities demands a nuanced and multidisciplinary approach. Besides the aforementioned groups, there are also challenging groups such as those with CKD, diabetes, HIV- and HBV- coinfection, and those who have undergone solid organ transplantation. Through careful selection of antiviral therapies, monitoring for adverse effects, and coordinating with other treatments, we can improve outcomes for these challenging patient populations.

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**In Hee Kim**

*Jeonbuk National University*

## Self Introduction

Prof. In Hee Kim is a Professor of the Department of Internal Medicine, Jeonbuk National University College of Medicine and is currently holding a position of Chief of the Department of Gastroenterology and Hepatology, Jeonbuk National University Hospital simultaneously.

Prof. Kim graduated from Jeonbuk National University College of Medicine with his medical degree in 1995 and completed his internship and residency at the Department of Internal Medicine at Jeonbuk National University Hospital, receiving his diploma in Internal Medicine in 2001.

Prof. Kim has been taking a number of roles, including Chairman of the Jeonbuk Brach of Korean Association for the Study of the Liver (2019-2022), Director of the Committee on Computational Information (2016-2017) and the Committee of Healthcare Policy (2024-) of the Korean Association for the Study of the Liver.

## Research Interests

- Viral hepatitis, hepatitis B, hepatitis C, hepatitis E
- Cirrhosis, Portal hypertension, Alcoholic liver disease, Non-alcoholic fatty liver disease
- Hepatocellular carcinoma
- Healthcare policy

## Representative Publications

1. Core indicators related to the elimination of hepatitis B and C virus infection in South Korea: A nationwide study. Clin Mol Hepatol 2023;29:779-793.
2. Efficacy and safety of sofosbuvir-velpatasvir and sofosbuvir-velpatasvir-voxilaprevir for hepatitis C in Korea: a Phase 3b study. Korean J Intern Med 2023;38:504-513.
3. Etiology and clinical characteristics of acute viral hepatitis in South Korea during 2020–2021: a prospective multicenter study. Scientific Reports 2023;13:14271
4. CAGE-B and SAGE-B models better predict the hepatitis B virus-related hepatocellular carcinoma after 5-year entecavir treatment than PAGE-B. JDigDis.2023;24:113–121.
5. Direct-Acting Antiviral Therapy and Risk of Hepatocellular Carcinoma Recurrence in Patients with Chronic Hepatitis C. Gut Liver. 2021 May 15;15(3):327-328.

# Viral Hepatitis Elimination: Progress towards WHO's 2030 Goal-Where Are We Now?

**In Hee Kim** *Jeonbuk National University*

Viral hepatitis accounts for a significant global disease burden and high mortality from liver cancer and cirrhosis. In 2016, the World Health Assembly adopted the Global Health Sector Strategy (GHSS) 2016–2021 on viral hepatitis, which for the first time called for the elimination of viral hepatitis B and C infection as a public health problem by 2030 (defined as a 90% reduction in incidence [95% for HBV and 80% for HCV] and 65% reduction in mortality) compared to the 2015 baseline.[1] As the GHSS 2016–2021 near the end of their implementation period, they have published a Global Progress Report to provide accountability for key performance and gaps to date.[2] The subsequent GHSS 2022–2030 expanded the concept of elimination of viral hepatitis with absolute impact targets and programmatic targets for 2025 and 2030, and provides the foundation for criteria for country validation of elimination and path to elimination.[3, 4]

## Global Progress towards WHO's 2030 Targets

Global targets aim to reduce the number of people newly infected with hepatitis B and C virus by 30% by 2020 and 90% by 2030. New estimates for 2019 show that 1.5 million people were newly infected with chronic hepatitis B infection and 1.5 million with chronic hepatitis C infection. The number of people developing new chronic infections from hepatitis B has declined, supported by an increase in the coverage of the highly effective hepatitis B vaccine among infants. Globally, 85% of all infants had received the recommended three doses of the hepatitis B vaccine in 2019, and the global target of the GHSS to reduce hepatitis B surface antigen (HBsAg) prevalence to less than 1% among children younger than five years by 2020 has been met. However, progress in reducing the prevalence of hepatitis B infection among children younger than five years is not matched with equal progress in addressing hepatitis B and C infection among adults.

Global targets call for a 10% reduction in the numbers of people dying from viral hepatitis B and C by 2020 and a 65% reduction by 2030. New estimates show that 1.1 million people died from viral hepatitis in 2019. Progress in service delivery has been insufficient. Treatment for hepatitis B is progressing

much slowly despite affordable treatments, only 10% of people living with chronic hepatitis B infection are diagnosed, and 6.6 million (2.2% coverage) are receiving treatment. Only 21% of people living with chronic hepatitis C infection know their status. Although 9.4 million people chronically infected with HCV were cumulatively receiving treatment at the end of 2019, a 10-fold increase from 1 million people receiving treatment at the end of 2015, yet treatment coverage is only 13% of the people in need. A huge scale-up and simplification of hepatitis diagnosis and treatment are required to achieve the targets for reduced mortality by 2030. The momentum to address viral hepatitis is growing. Only 17 countries had national hepatitis strategic plans in 2012, but this had increased to 124 by 2019.

## National Progress towards WHO's 2030 Targets

A nationwide study reported the indicators of viral hepatitis from 2018 to 2020 through domestic infectious disease reporting data, data from the National Health Insurance Service, and death data from Statistics Korea.[5] Since the introduction of the national vaccination program for hepatitis B in 1995 and the implementation of the perinatal infection prevention project in 2002, the prevalence of HBsAg in the age group of 10-18 years has decreased significantly to less than 0.1%. However, the prevalence of HBsAg in adults after the age of 30 is about 3~5%, and the linkage-to-care rate is only 39.4%, and the treatment rate among patients eligible for antiviral treatment is 67.3%. In particular, the liver-elated mortality related to hepatitis B is as high as 18.9 per 100,000 people, mostly due to liver cancer. Meanwhile, in Korea, the incidence rate of hepatitis C remained high at 11.9 per 100,000 people, the hepatitis C management rate was 65.5%, the cure rate was 56.8%, and the annual liver disease mortality rate from hepatitis C was 2.02 per 100,000 people. Recently, the Korea Disease Control and Prevention Agency, together with the Korean Association for the Study of the Liver, has developed an index related to country validation for the elimination of viral hepatitis in Korea in accordance with the WHO's guidance, as well as the primary viral hepatitis (hepatitis B· C) management basic plan was established and announced.

## Considerations to Accelerating Progress in Korea

As of 2024, the efforts to eliminate viral hepatitis by 2030 have seen mixed progress, with significant challenges remaining. Several key considerations need to be highlighted to accelerate the current state of progress.

**Hepatitis B:** In Korea, significant strides have been made in hepatitis B prevention through vaccination. In addition, HBsAg testing is included in the national screening for 40-year-olds, prenatal examination, conscription test, workplace recruitment examination, and private health screening. However, the linkage-to-care rate (39.4%) and treatment rate (67.3% of treatment eligible patients and about 20% of all

hepatitis B patients) are insufficiently low, and the liver disease mortality rate remains very high at 18.9 per 100,000 people compared to the WHO's 2030 target. Therefore, in order to increase the linkage-to-care rate and treatment rate, it is necessary to raise awareness of the patients and to strengthen the education on the treatment of hepatitis B using the simplified guidelines for primary care workers. The academic society should strive to make a consensus on the expansion of antiviral treatment indication to lowering mortality and revise practice guidelines. Further, the government need to expand the reimbursement criteria for treatment and provide sufficient financial support.

**Hepatitis C:** HCV is cured in more than 95% with 8-12 weeks of oral DAAs. Since no vaccination has been developed, the best strategy to prevent the outbreak of new infections is to diagnose and treat as many asymptomatic infected people as possible early so that they are cured of the virus. The most efficient way to diagnose asymptomatic infected people at an early stage is to introduce hepatitis C antibody test in the national screening. Based on the results reporting the cost-effectiveness of HCV screening, introducing the hepatitis C screening test in the national screening is currently awaiting final deliberation by the Ministry of Health and Welfare. The average treatment rate in Korea was 56.8%, and it did not meet the WHO's certification standard of 80%. In order to increase the treatment rate, it is necessary to make efforts to simplify the steps of care-cascade, and to establish treatment linkage system. Considering the high cost of DAA treatment, measures such as lowering the price of drugs and subsidizing treatment costs according to income levels should be prepared. In addition, efforts are needed to improve access to care for older patients, high-risk groups, and patients living in medically underserved areas. Above all, in order to expand screening and treatment, it is necessary to develop simplified treatment guidelines and strengthen education and promotion to help patients and primary care providers better understand.

## Conclusion

While there have been positive steps towards the 2030 elimination goals, significant gaps remain. The availability of effective hepatitis B vaccines, treatment for chronic hepatitis B infection and DAAs treatment cure for chronic hepatitis C infection offer great potential for eliminating these diseases as public health threats by 2030. A collective effort is needed to address gaps in the coverage of testing and treatment of hepatitis B and C and in harm-reduction services for people who inject drugs to achieve global goals.

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THE LIVER WEEK 2024

DAY 1: June 27 (Thu)

# PG Course 2

## Alcoholic and Steatotic Liver Diseases

**Chairs:**

**Kwang Cheol Koh** (Sungkyunkwan Univ.)
**Sehyun Cho** (The Catholic Univ. of Korea)

**Young-Joo Jin**

*Inha University*

## Self Introduction

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| 2013.8 | Ph.D. Doctor degree, University of Ulsan |
| 2006-2010 | Resident course Internal Medicine at Asan Medical Center |
| 2010-2012 | Fellowship, Gastroenterology, at Asan Medical Center |
| 2012-2014 | Clinical Professor, Gastroenterology, Inha University Hospital |
| 2014-2018 | Assistant Professor, Gastroenterology, Inha University Hospital |
| 2019-2023 | Associated Professor, Gastroenterology, Inha University Hospital |
| 2023-current) | Professor, Gastroenterology, Inha University Hospital |

### 학회 활동

현) 대한간학회 편집위원회 위원
현) 대한간학회 지방간연구회 연구이사
현) 대한간학회 경인지회 총무이사
전) 대한간학회 경인지회 재무이사, 대한간학회 학술위원회 위원, 대한간학회 연구기획위원회 위원
전) 대한간학회 전산정보위원회 위원, 대한간학회 교육위원회 위원, 대한간학회 보험위원회 위원
전) 대한간암학회 간암등록사업위원회 위원

## Research Interests

1. Hepatocellular carcinoma
2. Viral hepatitis (B or C)
3. Alcohol or Non-alcohol liver disease

## Representative Publications

1. Jungnam Lee, Jong-In Chang, Young-Joo Jin*, Jeong-Hoon Lee, Ju Yeon Kim, Dong Hyun Sinn, Soon Sun Kim, Hyun Woong Lee, Sun Hong Yoo, Jung Hwan Yu, Jin-Woo Lee. Recurrence of hepatocellular carcinoma in noncirrhotic patients with nonalcoholic fatty liver disease versus hepatitis B infection Eur J Gastroenterol Hepatol. 2023 Apr 1;35(4):431-439. Epub 2022 Dec 23.
2. Won-Mook Choi, Terry Cheuk-Fung Yip, Grace Lai-Hung Wong, W Ray Kim, Leland J Yee , Craig Brooks-Rooney, Tristan Curteis, Harriet Cant, Chien-Hung Chen, Chi-Yi Chen, Yi-Hsiang Huang, Young-Joo Jin, Dae Won Jun, Jin-Wook Kim, Neung Hwa Park, Cheng-Yuan Peng, Hyun Phil Shin, Jung Woo Shin, Yao-Hsu Yang, Young-Suk Lim. Hepatocellular carcinoma risk in patients with chronic hepatitis B receiving tenofovir- vs. entecavir-based regimens: Individual patient data meta-analysis. J Hepatol. 2023 Mar;78(3):534-542. Epub 2022 Dec 23.
3. Jihye Kim, Moon Haeng Hur, Seung Up Kim, Jin-Wook Kim, Dong Hyun Sinn, Hyun Woong Lee, Moon Young Kim, Jae Youn Cheong, Yong Jin Jung, Han Ah Lee, Young-Joo Jin, Jun Sik Yoon, Sung-Jae Park, Chang Hun Lee, In Hee Kim, June Sung Lee, Young Youn Cho, Hyung Joon Kim, Soo Young Park, Yeon Seok Seo, Hyunwoo Oh, Dae Won Jun, Mi Na Kim, Young Chang, Jae Young Jang, Sang Youn Hwang, Yoon Jun Kim. Inverse Propensity Score-Weighted Analysis of Entecavir and Tenofovir Disoproxil Fumarate in Patients with Chronic Hepatitis B: A Large-Scale Multicenter Study. Cancers (Basel) 2023 Jun; 15(11): 2936. Published online 2023 May 26
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# Alcohol and Its Contribution to Steatotic Liver Disease

**Young-Joo Jin** *Inha University*

Alcoholic liver diseae (ALD) encompasses a spectrum of injuries, ranging from simple steatosis, alcoholic steatohepatitis, fibrosis, cirrhosis, and liver cancer development. The prevalence of ALD has remained largely stable between the years of 2001 through 2016 in the US, accounting for 8% in 2015 to 2016. However, the prevalence of patients with ALD and stage ≥3 fibrosis has been increased from 2.2% (2001–2002) to 6.6% (2015–2016). Multiple factors, such as cultural influences, environmental factors, and diet, etc are associated with the development and severity of ALD. However, pathogenesis of ALD is still incompletely understood. There are three major pathways of alcohol metabolism. The primary pathway is initiated by alcohol dehydrogenase, a NAD+ requiring enzyme expressed at high levels in hepatocytes, which oxidizes ethanol to acetaldehyde. The second major pathway, the microsomal ethanol oxidizing system pathway, involves the NADPH-requiring enzyme cytochrome P450 enzyme 2E1, which is induced by chronic alcohol exposure. The third pathway for ethanol metabolism is carried out by catalase, a peroxisomal enzyme. The annual incidence rate per 1,000 PYs of primary liver cancer (PLCa), hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (Icca) increase in ALD compared to no steatotic liver disease. The cumulative incidence rate of PLCa, HCC, and iCCa was highest in ALD followed by MetALD, MASLD, and no SLD.. Prognosis of ALD, similarly to NAFLD, is mainly determined by fibrosis stage. MASLD and ALD show similar clinical pictures, have large overlaps in associated comorbidities, such as CVD, obesity, and cancer, and also share fibrosis as determinant of prognosis. However, longitudinal long-term studies on the natural history of MASLD and ALD are needed to better understand the dynamic of both diseases as well as to facilitate public health initiatives to improve prevention and therapy. In summary, 1) oncurrent alcohol consumption worsens the prognosis of MASLD, MetALD, and ALD. 2) The pathogenesis of ALD is multifactorial, incompletely understood, and the true impact of alcohol consumption on the development and progression of SLD has remained unclear. There might be a huge overlap between MASLD and ALD, including the new entity of MetALD. 3) As a subtype of SLD, treatment of ALD should focus on both alcohol abstinence and correction of cardiometabolic factors. 4) Further research is needed to delineate the relative risk conferred by metabolic factors, various amounts (and type) of alcohol, and further pathomechanistic factors that might influence disease development, progression, as well as treatment targets.

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**Bong-Jin Hahm**

*Seoul National University*

## Self Introduction

Bong-Jin Hahm is a Professor of the Department of Psychiatry and Behavioral Sciences, Seoul National University College of Medicine and working in Department of Psychiatry at Seoul National University Hospital & Integrated Cancer Care Center at Seoul National University Cancer Hospital.

He graduated from Seoul National University College of Medicine with his medical degree in 1991 and completed his internship and residency at the Department of Psychiatry at Seoul National University Hospital, receiving his diploma in Psychiatry in 1996. He founded Korean Psychooncology Society (KPOS) at 2014 and had been President of KPOS (2014-2018).

## Research Interests

- Psychosomatic medicine
- Consultation Liaision Psychiatry
- Psychooncology

## Representative Publications

1. Shim EJ, Ha H, Kim BR, Kim SM, Moon JY, Hwang JH, Hahm BJ. The Multi-dimensional Assessment of Suicide Risk in Chronic illness-20 (MASC-20): Development and validation. Gen Hosp Psychiatry. 2023;83:140-147
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# Alcohol Use Disorders in Liver Transplant Recipients

**Bong-Jin Hahm** *Seoul National University*

Alcoholic liver disease (ALD) is the leading indication for liver transplantation (LT). ALD is a complex medical and mental disease and highly prevalent among hazardous drinkers (26.0%) and those with alcohol use disorders (AUD) (55.1%). AUD is defined by a cluster of behavioral and physical symptoms including withdrawal, tolerance, and craving. It is more prevalent in individuals with bipolar disorder, schizophrenia, and antisocial personality disorder. Heavy drinking is frequently accompanied, and sometimes preceded, by symptoms of conduct problems, depression, anxiety, and insomnia. In Korea, the 12-month prevalence of AUD is estimated to be 2.6%. The course of AUD is variable, with periods of remission and relapse. A decision to quit drinking, often prompted by a crisis, usually leads to a period of abstinence. However, once drinking resumes, it often quickly escalates, leading to severe problems reoccurring. Although a small proportion, some individuals with AUD have the poorest course, involving many years of severe alcohol-related problems. Post-LT alcohol relapse is associated with poorer outcomes. Therefore, predicting the return to harmful drinking among those with ALD and AUD or harmful alcohol use is crucial for candidate selection and post-LT care. While the duration of abstinence (6-month rule) and psychosocial factors have been cited as predictors of a return to alcohol use, there is insufficient data to support their use as key predictive components. A comprehensive approach is recommended, considering subtypes of alcoholics, psychiatric comorbidities, continued alcohol use after an ALD diagnosis, social support, family history of AUD, and other factors. Intervention for AUD or harmful alcohol use should be personalized based on a comprehensive assessment. Managing comorbid psychiatric illnesses and alcohol withdrawal symptoms should be a priority. Medications such as naltrexone and acamprosate can be effective in controlling craving for alcohol. Behavioral and psychological therapy, along with lifestyle modifications, may help control persistent abusive behavior and improve the quality of life for those with AUD or harmful alcohol use. A comprehensive and multidisciplinary approach is essential for assessing and managing patients with ALD and AUD or harmful alcohol use.

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4. Im GY, Neuberger J. Debate on selection criteria for liver transplantation for alcoholic hepatitis: tighten or loosen? Liver Transpl. 2020 Jul;26(7):916-921.
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**Seung Kak Shin**

*Gachon University*

## Self Introduction

### *Education*

| | |
|---|---|
| 2009 | M.D.,M.S., Gachon University Graduate School of medicine, Inchoen, Republic of Korea |
| 2018 | Ph.D., Division of hepatology, Gachon University, Inchoen, Republic of Korea |
| 2022 | Visiting Scholar, Laboratory of Cancer Immunotherapy and Immunology, University of Tsukuba, Japan |

### *Professional Experience*

| | |
|---|---|
| 2009-2010 | Internship, Gachon University Gil Medical Center, Inchoen, Republic of Korea |
| 2010-2014 | Resident, Gachon University Gil Medical Center, Inchoen, Republic of Korea |
| 2014-2016 | Fellowship, Gachon University Gil Medical Center, Inchoen, Republic of Korea |
| 2023- | Associate professor, Gil Medical Center, Gachon University College of Medicine, Inchoen,Republic of Korea |

## Research Interests

1. Basic and clinical research of non-alcoholic fatty liver disease and liver fibrosis
2. Immune cell therapy for liver cancer
3. Regenerative medicine for liver fibrosis and cirrhosis

## Representative Publications

1. Shin SK, Oh S, Chun SK, Ahn MJ, Lee SM, Kim K, Kang H, Lee J, Shin SP, Lee J, Jung YK. Immune signature and therapeutic approach of natural killer cell in chronic liver disease and hepatocellular carcinoma. J Gastroenterol Hepatol. 2024 May 27. doi: 10.1111/jgh.16584
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4. Shin SK, Kim KO, Kim SH, Kwon OS, Choi CS, Jeong SH, Kim YS, Kim JH, Chung MH. Exogenous 8-hydroxydeoxyguanosine ameliorates liver fibrosis through the inhibition of Rac1-NADPH oxidase signaling. J Gastroenterol Hepatol. 2020 Jun;35(6):1078-1087.
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# Extrahepatic Complications of Steatotic Liver Disease

**Seung Kak Shin** *Gachon University*

## Introduction

Steatotic liver disease (SLD) is a new nomenclature that encompasses various etiologies of steatosis, and nonalcoholic fatty liver disease (NAFLD) has been newly named metabolic-dysfunction associated steaotic liver disease (MASLD) which defines steatosis and at least one of the five cardiometabolic risk factors.[1] MASLD is a multisystemic disease that affects extrahepatic organ systems. Common extrahepatic manifestations in MASLD include cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), extrahepatic malignancies, hypothyroidism, sleep apnea, and polycystic ovary syndrome (PCOS).[2,3] In this lecture, the extrahepatic complications associated with MASLD were mainly discussed.

## Extrahepatic complications of steatotic liver disease

### *Cardiovascular complications*

CVD are the leading cause of morbidity and mortality in patients with MASLD. The pathophysiological link between MASLD and CVD includes shared risk factors such as obesity, insulin resistance, and dyslipidemia.[4] MASLD is associated with an increased prevalence of atherosclerosis, coronary artery disease, and myocardial infarction. Studies have shown that the severity of liver disease correlates with the risk of cardiovascular events.[5,6]

### *Type 2 diabetes mellitus*

MASLD and T2DM have a bidirectional relationship, and insulin resistance plays a central role in the pathogenesis of both conditions.[7] Patients with MASLD are at a higher risk of developing T2DM, and those with T2DM have a higher prevalence and severity of MASLD.[8] The presence of MASLD in diabetic patients increases the risk of diabetic complications, including retinopathy, nephropathy, and neuropathy.[9]

### *Chronic kidney disease*

MASLD contributes to the development and progression of CKD through mechanisms such as systemic inflammation, insulin resistance, and hypertension. Patients with MASLD are more likely to develop al-

buminuria and reduced glomerular filtration rate, indicating deteriorating kidney function.[10]

### *Extrahepatic malignancies*

Several reports have suggested that extrahepatic malignancies associated with MASLD include uterine cancer, gastric cancer, pancreatic cancer, colon cancer, and breast cancer.[11]

### *Thyroid dysfunction*

The thyroid gland plays an integral part in maintaining metabolic homeostasis, with effects on obesity, dyslipidemia, and therefore may be linked with MASLD. There have been studies on the relationship between hypothyroidism or subclinical hypothyroidism and MASLD, and it has been reported that there is also a relationship with the severity of liver disease.[12] Recently, the US Food and Drug Administration (FDA) has approved the first drug, resmetirom which is an oral thyroid hormone receptor-$\beta$ (THR-$\beta$) agonist, for metabolic dysfunction-associated steatohepatitis (MASH).

### *Sleep apnea*

Obstructive sleep apnea (OSA) is commonly observed in individuals with MASLD, particularly in those with obesity. OSA leads to intermittent hypoxia, which can exacerbate liver injury and inflammation. Conversely, the presence of MASLD may worsen the severity of OSA.[13]

### *Polycystic ovary syndrome*

Women with PCOS are at a higher risk of developing MASLD. Both conditions share common pathophysiological features such as insulin resistance, obesity, and metabolic syndrome.[14] The presence of MASLD in women with PCOS is associated with more severe metabolic abnormalities and an increased risk of cardiovascular complications.

## Conclusion

MASLD is not only a liver-centric disease but also a systemic condition with wide-ranging extrahepatic complications. The interplay between MASLD and various organ systems necessitates a multidisciplinary approach to manage the disease effectively. Early detection and management of these complications are crucial in reducing the burden of MASLD and enhancing the quality of life for affected individuals.

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4. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010;363:1341-1350.
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## Hyuk Soo Eun

*Chungnam National University*


## Self Introduction

Professor Hyuk Soo Eun graduated from Chungnam National University College of Medicine and later completed an internship and residency at the Department of Internal Medicine at Chungnam National University Hospital.

Afterwards, he obtained a doctorate from the Graduate School of Medical Science and Engineering at the Korea Advanced Institute of Science and Technology, and later served as a fellowship and assistant professor in the Department of Gastroenterology and Internal Medicine at Chungnam National University Hospital, where he currently serves as an associate professor.

Professor Hyuk Soo Eun currently serves as an academic committee member of the Korean Association for the Study of the Liver and an executive committee member of the Korean Association for Liver Cancer.

## Research Interests

- Molecular Mechanism of HCC Development
- Liquid Biopsy for HCC
- Clinical Study of MASLD, HCC

## Representative Publications


1. Kim HN, Jeon HJ, Choi HG, Kwon IS, Rou WS, Lee JE, Lee TH, Kim SH, Lee BS, Shin KS et al: CT-based Hounsfield unit values reflect the degree of steatohepatitis in patients with low-grade fatty liver disease. BMC Gastroenterol 2023, 23(1):77. (Corresponding author)
2. Rou WS, Eun HS, Choung S, Jeon HJ, Joo JS, Kang SH, Lee ES, Kim SH, Kwon IS, Ku BJ et al: Prognostic Value of Erythroblastic Leukemia Viral Oncogene Homolog 2 and Neuregulin 4 in Hepatocellular Carcinoma. Cancers (Basel) 2023, 15(9). (Co-First author)
3. Jeon HJ, Eun HS, Kwon IS, Lee BS, Lee ES, Rou WS, Sung JK, Moon HS, Kang SH, Lee HS et al: Outcomes of laparoscopic radiofrequency ablation versus percutaneous radiofrequency ablation for hepatocellular carcinoma. Surg Endosc 2023. (Co-First author)
4. Yujin Jeong, Seunghwan Noh, Minsang Yu, Sung-pil Chang, Hyuksoo Eun, Jinchul Kim, Youngjun Song. Liquid Metal Electrodynamic Accumulation Microfluidics System for DNA Memory and Liquid Biopsy. Adv. Func. Mater. 2023. https://doi.org/10.1002/adfm.202305680 (Co-Corresponding author)

# Multidisciplinary Approach to the Management of Steatotic Liver Disease

**Hyuk Soo Eun** *Chungnam National University*

Steatotic liver disease is a metabolic associated systemic disease involved multiple organs. Especially, fibrosis is important in steatotic liver disease, and type 2 diabetes is one of the strongest risk factors. In addition, various metabolic diseases are involved in steatotic liver disease and are closely related to the progression and prognosis of the disease. Therefore, steatotic liver disease management should be conducted in a multidisciplinary framework to control risk factors common to cardiovascular disease.

There were various multidisciplinary cares, and according to several studies, total body weight loss or liver and metabolic health markers were improved through these multidisciplinary cares. Representatively, there is a multidisciplinary care program like "ICHANGE". Nevertheless, there is an UNMET NEED in the multidisciplinary care treatment of steatotic liver disease patients, and prosocial behavior is necessary due to cognitive, fatigue, and mental health issues, and collaboration with the psychiatry department may be necessary.

You can proceed on your own, and to do that consultation with the cardiology department, endocrinology department, psychiatry department, surgery as well as nutrition team, and exercise prescription team is required.


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THE LIVER WEEK 2024

DAY 1: June 27 (Thu)

# New KASL Guidelines 2024

**Chair:**

**Young Oh Kweon** (Kyungpook National Univ.)

Seung Up Kim

*Yonsei University*

## Self Introduction

Seung Up Kim, M.D., Ph.D. is a Professor of Yonsei University College of Medicine. He is a member of Korean Association of the Study of the Liver and Korean Liver Cancer Study Group. He has more than 300 SCI(E) original, peer reviewed publications as primary or corresponding author. He is a invited referee for more than 10 SCI(E) journals including Gastroenterology, Hepatology, Journal of Hepatology, etc. His major research interests include viral hepatitis, liver fibrosis, and liver cancer. He acts as an Editor-in-Chief, Emeritus of Clinical and Molecular Hepatology, an Editorial Board member of Clinical Gastroenterology and Hepatology, an academic editor of PLoS One, an Associate editor of World Journal of Gastroenterology, and Associate Editor of Gut and Liverr, and editorial board member of Journal of Gastroenterology and Hepatology.

## Research Interests

'Molecular biology of hepatitis B virus', 'Immunogenetics of hepatitis virus infection', 'Noninvasive assessment of liver fibrosis', and 'Diagnosis and treatment for viral hepatitis and liver cancer'.

## Representative Publications

1. Kim SU (Co-first), Seo YS, Lee HA, Kim MN, Lee YR, Lee HW, Park JY, Kim DY, Ahn SH, Han KH, Hwang SG, Rim KS, Um SH, Tak WY, Kweon YO, Kim BK, Park SY. A multi-center study of entecavir vs. tenofovir on prognosis of treatment-naïve chronic hepatitis B in the Republic of Korea. J Hepatol 2019; 71: 456-464.
2. Lee YH, Jung KS, Kim SU, Yoon HJ, Yun YJ, Lee BW, Kang ES, Han KH, Cha BS. Sarcopenia is associated with NAFLD independently of obesity and insulin resistance: nationwide surveys (KNHANES 2008-2011). J Hepatol 2015;63:486-93.
3. Kim BK, Kim SU (Corresponding), Kim KA, Chung YE, Kim MJ, Park MS, Park JY, Kim DY, Ahn SH, Kim MD, Park SI, Won JY, Lee DY, Han KH. Complete response at the first chemoembolization is still the robust predictor for favorable outcome in hepatocellular carcinoma. J Hepatol 2015 2015; 62: 1304-1310.
4. Kim MN, Kim SU (Co-corresponding), Kim BK, Park JY, Kim DY, Ahn SH, Song KJ, Park YN, Han KH. Increased risk of hepatocellular carcinoma in chronic hepatitis B patients with transient elastography-defined subclinical cirrhosis. Hepatology 2015 2015; 61: 1851-1959.

# KASL Clinical Practice Guidelines for Noninvasive Tests to Assess Liver Fibrosis in Chronic Liver Disease

**Seung Up Kim** *Yonsei University*

Liver fibrosis refers to scar-like changes that occur in the liver when inflammation persists over a long period of time. Assessing liver fibrosis is crucial for predicting the prognosis of chronic liver diseases (CLDs), making it of paramount important in the management of patients with these conditions. The standard test for evaluating liver fibrosis is a liver biopsy, which is invasive. Therefore, there have been ongoing efforts to evaluate liver fibrosis noninvasively using imaging studies and serum biomarkers. However, there is a lack of clinical guidelines providing practical information about noninvasive tests (NITs) for assessing liver fibrosis to healthcare providers treating patients with CLDs, highlighting the need for such guidelines.

We have systematically reviewed Korean and international studies to prepare guidelines based on evidence and to reflect domestic conditions as much as possible. In case related studies on clinically essential issues are lacking, we tried to present consensus opinions of experts. These guidelines have been developed through the reviews of medical evidence by experts to provide a practical reference for NITs to assess liver fibrosis in CLD. They are not absolute standards for treatment, and the best choice of practice for individual patients could be variable depending on the individual situation. If relevant evidence based on new research results is accumulated in the future, these guidelines can be revised and supplemented.

The target population of these guidelines is adult and pediatric patients with CLD, including chronic hepatitis B (CHB), chronic hepatitis C (CHC), nonalcoholic fatty liver disease (NAFLD), alcohol-related liver disease, and other CLDs including primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and congestive hepatopathy.

These guidelines aimed to provide clinical information useful for decision-making to healthcare providers treating patients with CLD, enabling effective evaluation of liver fibrosis through NITs. In addition, these guidelines were intended to provide specific and practical information to resident physicians, practitioners, and trainers.

The Clinical Practice Guideline Committee for Noninvasive Tests to Assess Liver Fibrosis in Chronic Liver Disease (Committee) was organized in accordance with proposals by the approval of the Korean Asso-

ciation for the Study of the Liver (KASL) Board of Executives and consists of 17 gastroenterologists, one radiologist, one surgeon, one cardiovascular surgeon, and one pediatrician specializing in hepatology. All expenses were paid by KASL and the financial support did not affect the independence of the contents of the guidelines. Each member collected, analyzed relevant evidence, and wrote the manuscript in his or her field.

The committee collected and analyzed relevant Korean and international literature through PubMed, MEDLINE, and KoreaMed to establish guidelines based on the latest research and evidence. Only Korean and English literature were searched, and search terms included 'noninvasive', 'liver fibrosis', 'chronic liver disease', 'chronic hepatitis', 'hepatitis B', 'hepatitis C', 'viral hepatitis', 'nonalcoholic fatty liver', 'nonalcoholic steatohepatitis', 'alcoholic liver disease', 'primary biliary cholangitis', 'autoimmune hepatitis', 'primary sclerosing cholangitis', 'congestive hepatopahy', 'hepatectomy', and specific terms of the subject.

Recently, there has been an effort to change the terminology from NAFLD to metabolic dysfunction-associated fatty liver disease or metabolic dysfunction-associated steatotic liver disease, and studies on noninvasive liver fibrosis assessment have been published in relation to this transition. As evidence accumulates, it is anticipated that revisions will be necessary in the future.

THE LIVER WEEK 2024

DAY 1: June 27 (Thu)

# PG Course 3

## Cirrhosis and Portal Hypertension

**Chairs:**

**So Young Kwon** (Konkuk Univ.)
**Il Han Song** (Dankook Univ.)

**Seong Hee Kang**

*Korea University*

## Self Introduction

### *Education*

Bachelor, Korea University, College of Medicine
Master's Degree of Medicine, Korea University, Graduate School of Medicine
Doctor's Degree of Medicine, Korea University, Graduate School of Medicine

### *Professional Experience*

Assistant professor, Wonju Severance Christian Hospital
Clinical associate professor, Korea University Ansan Hospital

## Research Interests

Nonalcoholic fatty liver disease, Alcoholic hepatitis, Portal hypertension, Hepatocellular carcinoma

## Representative Publications

1. (Outcome of Intermittent Thoracentesis versus Pigtail Catheter Drainage for Hepatic Hydrothorax) / 2022.12.01
2. (Long-Term Prediction Model for Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Receiving Antiviral Therapy: Based on Data from Korean Patients) / 2022.11.01
3. (Improved anti-fibrotic effects by combined treatments of simvastatin and NS-398 in experimental liver fibrosis models) / 2022.07.01
4. (Autoimmune Hepatitis Following Vaccination for SARS-Cov-2 in Korea: Coincidence or Autoimmunity?) / 2022.04.01
5. (Association between chronic hepatitis B infection and COVID-19 outcomes: a Korean nationwide cohort study) / 2021.10.01
6. (KASL clinical practice guidelines: Management of nonalcoholic fatty liver disease) / 2021.07.01
7. (From nonalcoholic fatty liver disease to metabolic-associated fatty liver disease: Big wave or ripple?)

# Pathophysiology, Diagnosis, and Management of HRS-AKI in Cirrhosis

**Seong Hee Kang** *Korea University*

Hepatorenal syndrome (HRS) is characterized by significant kidney impairment in advanced cirrhosis.[1] It includes an acute form, HRS-AKI, a type of acute kidney injury, and a chronic form, HRS-CKD, considered a type of chronic kidney disease.

## 1. Definition

The Acute Kidney Injury Network defined AKI to include all forms of acute renal failure, and the Kidney Disease Improving Global Outcome defined it as an increase in serum creatinine ≥0.3 mg/dL (26.5 μmol/L) or ≥1.5 times the baseline within seven days.[2] The International Club of Ascites allows using serum creatinine from the past three months as baseline if recent values are unavailable.[3]

HRS is divided into HRS-AKI (formerly type 1) and HRS-non-AKI (HRS-NAKI, formerly type 2). HRS-NAKI includes HRS-acute kidney disease (HRS-AKD, eGFR < 60 mL/min per 1.73 $m^2$ for less than 3 months) and HRS-chronic kidney disease (HRS-CKD, eGFR < 60 mL/min per 1.73 $m^2$ for more than 3 months). HRS-AKI involves AKI in cirrhosis patients with ascites, with no response after 2 days of diuretic withdrawal and albumin infusion (1 g/kg/day), absence of shock, no recent nephrotoxic drugs, and no structural kidney injury.[4]

**Table 1.** Stages of acute kidney injury according to the International Club of Ascites

| | |
|---|---|
| 1A | sCr≥0.3 mg/dL (but<X2) from baseline (Cr<1.5 mg/dL) |
| 1B | sCr≥0.3 mg/dL (but<X2) from baseline (Cr≥1.5 mg/dL) |
| 2 | sCr>X2-3 from baseline |
| 3 | sCr>X3 from baseline or Cr≥4.0 mg/dL with sCr≥0.3 mg/dL or RRT |

## 2. Pathophysiology

HRS pathophysiology lacks direct experimental evaluation due to the absence of suitable animal models. The primary mechanism involves splanchnic hypoperfusion leading to sodium retention and renal

vasoconstriction, characterized by uncompensated hyperdynamic circulation. Other factors include systemic inflammation, cirrhotic cardiomyopathy, cholemic nephropathy, and adrenal insufficiency.[5]

## 3. Diagnosis

Despite improved understanding of the pathogenesis and diagnostic criteria of HRS-AKI, it remains a diagnosis of exclusion and requires a period of observation after diuretic/nephrotoxic medication withdrawal. Moreover, the main diagnostic conundrum in patients with AKI is to distinguish between AKI due to acute tubular necrosis (ATN)-AKI and HRS-AKI. Novel urine biomarkers of tubular injury have long been sought to differentiate AKI-HRS and ATN in patients with cirrhosis. Candidate biomarkers include tubular proteins released during cell damage (N-acetyl-$\beta$-D-glucosaminidase, $\alpha$-glutathione S-transferase), tubular proteins up regulated by injury (kidney injury molecule-1, neutrophil gelatinase associated lipocalin [NGAL], liver-type fatty acid binding protein), plasma proteins with diminished tubular reabsorption ($\alpha$-1-microglobulin, $\beta$-2-microglobulin, retinol binding protein), and markers of inflammation (interleukin18).[6] Among these, NGAL has been the most widely studied biomarker in patients with cirrhosis and has shown the greatest diagnostic accuracy in differentiating ATN from AKI-HRS.[7,8]

## 4. Management

The specific treatment of AKI-HRS comprises vasoconstrictors in combination with albumin infusion and reversal of precipitant factors.[9] The updated diagnostic criteria, with removal of a minimum serum creatinine concentration, allow for earlier diagnosis and treatment of AKI-HRS.[10] Rather than waiting for a doubling of creatinine to reach 2.5 g/dL. This is likely to result in higher reversal rates and better outcomes.

Terlipressin, an analogue of vasopressin, is the firstly recommended vasoconstrictors for AKI-HRS treatment.[11] Terlipressin by stimulating vasopressin receptors in the vascular smooth muscle cells, induce splanchnic vasoconstriction, which in turn, reduce portal blood flow and portal pressure. In addition, albumin increases effective arterial volume and lead to increase in preload to the heart, cardiac output, and mean arterial pressure. This treatment is considered effective if serum Cr is reduced at least 25% within 3 days after initiation of treatment.

Norepinephrine and midodrine are systemic vasoconstrictors through activation of $\alpha$1 adrenergic receptors on vascular smooth muscle cells. Octreotide, a somatostatin analog, acts by inhibiting secretion of glucagon, a splanchnic vasodilator, and is a direct mesenteric vasoconstrictor.[12]

In non-responders to terlipressin and albumin, RRT is a useful option as a bridge to LT; by contrast, in patients in whom LT is contra-indicated RRT can be futile, and its use should be considered on a case-by-case basis.[13] The liver transplantation remains the optimal treatment, and timely referral for transplant evaluation is crucial to avoid permanent kidney damage and the need for simultaneous liver and

kidney transplant.[14]

## 5. Conclusions

HRS results from circulatory dysfunction causing renal hypoperfusion, with inflammation and cardiac dysfunction also playing roles. Improved biomarkers facilitate earlier diagnosis and treatment, primarily through vasoactive medications and albumin, applied during early disease stages for the greatest benefit.

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**Jung Gil Park**

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## Self Introduction

- Associate professor, Gastroenterology & Hepatology, Yeougnam University Hospital, Daegu, Korea
- Member, Committee of the Editorial Board in the KASL
- Editor in Chief, Clinical Ultrasound
- 2020.02-2021.02 University of California San Diego, NAFLD research center
- 2004 M.D., Kyungpook National University School of Medicine, Daegu, Korea
- 2015 M.S., Kyungpook National University School of Medicine, Daegu, Korea
- 2019 PhD., Kyungpook National University School of Medicine, Daegu, Korea

## Research Interests

MASLD, ArLD, Hepatocellular carcinoma, ncRNA, Biomarker

## Representative Publications

1. Liver stiffness by magnetic resonance elastography is associated with increased risk of cardiovascular disease in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2021;53(9):1030-1037.
2. Long-term effects of the changes in hepatic steatosis status on the risk of incident type 2 diabetes mellitus: A 15-year community-based prospective cohort study. Diabetes Res Clin Pract. 2022;184:109208
3. Impact of metabolic factors on risk of cardiovascular disease in nondiabetic metabolic dysfunction-associated fatty liver disease. Hepatol Int. 2023;17(3):626-635.
4. Fibrosis-4 index as a predictor for mortality in hospitalised patients with COVID-19: a retrospective multicentre cohort study. BMJ Open. 2020;10(11):e041989.
5. Expression of the Long Noncoding RNA GAS5 Correlates with Liver Fibrosis in Patients with Nonalcoholic Fatty Liver Disease. Genes (Basel). 2020;11(5):545.

# When to Start and Stop Anticoagulation Therapy for Benign Portal Vein Thrombosis

**Jung Gil Park** *Yeungnam University*

Portal vein thrombosis (PVT) is a serious complication of liver cirrhosis and is associated with poor outcomes. According to a recent meta-analysis, the incidence of PVT in liver cirrhosis is 4.59 per 100 patient-years.[1] Risk factors for PVT include poor liver function, lower platelet counts, and the use of non-selective beta-blockers.[1] Although societal guidelines recommend the use of anticoagulation in patients with recent-onset PVT, there is variation in practice patterns surrounding the management of anticoagulation.[2,3]

While non-portal hypertension-related bleeding is increased with anticoagulation, the rate of portal vein recanalization is also increased. Additionally, the beneficial effect of anticoagulation on survival is independent of thrombosis severity and recanalization.[4] However, patients with low platelet counts (e.g., <50 x 10^3/μL) who are at risk of bleeding complications on anticoagulation should be assessed on a case-by-case basis.[2]

For patients awaiting liver transplantation (LT), anticoagulation should continue even after recanalization. In all other cases, anticoagulation should be maintained until portal vein recanalization or for a minimum of six months.[2,5] If recanalization is not achieved with anticoagulation, transjugular intrahepatic portosystemic shunts are recommended, especially for patients awaiting LT.

Anticoagulation is preferably initiated with low molecular weight heparin (LMWH) and maintained with either LMWH, vitamin K antagonists, or direct oral anticoagulants (DOACs).[2,5] However, the evidence supporting the use of DOACs is not robust, and there are safety concerns regarding their use in patients with Child-Pugh class B/C.

In conclusion, anticoagulation should be considered in patients with recent PVT. Anticoagulation should be maintained for at least six months and can be discontinued on a case-by-case basis. The use of DOACs is safe in patients with Child-Pugh class A, but not in those with class B/C.

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lished Online First: 2022/06/11]
2. de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII-Renewing consensus in portal hypertension. Journal of hepatology 2022;76(4):959-74. doi: 10.1016/j.jhep.2021.12.022 [published Online First: 2022/02/06]
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4. Guerrero A, Campo LD, Piscaglia F, et al. Anticoagulation improves survival in patients with cirrhosis and portal vein thrombosis: The IMPORTAL competing-risk meta-analysis. Journal of hepatology 2023;79(1):69-78. doi: 10.1016/j.jhep.2023.02.023 [published Online First: 2023/03/02]
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**Do Seon Song**

*The Catholic University of Korea*

## Self Introduction

### *Education*

| | | |
|---|---|---|
| 1997.03-2003.02 | Bachelor's degree | The Catholic University of Korea |
| 2010.03-2016.02 | Doctor's degree | The Catholic University of Korea |

### *Training*

| | | |
|---|---|---|
| 2003.03-2004.02 | Intern | Catholic Medical Center |
| 2004.03-2008.02 | Resident of Internal Medicine | Catholic Medical Center |

### *Work*

| | | |
|---|---|---|
| 2011.05-2013.02 | Fellow | Seoul. St. Mary Hospital |
| 2013.03-2014.02 | Fellow | St. Vincent's Hospital |
| 2014.03-2017.02 | Clinical assistant professor | St. Vincent's Hospital |
| 2017.03-2022.02 | Assistant Professor | St. Vincent's Hospital |
| 2022.03- | Associate Professor | St. Vincent's Hospital |

## Research Interests

Portal hypertension, HCC, MASLD, Alcoholic liver disease

## Representative Publications

1. Association between serum TNF-$\alpha$ and sarcopenia in liver cirrhosis. Han JW, Kim DI, Nam HC, Chang UI, Yang JM, Song DS. Clin Mol Hepatol 2022; 28: 219-231
2. Effect of exercise-based interventions in nonalcoholic fatty liver disease: A systematic review with meta-analysis. Nam H, Yoo JJ, Cho Y, Kang SH, Ahn SB, Lee HW, Jun DW, Song DS, Choi M. Dig Liver Dis. 2023 Sep;55(9):1178-1186
3. Change in skeletal muscle mass is associated with hepatic steatosis in nonalcoholic fatty liver disease. Jo IH, Song DS, Chang UI, Yang JM Sci Rep. 2023 Apr 28;13(1):6920.
4. Improving the Prediction of Relapse After Nucleos(t)ide Analogue Discontinuation in Patients With Chronic Hepatitis B. Song DS, Jang JW, Yoo SH, Kwon JH, Nam SW, Bae SH, Choi JY, Yoon SK Clin Infect Dis. 2021 Aug 16;73(4):e892-e903

# Ammonia: Predictive Marker and Therapeutic Target in Cirrhotic Complications

**Do Seon Song** *The Catholic University of Korea*

Ammonia is a natural and endogenous molecule, produced by the metabolism of amino acids and other compound containing nitrogen. About half of circulating ammonia is derived from the gut. Ammonia is produced by the hydrolysis of glutamine in the enterocyte and produced through the catabolism of ingested protein by urease-containing gut flora.[1] And, ammonia generated in the gut diffuse into the portal circulation. The liver disposes the ammonia by two processes: urea cycle and glutamine synthesis. Kidneys also plays an important role in ammonia homeostasis. Renal excretion of ammonia is regulated in response to the acid-base disturbance. Ammonia produced in the kidney is selectively transported into the urine or the renal vein.[2] Although skeletal muscle have relatively low glutamine synthetase activity, skeletal muscle can greatly impact on ammonia metabolism due to large whole-body mass.[3]

In cirrhosis, liver dysfunction impairs both clearance mechanism, urea cycle and glutamine synthesis, while portal hypertension results in increased portosystemic shunting through collateral vessels, ultimately bypassing these processes.[4]

Ammonia plays a crucial role in the development of hepatic encephalopathy (HE). The accumulation and metabolism of ammonia in the brain lead to encephalopathy and neurotoxicity. Hyperammonemia can exacerbate fibrosis and portal hypertension through the activation of hepatic stellate cells.[5] Hyperammonemia induces immune cell dysfunction, manifested by suppressed neutrophil chemotaxis and phagocytosis, as well as reduced antigen uptake and impaired allogenic lymphocyte stimulation by dendritic cells.[6,7] Hyperammonemia also induces sarcopenia by upregulating muscle protein breakdown and downregulating protein synthesis.[3]

Due to its multifaceted impact on various organs in individuals with cirrhosis, significant attention has been directed towards investigating its implications for prognosis in cirrhotic patients. Elevated ammonia levels were predictive of hepatic decompensation, the development of acute-on-chronic liver failure (ACLF), and increased mortality in patients with cirrhosis.[8-10] In addition, elevated ammonia levels were additionally associated with increased mortality in patients with ACLF.[11]

Lowering ammonia level using poorly absorbed disaccharide or antibiotics has been the most crucial intervention in the treatment of HE. Recently, new ammonia lowering drugs, such as glycerol phenylbu-

tyrate L-ornithine L-aspartate, and ornithine phenylacetate, are being studied as a treatment of HE.[4] The administration of ammonia scavengers in animal model of nonalcoholic fatty liver disease demonstrates potential in impeding fibrosis progression, indicating that targeting ammonia reduction could serve as a treatment strategy of cirrhosis.[12] In addition, ammonia lowering treatment could reverse sarcopenia in preclinical study of cirrhosis.[13]

We aim to review the alterations in ammonia metabolism in cirrhosis and the prognostic significance of ammonia levels, as well as its potential as a therapeutic target.

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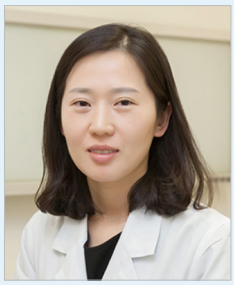

**Danbi Lee**

*University of Ulsan*

## Self Introduction

Prof. Danbi Lee is a clinical professor of the Department of internal medicine, Asan Medical Center, Seoul.

Prof. Lee graduated from Chonbuk National University with her medical degree in 2002 and got a master and PhD degree from University of Ulsan College of Medicine.

She completed her internship, residency, and fellowship at the Department of Internal Medicine at Asan Medical Center, Seoul. She received her diploma in Internal Medicine in 2002 and special boards of Gastrointestinal Endoscopy and Gastroenterology in 2008 and 2009, respectively.

## Research Interests

She is currently doing research work on HCC, cirrhosis and chronic hepatitis.

## Representative Publications

1. Predictive Biomarkers for Immune-Checkpoint Inhibitor Treatment Response in Patients with Hepatocellular Carcinoma. Jun Ho Ji, Sang Yun Ha, Danbi Lee, Kamya Sankar, Ekaterina K Koltsova, Ghassan K Abou-Alf, Ju Dong Yang.Int J Mol Sci, 2023 Apr 21;24(8):7640.
2. Risk of Hepatitis B Virus Reactivation in Patients Treated With Immunotherapy for Anti-cancer Treatment. Sun Yoo, Danbi Lee, Ju Hyun Shim, Kang Mo Kim, Young-Suk Lim, Han Chu Lee, Changhoon Yoo, Baek-Yeol Ryoo, Jonggi Choi. Clin Gastroenterol Hepatol. 2022 Apr;20(4):898-907.
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# Differentiation and Management of Infected Ascites in Patients with Cirrhosis

**Danbi Lee** *University of Ulsan*

Ascites is one of the most common complications of liver cirrhosis. It is commonly first sign of decompensated cirrhosis with portal hypertension along with hepatic encephalopathy and variceal bleeding. Patients with compensated cirrhosis develop ascites at a rate of 5-10% per year. It is also associated with a reduction in 5-year survival from 80% to 30% in patients with liver cirrhosis.[1] Although approximately 80% of ascites occurs in patients with liver cirrhosis, other causes such as tuberculosis, malignancy, heart failure and nephrotic syndrome.[2] Thus, initial evaluation of ascites needs to be careful for differential diagnosis.

In evaluating the etiology of ascites, the serum-ascites albumin gradient (SAAG) which is calculated by subtracting the ascetic fluid albumin from the serum albumin obtained on the same day is very useful. A SAAG ≥ 1.1 g/dL highly predicts that the patients has portal hypertension including cirrhosis, cardiac ascites, sinusoidal obstruction syndrome or liver metastasis with 97 percent accuracy. Total protein in ascites may also be of value in distinguishing cardiac ascites from liver cirrhosis. An ascitic protein >2.5g/dL supports a congestive heart failure, congestive pericarditis or sinusoidal obstructive syndrome. In addition, cell count and differential, culture, adenosine deaminase, LDH, glucose, and cytology are also effectively used for the differential diagnosis of ascites.

Spontaneous bacterial peritonitis (SBP) is defined as an ascitic fluid infection without an evident intra-abdominal surgically treatable source.[3] SBP occurs in 20-30% of patients with cirrhotic ascites. Because the presentation of SBP is variable and a delay in therapy can lead to increased mortality,[4] a diagnostic paracentesis should be performed as soon as a patient with cirrhosis and ascites is hospitalized emergently for any reason, even in the abscess of symptoms suggestive of infection or whenever a patient develops signs suggestive of infection. A diagnosis of SBP is established if the polymorphonuclear cell (PMN) count in the ascetic fluid is ≥ 250 cells/mm$^3$, culture results are positive, and secondary causes of peritonitis are excluded.[5] Common pathogens of SBP include *Escherichia coli, Klebsiella pneumoniae, Streptococcus species, Staphylococcus aureus*, and *Enterococcus species*.[6]

Approximately 4.5% of all peritonitis in cirrhotic patients develop secondary bacterial peritonitis caused by intestinal perforation or abscess.[7] Their mortality rate is very high at 66%. Secondary bacterial peritonitis may be suspected in the following patients: a) PMN count increases to > 1,000/mm3; b) multiple

organisms are seen by ascetic gram stain or culture; c) ascetic protein concentration ≥1g/dL; d) ascetic LDH level > ULN in serum; e) ascetic glucose level ≤ 50mg/dL; and f) PMN count in ascites does not drop after 48 hours after antibiotic treatment.[8]

Intravenous antibiotics should be started immediately in all patients who are suspected of ascitic infection. In general, antibiotics should be given after ascitic fluid has been obtained for culture and analysis. Traditionally, third-generation cephalosporins are recommended as the first-line antibiotics. They show a high resolution rate of 69-100% after 5 to 10 days of treatment.[9,10] According to various studies, extended-spectrum beta-lactamase (ESBL)-producing bacterial infections account for 5-30% of all SBP cases.[11] Especially, 46-66% of hospital-acquired SBP have ESBL-producing bacterial infections.[11] As infections by multidrug-resistant organisms increase, third-generation cephalosporins have become less effective in cases with nosocomial infection or recent hospitalization and critically ill patients admitted in the intensive care unit.[12] Therefore, initial use of carbapenem may be recommended for such patients.[13] In general, response to empirical antibiotics may be assessed by repeating diagnostic paracentesis 2 days after initiation. A decrease in ascitic PMN <25% from baseline indicates lack of response and should lead to more broadening antibiotics coverage. Intravenous albumin infusion plays an important role to improve survival in patients with cirrhosis and SBP.[14] It may prevent the progression of acute kidney injury. Thus, patients with SBP should be treated with IV albumin in addition to antibiotics. Patients with a prior episode of SBP are at a very high risk of SBP recurrence. Norfloxacin can decrease SBP recurrence rate (20% at 1-year) compared with placebo (68% at 1-year).[15] If norfloxacin is unavailable, oral ciprofloxacin is acceptable.

In conclusion, SBP is a frequent and serious complication and associated with increasing mortality in patients with liver cirrhosis. In patients who are suspected infection in their ascites, diagnostic paracentesis should be performed immediately, followed by empirical antibiotics treatment. Third-generation cephalosporins are generally recommended in patients with SBP. In critically ill patients with nosocomial infection or recent hospitalization, however, carbapenem may be considered as the initial antibiotics due to increasing infection by multidrug-resistant organism. Treatment response should be evaluated by diagnostic paracentesis on 2 days after initiation of antibiotics, and the treatment should be adjusted according to the results.

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DAY 1: June 27 (Thu)

THE LIVER WEEK 2024

# PG Course 4

## Liver Neoplasms

**Chairs:**

**Jin Mo Yang** (The Catholic Univ. of Korea)
**Sung Kyu Choi** (Chonnam National Univ.)

**Young-Sun Lee**

*Korea University*

## Self Introduction

### *Education*

2000.3-2006.2 M.D. in Korea University Medical College
2008.9-2010.8 M.S., Department of Medicine in Korea university medical college
2011.2 – 2015.2 Ph.D., Graduate School of Medical Science & Engineering, KAIST, Korea

### *Professional Experience*

2018.9 – 2021.2 Assistant Professor in Department of Internal Medicine, Division of Gastroenterology and Hepatology, Guro hospital, Korea University College of Medicine
2021.3 – present Associate Professor in Department of Internal Medicine, Division of Gastroenterology and Hepatology, Guro hospital, Korea University College of Medicine

## Research Interests

NAFLD, HCC, Immunity

## Representative Publications

1. Lee YS, Seki E. In Vivo and in Vitro Models to Study Liver Fibrosis: Mechanisms and Limitations. Cell Mol Gastroenterol Hepatol 2023.
2. Lee YS, Lee JE, Yi HS, et al. MRE-based NASH score for diagnosis of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease. Hepatol Int 2022;16:316-24.
3. Kim TH, Lee Y, Lee YS, et al. Circulating miRNA is a useful diagnostic biomarker for nonalcoholic steatohepatitis in nonalcoholic fatty liver disease. Sci Rep 2021;11:14639.
4. Lee YS, Jung YK, Kim JH, et al. Effect of urea cream on sorafenib-associated hand-foot skin reaction in patients with hepatocellular carcinoma: A multicenter, randomised, double-blind controlled study. Eur J Cancer 2020;140:19-27.
5. Hyun MH, Lee YS, Kim JH, et al. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: A meta-analysis of high-quality studies. Hepatology 2018;68:977-93.

# The Difference in Pathogenesis and Clinical Care between MASLD- and Viral-Related HCC

**Young-Sun Lee** *Korea University*

Hepatocellular carcinoma (HCC) exhibits distinct pathogenesis depending on the underlying etiology, particularly when associated with Hepatitis B virus (HBV), Hepatitis C virus (HCV), or non-viral causes such as alcohol related liver disease and metabolic dysfunction-associated steatotic liver disease (MASLD).[1] In aspect of clinical care, special considerations are required for management underlying liver disease during HCC treatment.

Certain genetic mutation profiles and altered gene expression patterns are observed in individuals diagnosed with HBV-related HCC. The molecular signatures resulting from chronic HBV and HCV infections have been extensively studied, providing valuable insights into the pathways involved in the development of HCC.[2] Multidimensional analyses have identified distinct immune subsets enriched in both HBV-related and non-viral HCCs, highlighting the importance of understanding the tumor microenvironment for potential therapeutic interventions.[3] Different immune responses to HBV, HCV, and non-viral HCC have significant implications for immunotherapy approaches. Understanding these differences can facilitate the development of targeted treatments for each HCC subtype.[4]

Therapeutically, the management strategies for MASLD-related HCC can be more challenging due to the metabolic comorbidities that accompany it.[5] Treatment options include surgical resection, liver transplantation, locoregional therapies (such as radiofrequency ablation and transarterial chemoembolization), and systemic therapies, including tyrosine kinase inhibitors and immunotherapy. For viral-related HCC, antiviral therapy plays a crucial role alongside traditional HCC treatments, aiming to control viral replication and reduce liver inflammation, thereby improving overall survival rates.

Patient outcomes in MASLD-related HCC are often poorer compared to viral-related HCC.6 This discrepancy is attributed to delayed diagnosis, advanced disease stage at presentation, and the presence of metabolic comorbidities which complicate treatment and recovery. Viral-related HCC, with its robust surveillance programs and antiviral treatments, often results in better clinical outcomes and prolonged survival.

In conclusion, while MASLD-related and viral-related HCC share similarities in their malignant nature, their differences in etiology significantly impact clinical care. Understanding these differences is crucial

for optimizing patient management and improving outcomes.

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3. Lim CJ, Lee YH, Pan L, et al. Multidimensional analyses reveal distinct immune microenvironment in hepatitis B virus-related hepatocellular carcinoma. Gut 2019;68:916-27.
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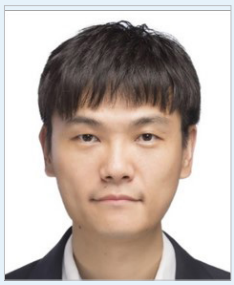

**Dong Ho Lee**

*Seoul National University*

## Self Introduction

### *Education*

College of Medicine-M.D Seoul National University (March 2001-February 2005)
Graduate School-M.S. Seoul National University (March (2008-February 2014)
Graduate School-Ph.D. Seoul National University (March 2014-August 2017)

### *Recent Activities*

1) Chair of research committee, Korean Liver Cancer Association
2) Secretary General, Korean Society of Imaging-Guided Tumor Ablation
3) Abdominal section editor, Ultrasonography (official journal of Korean Society of Ultrasound in Medicine)

## Research Interests

Liver imaging, Liver tumor ablation

## Representative Publications

1. Lee DH, Cho, E. J., Bae, J. S., Lee, J. Y., Yu, S. J., Kim, H., Lee, K. B., Han, J. K. & Choi, B. I. Accuracy of Two-Dimensional Shear Wave Elastography and Attenuation Imaging for Evaluation of Patients With Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol . 2021 Apr;19(4):797-805.e7
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3. Lee, D. H., Lee, J. Y., Bae, J. S., Yi, N. J., Lee, K. W., Suh, K. S., Kim, H., Lee, K. B. & Han, J. K. Shear-wave dispersion slope from US shear-wave elastography: Detection of allograft damage after liver transplantation. Radiology. 2019; 293(2): 327-333
4. Lee DH, Lee JM, Han JK, Choi BI. MR elastography of healthy liver parenchyma: Normal value and reliability of the liver stiffness value measurement. J Magn Reson Imaging. 2013 Nov;38(5):1215-23
5. Lee DH, Lee JM, Yi NJ, Lee KW, Suh KS, Lee JH, Lee KB, Han JK. Hepatic stiffness measurement by using MR elastography: prognostic values after hepatic resection for hepatocellular carcinoma. Eur Radiol. 2017 Apr;27(4):1713-1721.

# Advances in the Imaging Diagnosis and Evaluation of Solid Liver Lesions

**Dong Ho Lee** *Seoul National University*

Among various solid liver lesions, this presentation will focus on the imaging diagnosis and evaluation of primary liver cancers, specifically hepatocellular carcinoma (HCC) and cholangiocarcinoma. HCC is notable among malignant tumors for its unique characteristics and is the only malignancy that can be diagnosed through non-invasive imaging alone, without histopathological confirmation. This is due to the high accuracy of characteristic imaging features of HCC, which include arterial phase hyperenhancement followed by washout in the portal venous or delayed phase in high-risk populations.

The use of hepatocyte-specific contrast agents, such as gadoxetic acid, complicates the evaluation of washout compared to extracellular contrast agents, such as iodinated contrast for CT. Consequently, the interpretation of washout in gadoxetic acid-enhanced liver MR varies across different international guidelines. This presentation will discuss these variations in non-invasive imaging diagnosis of HCC among international HCC management guidelines, with a focus on interpreting washout. Additionally, key points from the recently updated KLCA-NCC guideline will be reviewed.

Another important primary malignant liver tumor is intrahepatic mass-forming cholangiocarcinoma. This presentation will also cover the characteristic imaging findings of intrahepatic cholangiocarcinoma with recent updates.

**Sang Youn Hwang**

*Dongnam Institute of Radiological & Medical Sciences*

## Self Introduction

### *Education*

| | |
|---|---|
| 2001.02 | Bachelor of Medicine (Pusan National University, School of Medicine, Korea) |
| 2006.08 | Master of Internal Medicine (Pusan National University) |
| 2015.02 | PhD of Internal Medicine (Pusan National University) |

### *Postgraduate training and fellowship appointments:*

| | |
|---|---|
| 2001-2002 | Internship program, Pusan National University Hospital |
| 2002-2006 | Residency, Pusan National University Hospital |
| 2008-2010 | Clinical fellowship, Gastroenterology, Seoul National University Hospital, |
| 2023-2023 | Visiting Professor, Hepatology, University of Calgary, Canada |

## Research Interests

- Liver Cancer (Hepatocelllular Carcinoma, Cholangiocarcinoma)
- Immunotherapy
- Radiotherapy

## Representative Publications

1. Hwang SY, Heo J et al. Outcome of Atezolizumab Plus Bevacizumab Combination Therapy in High-Risk Patients with Advanced Hepatocellular Carcinoma. Cancers. 2024 16(4), 838.
2. Hwang SY, Lee SS et al. Second-Line Treatment after Failure of Immune Checkpoint Inhibitors in Hepatocellular Carcinoma: Tyrosine Kinase Inhibitor, Retrial of Immunotherapy, or Locoregional Therapy?. Liver Cancer. 2023 https://doi.org/10.1159/000534303.
3. Hwang SY, Lee SS et al. Dysregulated Calcium Handling in Cirrhotic Cardiomyopathy. Biomedicines. 2023 Jul 4;11(7):1895.
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# Subclassification-Based Treatment Strategies for BCLC Stages B and C HCC

**Sang Youn Hwang** *Dongnam Institute of Radiological & Medical Sciences*

The Barcelona Clinic Liver Cancer (BCLC) staging system, which was first introduced in 1999, was is the most commonly used worldwide because BCLC staging system allocate specific treatments and provide more accurate prognostic information relatively compared with other systems. However several limitations of BCLC system have been suggested by clinicians in real world practice. For example, the classic only treatment option for intermediate stage (BCLC B) HCC patients is transarterial chemoembolization (TACE), although population of BCLC B is very heterogenous and include from patients who can be candidate for liver transplantation or hepatic resection to patients with TACE unsuitability. Similarly the classic only recommendation for advanced stage (BCLC C) HCC patients is systemic therapy, although hepatic resection or locoregional therapy (LRT) can be tried in selected patients. Therefore in this context, now days subclassification of BCLC B and C became an important issue. Especially in the era of immunotherapy, more powerful treatment options such as multidisciplinary combination treatments (LRT plus and immunotherapy etc.) not only increase the efficacy of treatment, but also affect subclassification pattern of BCLC B and C. We will discuss about the present & future of subclassification of BCLC B and C HCC patients in this lecture.

**Joo Kyung Park**

*Sungkyunkwan University*

## Self Introduction

### *Education*

1994-2000 M.D. Seoul National University College of Medicine
2003-2005 M.S. Graduate School, Seoul National University College of Medicine
2009-2014 Ph.D. Graduate School, Seoul National University College of Medicine

### *Professional Experience*

2004 Resident Dept. Internal Medicine, Seoul National University Hospital
2007 Fellow Dept. Internal Medicine, Seoul National University Hospital
2009 Assistant Professor Dept. Internal Medicine, Seoul National University Hospital
2011 Post-Doctoral Research Fellow, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
2014 Associate Professor Dept. of Internal Medicine, Seoul National University Hospital
2015-2023 Present Associate Professor Dept. Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine
2024-Present Professor Dept. Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine

## Research Interests

Interested in Pancreas and Biliary Tract Tumor Biology

## Representative Publications

1. Single-cell transcriptome analysis reveals subtype-specific clonal evolution and microenvironmental changes in liver metastasis of pancreatic adenocarcinoma and their clinical implications. Park JK, Jeong HO, Kim H, Choi JH, Lee EM, Kim S, Jang J, Choi DW, Lee SH, Kim KM, Jang KT, Lee KH, Lee KT, Lee MW, Lee JK, Lee S. Mol Cancer. 2024 May 3;23(1):87. doi: 10.1186/s12943-024-02003-0.
2. Characterization of background noise in capture-based targeted sequencing data. Park G, Park JK, Shin SH, Jeon HJ, Kim NKD, Kim YJ, Shin HT, Lee E, Lee KH, Son DS, Park WY, Park D. Genome Biol. 2017 Jul 21;18(1):136. doi: 10.1186/s13059-017-1275-2.
3. Establishment of a patient-specific avatar organoid model derived from endoscopic ultrasonography-guided fine needle biopsy for timely clinical application in pancreatic ductal adenocarcinoma. Kim H, Jang J, Choi JH, Song JH, Lee SH, Park J, Ryoo SK, Lee EM, Jeong HO, Kim S, Lee SH, Lee KH, Lee KT, Kim KM, Jang KT, Lee H, Lee S, Lee JK, Park JK. Gastrointest Endosc. 2024 Mar 4:S0016-5107(24)00132-9. doi: 10.1016/j.gie.2024.02.021. Online ahead of print.
4. Genetic assessment of pathogenic germline alterations in lysosomal genes among Asian patients with pancreatic ductal adenocarcinoma. Koh Y, Kim H, Joo SY, Song S, Choi YH, Kim HR, Moon B, Byun J, Hong J, Shin DY, Park S, Lee KH, Lee KT, Lee JK, Park D, Lee SH, Jang JY, Lee H, Kim JA, Yoon SS, Park JK. J Transl Med. 2023 Oct 17;21(1):730. doi: 10.1186/s12967-023-04549-x.
5. Association between non-alcoholic fatty liver disease and the risk of biliary tract cancers: A South Korean nationwide cohort study. Park JH, Hong JY, Kwon M, Lee J, Han K, Han IW, Kang W, Park JK. Eur J Cancer. 2021 Jun;150:73-82. doi: 10.1016/j.ejca.2021.03.024. Epub 2021 Apr 20.

# Recent Updates on the Management of Intrahepatic Cholangiocarcinoma

**Joo Kyung Park** *Sungkyunkwan University*

## Introduction

Intrahepatic cholangiocarcinoma (iCCA) is a type of liver cancer that arises from the bile ducts within the liver. The treatment landscape for iCCA has evolved significantly in recent years. Here are the key updates on treatment options: Early detection remains a challenge: Most patients are diagnosed at advanced stages, limiting curative options. New biomarkers for early detection are under investigation.

1. **Surgical Resection: Surgery for early-stage disease:** Surgical resection remains the best chance for cure, with some studies showing a 40% 5-year survival rate.
   A. Curative Intent: Surgery remains the primary curative treatment for iCCA
   B. The goal is complete resection with negative margins (R0 resection).
   C. Advanced Techniques: Enhanced imaging and surgical techniques have improved the resectability of tumors previously considered inoperable.

2. **Liver Transplantation:** In selected cases, liver transplantation is considered, especially for patients with underlying liver disease and early-stage tumors.

3. Locoregional Therapies
   A. **Transarterial Chemoembolization (TACE):** Used for unresectable tumors to deliver chemotherapy directly to the liver while restricting blood supply to the tumor.
   B. **Radiofrequency Ablation (RFA):** Effective for small, localized tumors, often used in combination with other treatments.
   C. **Selective Internal Radiation Therapy (SIRT):** Delivers radioactive particles to the tumor, providing an option for patients with limited systemic therapy options.

4. Systemic Therapies
   A. **Chemotherapy:** Gemcitabine and cisplatin combination remains the standard first-line therapy for advanced iCCA. Newer regimens and combination therapies are under investigation.
   B. **Standard first-line treatment:** The combination of durvalumab with gemcitabine and cisplatin (gemcis/cisplatin) has shown improved overall survival in the TOPAZ-1 trial.
   C. **Newer options under exploration:** Trials are ongoing for drugs targeting specific mutations, like

FGFR inhibitors for tumors with FGFR aberrations. However, a recent study with nab-paclitaxel added to gemcis/cisplatin did not improve overall survival.

D. **Adjuvant Therapy:** Post-surgery chemotherapy (e.g., capecitabine) is recommended to reduce recurrence risk.

E. **Neoadjuvant Therapy:** Preoperative treatment to shrink tumors, making surgery more feasible, is being studied, especially in combination with systemic therapies.

5. **Targeted Therapies:** Molecular profiling of tumors has identified actionable mutations. Targeted therapies for FGFR2 fusions (e.g., pemigatinib) and IDH1 mutations (e.g., ivosidenib) have shown promising results.

6. **Immunotherapy:** Immune checkpoint inhibitors (e.g., pembrolizumab) are being explored in clinical trials, showing potential in selected patients, especially those with high PD-L1 expression.

7. **Innovative Approaches:** Participation in clinical trials is encouraged, as ongoing research explores novel agents, combination therapies, and new indications for existing treatments.

8. **Personalized Medicine:** Efforts to personalize treatment based on genetic and molecular profiling of tumors are gaining traction, aiming for more effective and individualized therapies.

## Conclusion

The management of intrahepatic cholangiocarcinoma is advancing with a multidisciplinary approach. Combining surgical resection, systemic therapies, locoregional treatments, and participation in clinical trials offers the best outcomes for patients. Close collaboration between oncologists, hepatologists, surgeons, and researchers is crucial to navigate this evolving landscape and provide optimal care.

THE LIVER WEEK 2024

DAY 1: June 27 (Thu)

# Translational Research 1

## Microbiomes and Signaling Dynamics in Liver Disorders

**Chairs:**

**Young Seok Kim** (Soonchunhyang Univ.)
**Wonhyo Seo** (Ewha Womans Univ.)

**Soon Kyu Lee**

*The Catholic University of Korea*

## Self Introduction

Prof. Soon Kyu Lee is an assistant professor in the Division of Gastroenterology and Hepatology at the Catholic University of Korea. I am a qualified M.D., Ph.D. with basic and clinical research skills, specializing in hepatology. He is actively conducting both basic and clinical research related to transplantation, autoimmune liver disease, hepatocellular carcinoma, hepatitis virus infection, and alcoholic liver disease.

Prof. Soon Kyu Lee graduated from the Catholic University of Korea, College of Medicine with his medical degree in 2011 and completed his internship and residency at the Department of Internal Medicine at The Catholic University of Korea, receiving his Ph.D. in Internal Medicine in 2022.

Prof. Soon Kyu Lee has been taking a number of roles in the Korean Association of the Study of the Liver, the Korean Society of Gastroenterology and the Korean Liver Transplantation Society.

## Research Interests

Liver transplantation, Hepatocellular carcinoma, Gut microbiome, Autoimmune liver disease, Alcoholic liver disease, viral hepatitis

## Representative Publications

1. Expansion of effector regulatory T cells in steroid-responders of severe alcohol-associated hepatitis, Liver Transplantation (2024) DOI: 10.1097/LVT.0000000000000378
2. An Immunological Perspective on the Mechanism of Drug Induced Liver Injury: Focused on Drugs for Treatment of Hepatocellular Carcinoma and Liver Transplantation, IJMS 2023; 24(5), 5002
3. A decrease in functional microbiomes represented as Faecalibacterium affects immune homeostasis in long-term stable liver transplant patients, Gut microbes (2022); 14:1,2102885
4. Immune-mediated liver injury represented as overlap syndrome after SARS-CoV-2 vaccination, Journal of hepatology, (2022) 7:1207-1230
5. Patient-derived Avatar Mouse Model to Predict the Liver Immune Homeostasis of Long-term Stable Liver Transplant Patients, Frontiers in Immunology, (2022); 13:817006

# Functional Microbiomes in Immune Homeostasis in Liver Transplant Patients

**Soon Kyu Lee** *The Catholic University of Korea*

Liver transplantation (LT) is an eventual treatment for patients with end-stage liver disease or early hepatocellular carcinoma (HCC), improving of hepatic function and treating HCC simultaneously. In the setting of LT, three specific mechanisms that induce tolerance have been outlined as follows: donor passenger leukocytes (PLs), high-dose antigen effect, and the proliferation of Tregs along with the depletion of effector T cells (Tefs). PLs may activate recipient T-cells in lymphoid organs after LT, which induce a defective activation and eventual apoptosis of allo-reactive T-lymphocytes.[1] Moreover, high-antigen dose leads to tolerance by exhausting the finite T cell clone size.[2] Finally, the proliferation of Tregs and the deletion of Tefs induced by tolerogenic APCs and hepatocytes may induce tolerance in LT patients.[3]

With the above unique immunological features in human liver allograft, there have been many studies to withdraw IS (ISW) in LT patients. Approximately, 5%-20% of selected LT patients could achieve operational tolerance after LT. Tolerance is defined as long-term graft acceptance without IS therapy along with no graft rejection at one year since withdrawal of IS.[4] In the view of immune cells and mechanisms underlying tolerance, donor-derived dendritic cells (DCs), natural killer T cells, $CD4^+$ regulatory T (Treg) cells play important roles in successfully minimizing IS or tolerance after LT.[4] Indeed, in our previous study, an increase in the Treg cells implies the possibility of depreciation and tolerance during tapering IS, which may be used as biomarker for tolerance. Moreover, in our study, $FoxP3^+$ Treg cells in liver histology were also increased in tolerance patients compared to those in rejection patients.[5]

As gut microbiota modulates systemic immune functions along the gut-liver axis, identification of functional microbiome affecting immune homeostasis may provide the possibility of biomarker for assessing immune status and tolerance. Although gut dysbiosis partially recovers within 12 to 24 months post-LT, gut microbial composition of long-term post-LT patients was still different from healthy controls according to our study.[6] In our study, *Faecalibacterium* was the most decreased in the long-term post-LT patients along with a decrease in Treg with an increase in T helper 17 (Th17) cells, which were recovered by administration of F. prausnitzii and butyric acid in in vitro analysis. Moreover, in tolerant patients, *Faecalibacterium* was marginally increased, coupled with an increase in Treg cells.[7] These findings provide insight into the potential use of functional microbiomes, especially *Faecalibacterium,* as a

biomarker for assessing immune status and tolerance in long-term post-LT patients.

In addition to the recognized importance of Treg cells in tolerance, recent studies have also suggested a significant role for regulatory B cells (Bregs) in maintaining tolerance. Tolerance patients have been observed to exhibit a higher proportion of transitional B cells, which possess suppressive capacity through the secretion of IL-10. This suppressive action serves to limit the response of $CD4^+$ effector T cells. Moreover, the microbiome and its metabolites, including short-chain fatty acids (SCFA), are believed to play significant roles in creating a tolerogenic environment within the gut by regulating of B cell differentiation.[8] Further studies are needed to thoroughly analyze the interaction between Breg cells and immune homeostasis, particularly in the LT setting.

Meanwhile, LT patients have a risk of rejection after LT. Although liver is tolerogenic allograft, LT can lead to the activation of effector T cells, effector B cells, and natural killer cells, resulting liver allograft damage. Acute rejection after LT occurs about 15%-25% of LT patients on tacrolimus-based IS regimens. Recent studies revealed the importance of Treg and Th 17 cells in rejection. The population of Th17 in peripheral blood is correlated positively with histologic score of liver tissue in LT patients with rejection; reciprocally, a proportion of Tregs were negatively correlated with rejection severity. An early reduction in the number of Treg cells and an increase in the number of Th17 cells after LT were also associated with acute rejection, which could be a potential biomarker for predicting rejection.[9]

There have also been several studies to evaluate microbial changes related to rejection after LT. In the early phase of post-LT, gut dysbiosis could persist and even get worse with a decrease in potentially beneficial genera, including *Faecalibacterium*, *Bifidobacterium*, and *Lactobacillus*. Moreover, in animal model and patients with ACR after LT, there have been an increase in Bacteroides coupled with a decrease in *Peptostreptococcus* and *Faecalibacterium*.[10] An increase in *Proteobacteria* coupled with a decrease in *Firmicutes* were also associated with a decrease in cognitive function of LT patients.[11] As this gut microbial imbalance was improved in tolerant patients according to our study, we could assume that functional microbiomes including *Faecalibacterium* may have potential role as biomarker for rejection and tolerance in LT patients.[7]

In conclusion, the liver is immune tolerogenic organ with the unique immunological feature, which could lead to achieve tolerance in some LT patients along with a substantial risk of rejection. Considering the immunomodulatory effect of gut microbiome in LT patients, it is pivotal to find functional microbiomes and metabolites for improving immunological balance coupled with reducing the risk of rejection in LT patients.

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exploit the high dose effect? Clin Dev Immunol 2013;2013:419692.
3. Dai H, Zheng Y, Thomson AW, Rogers NM. Transplant Tolerance Induction: Insights From the Liver. Front Immunol 2020;11:1044.
4. Thomson AW, Vionnet J, Sanchez-Fueyo A. Understanding, predicting and achieving liver transplant tolerance: from bench to bedside. Nat Rev Gastroenterol Hepatol 2020;17:719-739.
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9. Han JW, Joo DJ, Kim JH, et al. Early reduction of regulatory T cells is associated with acute rejection in liver transplantation under tacrolimus-based immunosuppression with basiliximab induction. Am J Transplant 2020;20:2058-2069.
10. Ren Z, Jiang J, Lu H, et al. Intestinal microbial variation may predict early acute rejection after liver transplantation in rats. Transplantation 2014;98:844-52.
11. Bajaj JS, Fagan A, Sikaroodi M, et al. Liver transplant modulates gut microbial dysbiosis and cognitive function in cirrhosis. Liver Transpl 2017;23:907-914.

**Ki Tae Suk**

*Hallym University*

## Self Introduction

| | |
|---|---|
| Feb. 1993-1999 | Medical Degree, Yonsei University,Wonju College of Medicine, Korea |
| Feb. 2003-2015 | Master of Medicine, Graduate School, Yonsei University, Seoul, Korea |
| Aug. 2010-2012 | Doctor of Medicine, Graduate School, Yonsei University, Seoul, Korea |
| Sep. 2014-2016 | post-Doctor Research Scholar, Medicine, Columbia University, New York, USA. |
| Sep. 2016- | Professor, Hallym University, Chuncheon, Korea |

## Research Interests

- Liver disease
  Cirrhosis and hepatocellular carcinoma
- Microbiota
  Metabolites of microbiome
  Post-bioitcs
  Multi-omics associated mechanism
- Pharmabiotics
  Therapeutics and diagnostic marker

## Representative Publications

1. Suk KT. A metabolomics approach to the validation of predictive metabolites and phenotypic expression in non-alcoholic fatty liver disease. Life Sci. 2023 Mar 30:121626.
2. Suk KT. Characteristics of microbiome-derived metabolomics according to the progression of alcoholic liver disease. Hepatol Int. 2023 Mar 31.
3. Suk KT, Yoon JH, Kim MY et al. Transplantation with autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: Phase 2 trial. Hepatology. 2016 Dec;64(6):2185-2197.
4. Suk KT, Mederacke I, Gwak GY, Cho SW, Adeyemi A, Friedman R, Schwabe RF. Opposite roles of cannabinoid receptors 1 and 2 in hepatocarcinogenesis. Gut. 2016 Oct;65(10):1721-32.
5. Suk KT. Lactobacillus lactis and Pediococcus pentosaceus-driven reprogramming of gut microbiome and metabolome ameliorates the progression of non-alcoholic fatty liver disease. Clin Transl Med. 2021 Dec;11(12):e634.

# Microbiome-Released Metabolites to Modulate Liver Disease

**Ki Tae Suk** *Hallym University*

## ALD

**Background and aim:** The prevalence and severity of alcoholic liver disease (ALD) are increasing. The patients with alcohol-related cirrhosis develops at an annual risk up to 2.5%. This study aimed to identify novel metabolites mechanism for the development of ALD in patients with metabolic dysfunctions. The gut microbiome -derived metabolites are growing in targeted therapies. Identifying metabolic compounds are challenging due to the complex patterns that have long-term effects of ALD. We investigated the specific metabolite signatures in ALD patients.

**Methods:** This study includes 247 patients (cases: n = 185 and heathy control, HC: n= 62) recruited from Korea. In total cases, patients with alcoholic fatty liver, AFL; n = 25, alcoholic hepatitis, AH; n = 80, and alcoholic cirrhosis, AC, n = 80 were identified, and collected stool samples. Metagenomics was performed with 16S rRNA sequencing. Metabolomics was performed with gas chromatography-mass spectrometry (GC-MS) and liquid chromatography coupled to time-of-flight–mass spectrometry (LC–TOF-MS). The untargeted metabolites in AFL, AH, and AC were evaluated by multivariate statistical analysis and metabolic pathotypic expression. Metabolic network classifiers were used to predict the pathways expression of AFL, AH, and AC stages.

**Results:** The relative abundance of Proteobacteria increased in ALD, while Bacteroides decreased ($p$=0.001) from HC. Fusobacteria levels were found to be higher in AH ($p$=0.0001) from HC. From untargeted metabolomics, 103 metabolites were quantitatively screened from each stool samples. Indole-3-propionic acid (IPA) levels are significantly lower in AH and AC ($p$=0.001) from HC. Surprisingly, AC increases indole-3-lactic acid (ILA: $p$=0.04). With comparison of HC, AC had significantly decreased the levels of short-chain fatty acids (SCFAs: acetic acid, butyric acid, propionic acid, iso-butyric acid, and iso-valeric acid) and bile acids (BAs: lithocholic acids). The acetylcholine and cholic acids were significantly increased in AFL, AH, and AC from HC. The levels of stercobilin, hexadecanedioic acid, and 3-methyladipic acid were significantly decreased in ALD from HC condition. The pathways of linoleic acid metabolism, indole compounds, histidine metabolism, fatty acid degradation, and glutamate metabolism were closely associated with ALD metabolism.

## NAFLD

**Background/Aims:** Non-alcoholic fatty liver disease (NAFLD) is becoming more common and severe. Individuals with NAFLD have an altered composition of gut microbial metabolites. We used metabolomics profiling to identify microbial metabolites that could indicate gut-liver metabolic severity. Non-invasive biomarkers are required for NAFLD, especially for patients at high risk of disease progression. The microbiome-derived metabolic phenotypic expression represents a significant role for NAFLD biomarker discovery.

**Methods:** We compared the stool metabolomes, untargeted metabolomics, and clinical data of 80 patients. The non-alcoholic fatty liver, NAFL: n=16; non-alcoholic steatohepatitis, NASH: n=26; cirrhosis, n=19; and healthy control, HC: n=19, were considered. The identified metabolites in NAFLD were evaluated by multivariate statistical analysis and metabolic pathotypic expression. Gas chromatography-mass spectrometry (GC-MS) and liquid chromatography coupled to time-of-flight–mass spectrometry (LC–TOF-MS) were used to analyze metabolites.

**Results:** Untargeted metabolomics identified a total 103 metabolites and quantified. Principle component analysis (PCA) was used to assess the metabolic discrimination of NAFL, NASH, and cirrhosis. Short-chain fatty acids (SCFAs) levels were significantly lower in NAFLD patients, including acetate ($p$=0.03), butyrate ($p$=0.0008), and propionate. The stool cholic acid ($p$=0.001) level was significantly increased in NAFLD. Palmitoylcarnitine and L-carnitine levels were significantly increased in NASH and cirrhosis patients. The phenotypic expression of these metabolites was linked to $\beta$-oxidation. The fold value of sitagliptin has increased in NAFL and cirrhosis compared with NASH. In stool NAFLD, stercobilin and kynurenic acid were down-regulated. Indole-3-propionic acid (IPA: $p$=0.001) was significantly down-regulated in NASH and cirrhosis. IPA was significantly increased in the NAFL. Briefly, microbiota-derived SCFA signaling reverses the reduction of acetic acid ($p$=0.01 in NASH and $p$=0.03 in cirrhosis) and propionic acid in NAFLD. NAFLD-associated microbial metabolome phenotypic expression was effective in therapeutic clinical biomarkers for NAFLD/NASH, and liver cancer prevention.

**Conclusion:** We demonstrated a distinct metabolome profile in NAFLD patients with NAFL, NASH, and cirrhosis. We also discovered that certain metabolites and metabolic pathway expression were linked to NAFLD. However, circulating microbial metabolite composition and pathway phenotype expression were efficient noninvasive markers for detecting end-stage liver disease. These results indicate that amino acids, fatty acids, and several small molecules suggest a novel microbial marker in NAFL, NASH, and cirrhosis. This microbial composition may fail to process their chemical metabolic pathway expressions.


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**Won-Il Jeong**

*KAIST*

## Self Introduction

### *Education*

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| 1992.03-1999.02 | Doctor of Veterinary Medicine (D.V.M), College of Veterinary Medicine, Kyungpook National University, Daegu, Korea |
| 1999.03-2001.02 | M.S., Department of Pathology, College of Veterinary Medicine, Kyungpook National University, Daegu, Korea |
| 2001.03-2004.02 | Ph.D., Department of Pathology, College of Veterinary Medicine, Kyungpook National University, Daegu, Korea |

### *Career:*

| | |
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| 2004.03-2005.02 | Post-Doc of the Brain Korea 21 Project in 2003, Kyungpook National University, Daegu, Korea |
| 2005.02-2008.11 | Visiting Fellow, NIAAA/National Institutes of Health, Bethesda, MD, U.S.A. |
| 2008.12-2012.08 | Assistant professor, KAIST, Daejeon, Korea. |
| 2012.09-2019.08 | Associate professor, KAIST, Daejeon, Korea |
| 2019.09-present: | Professor, KAIST, Daejeon, Korea |

## Research Interests

Alcohol-associated liver disease (ALD) / Steatotic liver disease (SLD) / Metabolic dysfunction-associated steatotic liver disease (MASLD)/ Liver Fibrosis / Hepatocellular Carcinoma/ Liver Immunology / Liver Neurology

## Representative Publications

1. Body Temperature-Responsive, Stiffness-Varying and Non-Reusable Intravenous Needle with On-Site Temperature Sensing for Improved Patient Care. Nature Biomedical Engineering, 2023
2. xCT-mediated glutamate excretion in white adipocytes stimulates interferon-$\gamma$ production by natural killer cells in obesity. Cell Reports, 2023
3. Catecholamine induces Kupffer cell apoptosis via growth differentiation factor 15 in alcohol-associated liver disease. Experimental and Molecular Medicine, 2022
4. Metabotropic glutamate receptor 5 in natural killer cells attenuates liver fibrosis by exerting cytotoxicity to activated stellate cells. Hepatology, 2021
5. Mitochondrial double-stranded RNA in exosome promotes interleukin-17 production through toll-like receptor 3 in alcoholic liver injury. Hepatology, 2020
6. Glutamate signaling in hepatic stellate cells drives alcoholic steatosis. Cell Metabolism, 2019
7. Pro-inflammatory hepatic macrophages generate ROS through NADPH oxidase 2 via endocytosis of monomeric TLR4-MD2 complex. Nature Communications, 2017

# Friend or Foe: Neurological Transmitter and Alcohol-Associated Liver Disease

**Won-Il Jeong** *KAIST*

Traditionally, alcohol-related liver disease (ALD) is induced by multiple factors that occur during various metabolic processes of hepatocyte, diverse absorption of pathogen- or damage-associated molecular patterns (PAMS or DAMPs) from intestine, and delivery of free fatty acids and pro-inflammatory cytokines from adipose tissue. These factors cause fat accumulation in hepatocyte at early stage but continuous drinking promotes more serious diseases such as inflammation, fibrosis and even tumor. However, interestingly, our research team recently discovered the existence of glutamatergic signaling pathways in the liver and reported that ALD can be occurred by them.[1-3] Briefly, we have revealed that chronic alcohol consumption increases glutamate production especially by aldehyde dehydrogenase 4 family member A1 (ALDH4A1) enzyme in hepatocyte, and generated hepatic glutamate is stored within the hepatocytes, and then secreted through xCT or granules.[1] Simultaneously, metabotropic glutamate receptor 5 (mGluR5) is expressed in various non-parenchymal cells (NPCs) and exerts pathophysiological effects through interaction with secreted glutamate. In addition, released glutamate is mainly absorbed by hepatocytes and NPCs. Today, I would like to briefly introduce the roles of hepatic glutamate, as a hepatotransmitter,[4] in inducing and suppressing the development of ALD.

**Steatosis by hepatic glutamate.** In alcohol-mediated hepatic steatosis, oxidative stress increases at perivenous hepatocytes by alcohol metabolism, where the amount of glutathione (GSH) decreases due to a lack of cysteine in the liver. To compensate this, perivenous hepatocytes express xCT for the absorption of cysteine coupled to the excretion of glutamate because of antiporter xCT. Interestingly, neighboring hepatic stellate cells (HSCs) express mGluR5 and produce 2-arachidonoyl glycerol (2-AG), an endocannabinoid, through the interaction between mGluR5 and glutamate. Then, generated 2-AG reversely stimulates CB1 receptor in hepatocytes, leading to the development of steatosis.[1] **Steatohepatitis by hepatic glutamate.** Next, we investigated the role of glutamate in the development of steatohepatitis. Although it has not yet been published, the secreted glutamate from hepatocytes triggers inflammation through mGluR5 in Kupffer cells. Similar with glutamate-mediated hepatic steatosis, chronic alcohol consumption increased the production of hepatic glutamate by ALDH4A1 and then it was stored in granules. Then binge drinking triggered release of glutamate from the granules to stimulate Kupffer cells, consequently leading to steatohepatitis in liver. **Anti-fibrotic effects of hepatic**

**glutamate.** Lastly, although it is not a model of alcohol-mediated liver fibrosis, glutamate derived from hepatocytes promoted mGluR5 activation of natural killer (NK) cells to secrete interferon-gamma (IFN-γ) and other anti-fibrotic mediators in carbon tetrachloride-induced liver fibrosis. Similarly, we also found that adipocyte-derived glutamate stimulated IFN-γ production of NK cells through mGluR5.[5] Thereby, activated NK cells attenuated liver fibrosis by killing activated HSCs.[2]

In conclusion, hepatic glutamate produced by non-canonical pathway has a double-edged sword in the development of liver diseases, including ALD. Therefore, it is believed that our study will contribute to the discovery of therapeutic targets and development of treatments for liver diseases.

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4. Woo C, Jeong WI. Immunopathogenesis of liver fibrosis in steatotic liver disease. Clin Mol Hepatol 2024;30:299-302.
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**Yong-Hyun Han**

*Kangwon National University*

## Self Introduction

Prof. Yong-Hyun Han is a Assistant Professor of the College of Pharmacy at Kangwon National University and is currently member of Scientific Committee of the Korean Association for the Study of the Liver.

Prof. Yong-Hyun Han graduated from Kangwon National University College of Pharmacy with his BS degree in 2011 and completed his PhD degree at the College of Pharmacy at Seoul National University in 2018.

Currently, he is Associate Editor of the Gut and Liver Journal (2024- ).

## Research Interests

1. Identification of roles of liver macrophage heterogeneity in liver disease
2. Novel findings of functional endotoxin neutralizer in portal vein such as immune cell, lipid metabolites and microbiome
3. Deciphering roles of adaptive immunity system to modulate liver pathology (B and T lymphocyte)
4. Finding drug candidates targeting NLRP3 inflammasome

## Representative Publications

1. Kim MY*, Jeong B*, Lee GS, Jeon H, Yang YM, Yang H#, Han YH#. Panaxydol extracted from Panax ginseng inhibits NLRP3 inflammasome activation to ameliorate NASH-induced liver injury. Int Immunopharmacol. (2024) Feb 15;128:111565
2. Kim DH, Lee KJ, Park J, Chi S, Han J, Bang Y, Kim SM, Kang SG#, Cha SH#, Han YH#. Disruption of IL-18 signaling via engineered IL-18BP biologics alleviates experimental cholestatic liver disease. Biomed Pharmacother. (2023) Nov;167:115587
3. Kim MY*, Lee SJ*, Randolph GJ, Han YH. Lubiprostone significantly represses fatty liver diseases via induction of mucin and HDL release in mice. Life Sci. (2022) Dec 15;311:121176.
4. Han YH*, Onufer EJ, Huang LH, Sprung RW, Davidson WS, Czepielewski RS, Wohltmann M, Sorci-Thomas MG, Warner BW, Randolph GJ*. Enterically derived high-density lipoprotein restrains liver injury through the portal vein. Science, (2021) July 23;373:eabe6729.
5. Han YH, Shin KO, Khadka D, Kim JY, Kim HJ, Cho WJ, Cha JY, Lee YM, Lee BJ, Lee MO. A maresin 1/ROR$\alpha$/12-lipoxygenase autoregulatory circuit prevents inflammation and progression of nonalcoholic steatohepatitis. J Clin Invest, (2019) Mar 11;130:1684-1698

# Inflammasome: Key Factor to Progress Liver Inflammation and Fibrosis

**Yong-Hyun Han** *Kangwon National University*

Activation of NOD-like receptor protein 3 (NLRP3) inflammasome exacerbates liver inflammation and fibrosis in metabolic dysfunction-associated steatohepatitis (MASH), suggesting that development of inflammasome inhibitor can become leading candidate to ameliorate NASH. In particular, we found that inflammasome-mediated IL-18 signaling was enhanced under NASH condition. IL-18 binding protein (IL-18BP) is a soluble protein that can inhibit IL-18 actions and therapeutic potential of IL-18BP for NASH-induced fibrosis is largely unrevealed. Hepatic and plasma levels of IL-18BP and IL-18 were elevated in mice and human with MASH. We found that augmented IL-18 trigger increased IFN $\gamma$ production in T cells and thereby increased hepatic IL-18BP expression. Loss of IL-18BP exhibited exacerbated symptoms of liver injuries including hepatic inflammation and fibrosis. These results provide new insight of therapeutic potential of inflammasome modulator and could offer potential therapeutic candidate for reliving MASH.


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# Young Investigator Meeting

## Inspiring the Next Wave: A Roadmap for Young Investigators in Academia

**Chairs:**

**Soon Koo Baik** (Yonsei Univ. Wonju)
**Young-Suk Lim** (Univ. of Ulsan)


## Soon Koo Baik

*Yonsei University Wonju*


## Self Introduction

I am currently Professor of division of Gastroenterology and Hepatoloy, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine.

I am a former Director of the Scientific Committee, The Korean Association for the Study of the Liver(KASL), and worked as a Director of Scientific Committee of APASL STC, 2016 at Busan. Also, I was an Editor-in Chief of Clinical and Molecular Hepatology, an official journal of KASL from 2012 to 2013, and serve on editorial board in Journal of Hepatology.

My interest is portal hypertension and cirrhosis, regenerative medicine and stem cell therapy. I have published more than 200 papers in international peer-reviewed journal, and was a contributor of Zakim and Boyer 5th edition.

## Research Interests

- Cirrhosis and portal hypertension
- Hepatic fibrosis
- Stem cell therapy for chronic liver disease
- Functional Ultrasonography

## Representative Publications


1. Alfaifi M, Eom YW, Newsome PN, Baik SK. Mesenchymal stromal cell therapy for liver diseases. J Hepatol 2018;68(6):1272–1285.
2. Jang YO, Kim SH, Cho MY, Kim KS, Park KS, Cha SK, Kim MY, Chang SJ, Baik SK. Synergistic effects of simvastatin and bone marrow-derived mesenchymal stem cells on hepatic fibrosis. Biochem Biophys Res Commun. 2018;497(1):264-271.
3. Kang SH, Kim MY, Baik SK. Novelties in the pathophysiology and management of portal hypertension: new treatments on the horizon. Hepatol Int. 2018;12(Suppl 1):112-121.
4. Suk KT, Yoon JH, Kim MY, Kim CW, Kim JK, Park H, Hwang SG, Kim DJ, Lee BS, Lee SH, Kim HS, Jang JY, Lee CH, Kim BS, Jang YO, Cho MY, Jung ES, Kim YM, Bae SH, Baik SK. Transplantation with Autologous Bone Marrow-Derived Mesenchymal Stem Cells for Alcoholic Cirrhosis: Phase 2 Trial. Hepatology. 2016;64(6):2185-2197.
5. Jang YO, Cho MY, Yun CO, Baik SK, Park KS, Cha SK, Chang SJ, Kim MY, Lim YL, Kwon SO. Effect of Function-Enhanced Mesenchymal Stem Cells Infected With Decorin-Expressing Adenovirus on Hepatic Fibrosis. Stem Cells Transl Med. 2016;5(9):1247-56.

# Why Should We Pursue an Academic Career?

**Soon Koo Baik** *Yonsei University Wonju*

**Won-Mook Choi**

*University of Ulsan*

## Self Introduction

Prof. Won-Mook Choi is an Assistant Professor of the Department of Gastroenterology, Asan Medical Center

Prof. Choi graduated from Seoul National University College of Medicine with his medical degree in 2010 and graduated from KAIST with his PhD degree in 2019. He completed his internship and residency at the Department of Internal Medicine at Seoul National University Hospital in 2015 and completed his fellowship at the Department of Gastroenterology at Asan Medical Center in 2021.

Since 2022, Prof. Choi has been taking a number of roles, including Scientific Committee Member and Medical Policy Committee Assistant Director of the Korean Association of the Study of the Liver (2023- ), and External Affairs Committee Assistant Direction Chairman of the Korean Liver Cancer Association (2023- ).

## Research Interests

- Chronic hepatitis B
- Hepatocellular Carcinoma
- Liver fibrosis

## Representative Publications

1. Jeon D, Cha HR, Chung SW, Choi J, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, Lee SW, Choi WM (corresponding). Association between statin use and the prognosis of hepatocellular carcinoma after resection: a nationwide cohort study. EClinicalMedicine (IF 15.1). 2023 Nov 1:65:102300.
2. Choi WM, Kim GA, Choi J, Choi GH, Lee YB, Sinn DH, Lim YS. Non-linear association of baseline viral load with on-treatment hepatocellular carcinoma risk in chronic hepatitis B. Gut (IF 24.5). 2024 Mar 7;73(4):649-658.
3. Choi WM, Yip TC, Wong GL, Kim WR, Yee LJ, Brooks-Rooney C, Curteis T, Cant H, Chen CH, Chen CY, Huang YH, Jin YJ, Jun DW, Kim JW, Park NH, Peng CY, Shin HP, Shin JW, Yang YH, Lim YS. Hepatocellular carcinoma risk in patients with chronic hepatitis B receiving tenofovir- vs. entecavir-based regimens: Individual patient data meta-analysis. J Hepatol (IF 25.7). 2023 Mar;78(3):534-542.
4. Choi WM, Kim GA, Choi J, Han S, Lim YS. Increasing on-treatment hepatocellular carcinoma risk with decreasing baseline viral load in HBeAg-positive chronic hepatitis B. J Clin Invest (IF 15.9). 2022 May 16;132(10):e154833.
5. Choi WM, Kim HH, Kim MH, Cinar R, Yi HS, Eun HS, Kim SH, Choi YJ, Lee YS, Kim SY, Seo W, Lee JH, Shim YR, Kim YE, Yang K, Ryu T, Hwang JH, Lee CH, Choi HS, Gao B, Kim W, Kim SK, Kunos G, Jeong WI. Glutamate Signaling in Hepatic Stellate Cells Drives Alcoholic Steatosis. Cell Metab (IF 29.0). 2019 Nov 5;30(5):877-889.e7.

# From Research to Manuscript: Case 1

**Won-Mook Choi** *University of Ulsan*

Why should we pursue an academic career? In this talk, I want to explore the reasons as I reflect on my academic journey so far. I have a unique background as I've treaded the path of a physician-scientist. I began my clinical research during my second year of residency training, and fueled by curiosity in basic research, I entered a graduate program in medical science and engineering at KAIST, dedicating four years to basic research. Currently, I am engaged in translational and clinical research at Asan Medical Center. Through my diverse experiences from basic to clinical research, I believe the foremost reason why we pursue an academic career is the pursuit of intellectual excitement and joy through research. Moreover, the ample rewards that follow contribute significantly to the motivation for pursuing an academic career. Ultimately, I think the pursuit of academic career, sparked by such motivations, culminates in the advancement of medicine and improvement of human health. I believe the three virtues necessary to become a good researcher are curiosity, patience, and the encounter with a good mentor who can help one realize one's potential. In this regard, I express my respect to senior professors who have nurtured a conducive environment for young investigators like us to thrive, and I anticipate that our medical society, the Korean Association for the Study of the Liver, will continue to serve as a strong support for young aspiring investigators in their pursuit of academic careers.


## Han Ah Lee

*Chung-Ang University*


## Self Introduction

| | |
|---|---|
| 2018 | Ph.D. in Korea University |
| 2016-2017 | Clinical Fellow in Hepatology (Korea University Anam Hospital) |
| 2018-2020 | Clinical Assistant Professor in Hepatology (Korea University Anam Hospital) |
| 2021 | Clinical Assistant Professor in Hepatology (Inje University Sanggye Baik Hospital) |
| 2022-2023 | Clinical Assistant Professor in Hepatology (Ewha Womans University Mokdong Hospital) |
| 2024 | Clinical Assistant Professor in Hepatology (Chung-Ang University Seoul Hospital) |

## Research Interests

Nonalcoholic fatty liver disease, Hepatitis B virus, Hepatocellular carcinoma

## Representative Publications


1. Metabolic Dysfunction-Associated Steatotic Liver Disease and Risk of Cardiovascular Disease: A Nationwide Cohort Study (Gut. 2023)
2. Identification of patients with favorable prognosis after resection in intermediate-stage hepatocellular carcinoma. (Int J Surg. 2023)
3. Comparable outcomes between immune-tolerant and active phases in noncirrhotic chronic hepatitis B: a meta-analysis (Hepatol Commun. 2023)
4. Impact of HBeAg on Hepatocellular Carcinoma Risk During Oral Antiviral Treatment in Patients With Chronic Hepatitis B (Clin Gastroenterol Hepatol. 2022)
5. Efficacy and feasibility of surgery and external radiotherapy for hepatocellular carcinoma with portal invasion: A meta-analysis (Int J Surg. 2022)

# From Research to Manuscript: Case 2

**Han Ah Lee** *Chung-Ang University*

In the evolving landscape of academia, the journey from conceptualizing research to publishing a manuscript is fraught with challenges and opportunities. Academic research is a multifaceted endeavor that requires meticulous planning, rigorous execution, and strategic dissemination. For young investigators, navigating this complex process can be daunting. Although I am still a premature researcher with limited experience, I would like to share my experiences of conducting randomized controlled trials, big data research, multicenter retrospective studies, and meta-analyses. By focusing on detailed case studies, the essential steps involved in transforming a research idea into a published manuscript, key strategies, and common pitfalls will be presented.

## 1. Research Conceptualization

The journey begins with the conceptualization of research. Identifying a compelling research question, conducting a thorough literature review, and establishing a clear hypothesis are important. The case study will demonstrate how to frame a research question that addresses a gap in the existing literature and aligns with broader academic and societal interests. Key considerations include the relevance, originality, and feasibility of the research idea.

## 2. Designing the Study

A well-designed study is the cornerstone of research process. Exploring various research methodologies, including experimental, observational, and qualitative approaches, and discuss their applicability to different research questions is important. The case study will illustrate the process of selecting an appropriate research design, defining the study population, and developing a detailed protocol.

## 3. Data Collection and Analysis

Data collection is a critical phase that demands precision and consistency. I will cover my experiences for data collection, emphasizing the importance of maintaining data integrity and minimizing bias. The case study will highlight practical challenges encountered during data collection and offer solutions to

address them. Following data collection, we will delve into data analysis techniques, discussing statistical methods, data interpretation, and the use of software tools. Most importantly, continuous discussions with a statistician or an expert in the field are necessary.

## 4. Manuscript Preparation

The transition from research findings to manuscript preparation involves several key steps. I will provide a detailed overview of the manuscript structure, including the introduction, methods, results, discussion, and conclusion sections. Additionally, adhering to journal guidelines and formatting requirements are important.

## 5. Peer Review and Revision

The peer review process is an integral part of academic publishing. It is important to thoroughly understand the points raised by the reviewers and provide responses and corresponding manuscript revisions that address their concerns as accurately as possible. I will share my experience of revising a manuscript and responding to feedback regarding a long and complex revision.

## 6. Conclusion

The journey from research to manuscript is a challenging yet rewarding process that requires dedication, perseverance, and strategic planning. In research, the key is to find important and interesting topics, to repeatedly refine the design and endpoints, to meticulously verify the accuracy of the study, to analyze the data in various ways to uncover implications, and to express the findings in well-organized writing, revising it multiple times. Most importantly, I believe that discussing with colleagues, trusting them, and collaborating effectively is crucial.

**Keywords:** Research, Manuscript Preparation, Data Analysis, Peer Review, Academic Publishing, Young Investigators

THE LIVER WEEK 2024

DAY 1: June 27 (Thu)

# Current Issues in Nomenclature for Steatotic Liver Diseases

## Korean Terminology for Steatotic Liver Diseases

**Chair:**

**Yoon Jun Kim** (Seoul National Univ.)

# Current Issues in Nomenclature for Steatotic Liver Diseases: Korean Terminology

**Won Sohn, Su Jong Yu, Byoung Kuk Jang** *on behalf of the Korean Association for the Study of the Liver (KASL)*

Nonalcoholic steatohepatitis (NASH), coined by Ludwig et al., was described as a progressive form of fatty liver disease in patients who denied any alcohol abuse.[1] Thereafter, the spectrum of nonalcoholic fatty liver disease (NAFLD) was described and the term NAFLD was introduced in 1986.[2] NAFLD was defined as hepatic steatosis in the absence of a secondary cause such as significant alcohol intake, hepatotoxic drugs, viral hepatitis, etc. NAFLD is closely associated with cardiometabolic factors (obesity, insulin resistance, hypertension, dyslipidemia, and type 2 diabetes mellitus).

Metabolic dysfunction is associated with disease severity and prognosis in patients with NAFLD. The risk of steatohepatitis and liver fibrosis in NAFLD is increased as the number of cardiometabolic factors increases.[3] However, the term 'nonalcoholic' is indistinct to reflect the characteristics of the disease. There is a lack of patient awareness of metabolic dysfunction. The diagnosis of NAFLD is based on the exclusion of any other liver disease. It is needed to diagnose the disease using positive criteria as hepatic steatosis is present coexisting with cardiometabolic factors. Several years ago, Eslam et al. proposed the term "metabolic dysfunction-associated fatty liver disease" (MAFLD), which was diagnosed with hepatic steatosis and cardiometabolic factors regardless of any other liver disease such as alcoholic liver disease, viral hepatitis, and autoimmune liver disease.[4] Although MAFLD better reflects the importance of cardiometabolic factors, someone pointed out problems with mixed etiologies and the lack of the term "steatohepatitis" which is a criterion for clinical trial enrollment. Moreover, the term "fatty" has been considered to be stigmatizing by many. Therefore, the new nomenclature for Beyond their stigmatizing nature, experts also pointed out they did not accurately describe the etiology of the disease. There is a need for a new nomenclature of the disease that is affirmative and non-stigmatizing.

In late 2021, a coalition of experts from the pan-national liver societies convened to address this issue, and a multi-society Delphi consensus statement on new fatty liver disease nomenclature was released in 2023. During the Delphi process from the Nomenclature Development Initiative, the terms "nonalcoholic" and "fatty" were felt to be stigmatizing by 61% and 66% of respondents, respectively.[5] Through the modified Delphi method, a consensus was reached to utilize the term 'steatotic liver disease (SLD)' and 'metabolic dysfunction-associated steatotic liver disease (MASLD)' as a specific subtype within the broader category. The term steatohepatitis was retained in terms of an important pathophysiological

concept. The proposed new terminology MASLD to replace NAFLD, and metabolic dysfunction-associated steatohepatitis (MASH) to replace nonalcoholic steatohepatitis. MASLD defines hepatic steatosis with at least one of five cardiometabolic risk factors.

Recognizing the necessity for a unified and precise nomenclature, the Korean Association for the Study of the Liver (KASL) initiated an effort to establish new terminology for SLD and to translate this terminology into Korean. In February 2024, KASL launched a specialized task force to address the nomenclature issue. This task force, consisting of eight well-experienced and qualified Korean hepatology experts, aimed to develop a Korean term that accurately represents the nature of SLD and enhances patient comprehension. The task force commenced its work by surveying KASL members to gather their opinions on the existing terminology and to solicit suggestions for the new Korean nomenclature. The KASL will present its position statement on the new nomenclature for SLD, including the Korean terminology, at The Liver Week 2024 on June 27, 2024.

## References

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2. Schaffner F, Thaler H. Nonalcoholic fatty liver disease. Prog Liver Dis 1986;8:283-298.
3. Hossain N, Afendy A, Stepanova M, Nader F, Srishord M, Rafiq N, et al. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1224-1229, 1229 e1221-1222.
4. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202-209.
5. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79:1542-1556.


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THE LIVER WEEK 2024

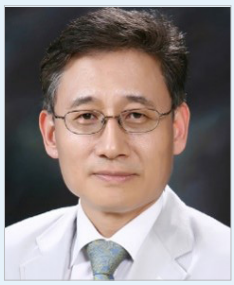
DAY 1: June 27 (Thu)

# Collaboration Workshop

## Uniting Two Worlds: Success Stories in Basic and Clinical Research Collaboration

**Chairs:**

**Neung Hwa Park** (Univ. of Ulsan)
**Yong-Han Paik** (Sungkyunkwan Univ.)



**Sang Geon Kim**

*Dongguk University*

## Self Introduction

Sang Geon Kim is a Professor at the College of Pharmacy and Integrated Research Institute for Drug Development, Dongguk University. He received his B.S. and M.S. from the College of Pharmacy, Seoul National University (SNU) in 1982 and 1985, respectively, and earned his Ph.D. from the Department of Pharmacology, Northwestern University Medical School in 1989. He served as an Assistant Professor(Research)/Research Associate at the Institute of Chemical Toxicology, Wayne State University (1990–1992), an Associate/Assistant Professor at the College of Pharmacy, Duksung Women's University (1992–1999), an Associate/Assistant Professor at the College of Pharmacy, SNU (1999–2006), and was promoted to Professor in 2006. He was also the President of the Korean Pharmacological Society, and the president of Korean Society of Toxicology.

## Research Interests

GPCR, G12 signaling axis
Drug-induced liver injury
New drug development: Hepatoprotective agents
Diabetes and liver diseases

## Representative Publications

1. Tak JH, Joo MS, Kim YS, Park HW, Lee CH, Park GC, Shin, Hwang S, Kim SG* (2024) Dual regulation of NEMO by Nrf2 and miR-125a inhibits ferroptosis and protects liver from endoplasmic reticulum stress-induced injury. Theranostics 14(5): 1841-1859. doi: 10.7150/thno.89703
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4. Ablation of USP21 in skeletal muscle promotes oxidative fiber phenotype, inhibiting obesity and type 2 diabetes, A Kim, JH Koo, X Jin, WD Kim, SY Park, SH Park, EP Rhee, CS Choi, and Kim SG*. Journal of Cachexia, Sarcopenia and Muscle, 2021, DOI: 10.1002/jcsm.12777
5. Kim YS, Nam HJ, Han CY, Joo MS, Jang K, Jun DW, Kim SG*. Liver X Receptor Alpha Activation Inhibits Autophagy and Lipophagy in Hepatocytes by Dysregulating Autophagy-Related 4B Cysteine Peptidase and Rab-8B, Reducing Mitochondrial Fuel Oxidation. Hepatology.2021 Apr;73(4):1307-1326. doi: 10.1002/hep.31423. Epub 2021 Mar 16.
6. Kim TH, Koo JH, Heo MJ, Han CH, Kim YI, Park SH, Cho IJ, Lee CH, Choi CS, Lee JW, Kim W, Cho JY, and Kim SG*. Inter-alpha-trypsin inhibitor heavy chain 1 overproduction by loss of Ga13 in liver exacerbates systemic insulin resistance. Science Translational Medicine, Oct 9;11(513). pii: eaan4735. doi: 10.1126/scitranslmed.aan4735. (2019)

# Intervening to Improve Collaboration in Translational Research: A Basic Scientist's Perspective

**Sang Geon Kim** *Dongguk University*

The liver is the major organ that regulates lipid metabolism and homeostasis and controls biochemical, signaling, and cellular pathways. Especially, lipids are hydrophobic biomolecules that involve a wide array of metabolic pathways. Therefore, liver disease like MASLD develops when lipid homeostasis is not properly regulated and persists. As a basic scientist pursuing translational research, collaboration with clinicians by sharing communication and outcomes seemed to be at the core of this effort and success, where engaging in dialogue with clinicians has lit new pathways for translational study. In this talk, I will introduce some of the stories that we experienced in the aspects of exchanging insights and perspectives, which of no doubt bridging the gap between bench and bedside.

For the liver studies in our laboraotry particularly for 'Liver secretome study',' LXR$\alpha$ biology' and 'Alcohol studies', we had the oppotunities to work with Prof. Won Kim, Internal Medicine at Boramae Hospital. In the current institute, liver to placental insulin resistance are in research progress in collaboration with Prof. Heesun Kim, Gynecology, Dongguk University Hospital.

Human liver specimens had been used to confirm the key roles of the identified targets such as nuclear receptors and the related miRNAs in association with mitochondrial dysfunction. We have unveiled a new signaling axis, regulators, and the underlying mechanisms as to lipid metabolism and provided proof-of-concept that the manipulation of identified targets could be exploited for preventing disease progression. This mutual comprehension has laid the foundation for collaborative projects, where the fusion of basic science principles with clinical data has unlocked new inquiry.

Although the molecular pathways involved in MASLD development have been intensively studied, many issues regarding the roles of nuclear receptors including LXR$\alpha$, FXR, AhR, LRH-1, and PXR remain to be resolved. We investigated the multifactorial roles of nuclear receptors in *de novo* synthesis and catabolism of lipids in the liver, trying to identify the new regulatory molecules culminating in the disease progression. Genetic knockout mice fed on a high-fat diet and in vitro hepatocyte models were used for the molecular studies.

Hepatocytes have numerous endoplasmic reticulum (ER) numbers due to their protein synthesis capability. Of note, enhanced fat metabolism triggers the excess storage of misfolded or unfolded

proteins, resulting in ER stress. Toxicant-induced liver injury also involves ER stress, necessitating the identification of targets and therapeutic agents. In this translational research, we have accomplished a complementary co-work with Prof. Shin Hwang, Surgery Department at Seoul Asan Hospital, and found out the roles of $G\alpha_{12}$ and NEMO in toxicant-induced ferroptosis, which may help provide ways to understand toxicant-induced hepatic injury. In this study, $G\alpha_{12}$ signaling axis has been implicated in cell viability; $G\alpha_{12}$ overexpression in hepatocytes increased toxicity, promoting lipid peroxidation, inflammation, and ferroptosis. IRE1$\alpha$-dependent Xbp1 transactivated *Gna12*. Thus, $G\alpha_{12}$ overexpression by ER stress contributes to hepatocyte ferroptosis through ROCK1 and ALOX12 dysregulation. The importance of the targets identified in this approach was validated using human liver specimens provided by Prof. Hwang at Seoul Asan Hospital. Together, we were able to finish our work, reporting that $G\alpha$ 12 overexpression by toxicant-induced ER stress causes ferroptosis in the liver, and which may be overcome by Nrf2-dependent NEMO induction.

In nurturing collaboration, mutual willingness has been principal. Encouraging mutual respect and providing constructive feedback has fostered a culture of trust and cooperation. Recently, we put more efforts to explore the basic information regarding the link between 'Liver and eye retina', and 'New vessel formation' in the diabetic conditions. For this investigation, we are doing work with Prof. Jee Myeong Yang, previously at Dongguk University Hospital and now at Seoul Asan Hospital. I will share some of our research results with the audience.

Together, we have shared resources and information, leveraging our collective expertise to propel translational research forward. Through these efforts to promote collaboration, strengthening the relationship between basic scientists and clinicians, we were able to enhance the quality of translational research, which would contribute to advancements in both medicine and science.


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**Jaeyoun Cheong**

*Ajou University*

## Self Introduction

Dr. Jaeyoun Cheong is currently a Professor at the Department of Gastroenterology, Ajou University School of Medicine in South Korea. He graduated from Yonsei University Medical College in Seoul, South Korea and did residency training at Yonsei University Severance Hospital from 1996 to 1999. This was followed by a clinical fellowship in Hepatology at Yonsei University Severance Hospital and Ajou University Hospital. He was a Visiting Scholar at University of North Carolina at Chapel Hill, North Carolina between 2014 and 2015.

## Research Interests

His research topics have been focused on biomarker discovery for hepatocellular carcinoma and other liver diseases, medical big data and AI solution and research interest include 1) exosomal, cell free DNA biomarker for prediction of treatment response and prognosis in patients with hepatocellular carcinoma, 2) gut microbiome in liver disease, 3) genomic study on factors predicting liver disease outcome, 4) data science using medical big data, AI in cancer and liver disease.

## Representative Publications

1. Eun JW, Yoon JH, Ahn HR, Kim S, Kim YB, Lim SU, Park W, Kang TW, Baek GO, Yoon MG, Son JA, Weon JH, Kim SS, Cho HJ, Cheong JY. Cancer-associated fibroblast-derived secreted phosphoprotein 1 contributes to resistance of Hepatocellular carcinoma to sorafenib and lenvatinib. Cancer Commun (Lond). 2023 Apr;43(4):455-479
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# Intervening to Improve Collaboration in Translational Research: A Clinician's Perspective

**Jaeyoun Cheong** *Ajou University*

Translational research aims to bridge the gap between basic science discoveries and clinical applications. Effective collaboration between clinicians and basic scientists is critical for advancing medical science and improving patient care. From a clinician's perspective, certain strategies can significantly enhance the performance and outcomes of these collaborative efforts.

## 1. Effective Communication

Clear and continuous communication is fundamental. Clinicians and scientists often have different terminologies and perspectives. Establishing regular meetings and utilizing common language can help in aligning goals and expectations. Using visual aids, summaries, and simplified explanations can bridge knowledge gaps and ensure mutual understanding.

## 2. Defined Roles and Responsibilities

Clearly defining the roles and responsibilities of each team member is crucial. Clinicians should articulate clinical needs and patient perspectives, while scientists can focus on the technical and mechanistic aspects of the research. This demarcation ensures that both parties contribute effectively without overlap or misunderstanding.

## 3. Integrated Project Planning

Jointly developing a detailed project plan with timelines, milestones, and deliverables can streamline the research process. Clinicians should be involved in every stage of planning to provide insights on feasibility and relevance to patient care. This collaborative approach ensures that the research stays on track and meets clinical needs.

## 4. Focus on Clinically Relevant Questions

The collaboration should prioritize questions that have direct clinical implications. Clinicians can identify pressing issues in patient care that need scientific exploration. This focus ensures that the research has

practical applications, thereby increasing its impact and relevance.

## 5. Training and Education

Mutual training sessions can enhance understanding and respect for each other's expertise. Clinicians can learn basic scientific principles and methodologies, while scientists can gain insights into clinical practice and patient care. This cross-training fosters a collaborative spirit and enhances the overall quality of research.

## 6. Resource Sharing

Efficient resource sharing, including data, technology, and facilities, can enhance research outcomes. Clinicians and scientists should work together to leverage each other's resources. For example, clinicians can provide patient data and clinical insights, while scientists can offer laboratory facilities and technical expertise.

## 7. Building Long-term Relationships

Developing long-term partnerships rather than one-off collaborations can lead to more substantial and sustained research outcomes. Trust and mutual respect are built over time, leading to more effective and cohesive teamwork. Regular follow-up meetings and continuous engagement can maintain and strengthen these relationships.

## 8. Dissemination of Findings

Effective dissemination of research findings is crucial. Clinicians play a key role in translating scientific discoveries into clinical practice. Collaborative publications, presentations at conferences, and workshops can help in sharing results with a broader audience, including healthcare providers, policymakers, and the public.

Effective collaboration between clinicians and basic scientists is vital for the success of translational research. By employing strategies such as clear communication, defined roles, integrated planning, focus on clinical relevance, mutual training, resource sharing, long-term relationship building and effective dissemination, these collaborations can be significantly enhanced. From a clinician's perspective, these strategies ensure that research efforts are aligned with patient care needs, ultimately leading to improved health outcomes.


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## Wonhyo Seo

*Ewha Womans University*


## Self Introduction

### *Education*

| | |
|---|---|
| 2013-2016 | PhD (Biomedical Engineering), KAIST |
| 2010-2012 | MSc (veterinary medicine), University of Pretoria |
| 1999-2008 | BSc (veterinary medicine), Kyungpook National University |

### *Professional Experience*

| | |
|---|---|
| 2021.03-Present | Assistant professor (College of Pharmacy, Ewha Womans University) |
| 2016.06- 2021.02 | Postdoc fellow (Lab of Liver Disease, NIH) |
| 2016.03-2016.06 | Postdoc fellow (GSMSE, KAIST) |
| 2011 | Junior researcher (stagiaire) (Viral Neuro-immunology, Institut Pasteur) |

## Representative Publications


1. Wonhyo Seo, Seol Hee Park, Lin Yuhong, Dechun Feng, Bin Gao. A development of new mouse model: Alcohol-associated hepatocellular carcinoma. (2024) In preparation
2. M. Jeong, S. Shin, G. Lee, Y. Lee, S. Im, W. Seo, H. Lee. Therapeutic gene silencing of GTSE1 with engineered lipid nanoparticles enables the treatment of liver fibrosis. Bioactive Materials (2024) Submitted
3. Ji-Soo Kang, Mushira Khanam, Seo Bhin Park, Sumin Shin, Wonhyo Seo. Impact of binge drinking in alcoholic liver diseaes. Archives of Pharmacal Research (2024) Submitted
4. Seojeong Park, Seohui Hwang, Jingyang Sun, Naeun Sheen, Sumin Shin, Tae Hyun Kim, Wonhyo Seo, Jae-Sang Ryu, and Youngjoo Kwon. A novel A2a adenosine receptor inhibitor effectively mitigates hepatic fibrosis in a metabolic dysfunction-associated steatohepatitis mouse model. International Journal of Biological Sciences (2024) doi: 10.7150/ijbs.92371
5. Ji-Su Kim, Dong-ha Kim, Myung-Chul Gil, Hyo-Jung Kwon, Wonhyo Seo, Do-Kyun Kim, Young-Eun Cho. Pomegranate-Derived Exosomes-Like Nanovesicles Alleviate Binge Alcohol-Induced Leaky Gut and Liver Injury. Journal of Medicinal Food (2023). doi: 10.1089/jmf.2023.K.0060.
6. Seol Hee Park, Eun Kyeong Lee, Joowon Yim, Min Hoo Lee, EoJin Lee, Young-Sun Lee, Wonhyo Seo. Exosomes: nomenclature, isolation, and biological roles in liver diseases Biomolecules & Therapeutics (2023) May 1; 31(3): 253–263.
7. Seol Hee Park, Wonhyo Seo, Ming-Jiang Xu, Bryan Mackowiak, Yuhong Lin, Yong He, Yaojie Fu, Seonghwan Hwang, Seung-Jin Kim, Yukun Guan, Dechun Feng, Liqing Yu, Richard Lehner, Suthat Liangpunsakul, Bin Gao. Ethanol and its nonoxidative metabolites promote acute liver injury by inducing ER stress, adipocyte death and lipolysis. Cellular and Molecular Gastroenterology and Hepatology (2022) Oct 13:S2352-345X(22)00213-2
8. Seol Hee Park, Young-Sun Lee, Jaemin Sim, Seonkyung Seo, Wonhyo Seo. Alcoholic liver disease: a new insight into the pathogenesis of liver disease. Archives of Pharmacal Research. 2022 Jul;45(7):447-459.
9. Seo W, Gao Y, He Y, Sun J, Xu H, Feng D, Hee Park S, Cho YE, Guillot A, Ren T, Wu R, Wang J, Kim SJ, Hwang S, Liangpunsakul S, Yang Y, Niu J, Gao B. ALDH2 deficiency promotes alcohol-associated liver cancer by activating oncogenic pathways via oxidized DNA enriched extracellular vesicles. Journal of Hepatology. 2019 Nov;71(5):1000-1011.

# Positive Collaboration Experiences: Case 1 (Basic)

**Wonhyo Seo** *Ewha Womans University*

Translational research, also known as translational medicine, seeks to convert findings from basic scientific research into practical applications that enhance human health. This field aims to bridge the gap between laboratory discoveries and their implementation in clinical settings, ensuring that new knowledge translates into tangible health improvements. The multidisciplinary collaboration integral to translational research fosters innovative approaches and provides robust evidence for establishing therapeutic strategies. Joint efforts contribute to the development of novel therapies and diagnostic tools, accelerating the translation of basic research findings into clinical applications. The collaboration between basic scientists and clinicians offers several advantages, including a comprehensive understanding of diseases, advancements in education and training, increased funding opportunities, and high chance to submit high-impact factor journals.

In conclusion, the multidisciplinary collaboration between basic scientists and clinician (hepatologists) is highly beneficial, driving significant progress in the understanding and treatment of liver diseases. Joint works of basic scientists and clinician highlight the importance of fostering interdisciplinary collaborations to achieve breakthroughs in medical research and patient care. This session aims to present examples of successful collaborations between clinicians and basic researchers.


## Hyun Woong Lee

*Yonsei University*


## Self Introduction

| | |
|---|---|
| 1997.02 | M.D.- Graduate Yonsei University College of Medicine, Seoul, Korea |
| 1999.09 | Master of Medical Science-Yonsei University Graduate School, Korea |
| 2001.08 | Graduate Yonsei University Graduate School, Seoul, Korea |
| 2008.02 | Doctor of Medical Science-Yonsei University Graduate School, |
| 2016.03-2018.02 | Professor of Chung Ang University College of Medicine |
| 2018.03-2022.02 | Associate professor of Yonsei University College of Medicine, |
| 2022.03-Present | Professor of Yonsei University College of Medicine |

## Research Interests

Chronic hepatitis B, C, and acute hepatitis A, ranging from immunology, virology to bioinformatics. Recently, I run a research about "HBcrAg level and HBV genetic diversity as predictors of disease progression in patients with HBV related HCC".

## Representative Publications


1. Hwang SY, Yoo SH, Chang HY, Kim S, Lee JI, Lee KS, Cho YY, Joon KH, Lee HW. Baseline and on-treatment HBcrAg levels as predictors of HBeAg seroconversion in chronic hepatitis B patients treated with antivirals. J Viral Hepat. 2023 Jan;30(1):39-45.
2. Lee HA, Lee HW, Park Y, Kim HS, Seo YS. Hepatitis B Core-Related Antigen Is Useful for Predicting Phase and Prognosis of Hepatitis B e Antigen-Positive Patients. J. Clin. Med. 2022, 11(6), 1729
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4. Sohn W, Lee HW, Lee S, Lim JH, Lee MW, Park CH, Yoon SK. Obesity and the risk of primary liver cancer: A systematic review and meta-analysis. Clin Mol Hepatol. 2021 Jan;27(1):157-174.
5. Kim J, Chang DY, Lee HW, Lee H, Kim JH, Sung PS, Kim KH, Hong SH, Kang W, Lee J, Shin SY, Yu HT, You S, Choi YS, Oh I, Lee DH, Lee DH, Jung MK, Suh KS, Hwang S, Kim W, Park SH, Kim HJ, Shin EC. Innate-like Cytotoxic Function of Bystander-Activated CD8+ T Cells Is Associated with Liver Injury in Acute Hepatitis A. Immunity. 2018 Jan 16;48(1):161-173.

# Positive Collaboration Experiences: Case 2 (Clinical)

**Hyun Woong Lee** *Yonsei University*

For a clinician to collaborate effectively with basic medical science professors on a joint research project, the following elements are essential:

1) Clear Research Goals and Plan: Establish clear objectives, hypotheses, and methodologies for the research. Share and agree upon these with the basic medical science professors.

2) Diverse Research Team Composition: Include not only clinicians and basic medical science professors but also data analysts, statisticians, research coordinators, and other relevant experts to form a comprehensive team.

3) Effective Communication: Maintain smooth communication among team members through regular meetings and updates. Utilize tools such as emails, video conferences, and collaborative software.

4) Research Funding: Secure funding for the research. This can be achieved by applying for research grants or seeking support from hospitals or universities.

5) Research Infrastructure: Prepare necessary infrastructure such as laboratories, equipment, and databases. For clinical research, access to patient data within the hospital may be required.

6) Compliance with Ethics and Regulations: Obtain approval from the Institutional Review Board (IRB) to ensure the research is conducted ethically and complies with relevant regulations. Informed consent from research participants is also crucial.

7) Data Management: Establish systems and processes for efficient data management and analysis. Ensure data security and the protection of personal information.

8) Continuous Education and Learning: Pursue ongoing education and learning to stay updated with the latest research trends and techniques. Attend seminars, workshops, and conferences.

9) Publication and Presentation Plans: Develop plans to publish research results in academic journals or present them at conferences. This helps to disseminate findings and contribute to the academic community.

10) Mutual Respect and Collaborative Spirit: Foster a culture of mutual respect and collaboration among team members. Recognize and value each other's expertise to create synergy.

By preparing and addressing these elements, a clinician can successfully collaborate with basic medical science professors on a joint research project.

THE LIVER WEEK 2024

DAY 1: June 27 (Thu)

# Procedures in Liver Diseases

## Advances in Diagnostic and Therapeutic Procedures for Liver Disease

**Chairs:**

**Byung Ik Kim** (Sungkyunkwan Univ.)
**Jaeseok Hwang** (Keimyung Univ.)

**Bohyun Kim**

*The Catholic University of Korea*

## Self Introduction

Dr. Kim began her medical education at Chonbuk National University, School of Medicine, where she obtained their M.D. degree in February 2008. Following this, she pursued advanced studies at Ulsan University, College of Medicine, earning a Master's degree in February 2014 and a Ph.D. in February 2016.

Her clinical training commenced with an internship at Asan Medical Center from March 2008 to February 2009. She continued her residency in the Department of Radiology at Asan Medical Center from March 2009 to February 2013, followed by a fellowship in the same department, which she completed in February 2015.

Dr. Kim embarked on her academic career as a Clinical Assistant Professor at Ajou University Hospital in March 2015, a role she held until August 2016. Subsequently, she was appointed as an Assistant Professor at Ajou University School of Medicine from September 2016 to February 2020. Afterward, Dr. Kim served as a Clinical Assistant Professor at Seoul St. Mary's Hospital for a year until February 2021. She then joined the Catholic University College of Medicine, where she held the position of Assistant Professor from March 2021 to February 2023. In March 2023, Dr. Kim was promoted to Associate Professor at the Catholic University College of Medicine, a position she currently hold.

## Research Interests

Dr. Kim's research interests primarily focus on the radiologic diagnosis, treatment response assessment, and post-treatment prognostication of hepatocellular carcinomas (HCCs). Additionally, she is deeply invested in advancing fast imaging techniques in liver MRI.

## Representative Publications

1. Estimating postsurgical outcomes of patients with a single hepatocellular carcinoma using gadoxetic acid–enhanced MRI: risk scoring system development and validation (2023). SH Park, B Kim, S Kim, S Park, YH Park, SK Shin, PS Sung, JI Choi. European Radiology 33 (5), 3566-3579
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# Approach and Precautions for Liver Biopsy

**Bohyun Kim** *The Catholic University of Korea*

Liver biopsy provides clinically important information for the diagnosis of both focal lesions and diffuse diseases. Among the various feasible radiologic modalities for guidance, the percutaneous approach under ultrasound (US) or computed tomography (CT) guidance is often used. US is preferred over CT or magnetic resonance imaging (MRI) as the guidance tool due to its wide availability, portability, relatively short procedure time, and real-time visualization of the biopsy needle tip. CT or MRI guided-biopsy is performed in selected patients whose target lesions are poorly visible or whose biopsy routes are inaccessible on US.

Despite its common usage, percutaneous liver biopsy carries risks such as bleeding, organ perforation, sepsis, and death. Bleeding is reported in up to 10% of cases, with major bleeding occurring in less than 2%. To minimize the risk of bleeding and other complications, it is essential to perform screening coagulation tests, including PT/INR, platelet count, and hemoglobin levels, along with cessation of antiplatelet or anticoagulation medications. While the threshold for prophylactic correction of coagulation profiles with platelet infusion is debated, a platelet count of less than 50 x $10^9$/L is considered an indicator for platelet transfusion or the need for a transjugular biopsy. Recent studies have shown that fresh frozen plasma is ineffectiveness in reducing hemostatic failure.

When selecting the biopsy route, it is highly recommended to review recent (< 3 months for patients with stable liver disease) liver CT or MR images to simulate approach route. Using color Doppler during US guidance helps in identifying the safest needle path, avoiding major vessels. For diffuse liver disease, a subcostal approach targeting the left liver or an intercostal approach for segment 5 is preferred. In cases of focal liver lesions, the route of approach largely depends on the location of the target lesion. During the biopsy, the needle should be placed parallel to the long axis of the US transducer to constantly visualize the entire needle shaft and tip. Additionally, to avoid capsule laceration, the needle should pierce the liver capsule as orthogonally possible, with a swift advance into the parenchyma once the capsule has been punctured.

After the sample has been retrieved, careful inspection along the course of the needle insertion tract using color Doppler is necessary to ensure the absence of post-biopsy bleeding. If there is linear color flow in the biopsy trajectory (the "patent tract" sign), compression with the US probe until the disap-

pearance of Doppler signal is mandatory. Another immediately identifiable complication using US is a perihepatic hematoma, observed as an echogenic lump in the perihepatic space with or without color flow. Patients should be monitored for at least 3 hours after a liver biopsy with regular clinical observations and measurement of vital signs.

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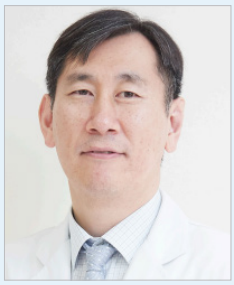

**Jooho Lee**

*CHA University*

## Self Introduction

Professor Jooho Lee is currently a professor in the Division of Hepatology at CHA Bundang Hospital and is the director of the Liver Transplantation Center. After graduating from Pusan National University School of Medicine, he obtained a doctorate in hepatology at Ulsan University Asan Medical Center. He did a short-term training at Keio University Tumor Immunology Institute in Japan and served as an advisory member of the Japanese New Regenerative Medicine Committee.

He is a member of the Korean Association for the Study of the Liver and the Liver Cancer Society and has been trained under Professor Masatoshi Kudo of Kindai University in Japan, who is a worldwide master of liver cancer treatment. His main research interest is immunotherapy for chronic hepatitis and liver cancer, early detection of liver cancer using contrast-enhanced ultrasound, and locoregional treatment of liver cancer. Now, he is a also a member of 'The Korean Association of Clinical Ultrasound'.

## Research Interests

- Immune Cell therapy of hepatocellular carcinoma
- NK cell immune signature and its functional role in hepatocellular carcinogenesis
- Immunologic biology and cancer signaling of hepatocellular carcinoma.
- Contrast-enhanced ultrasonography in hepatocellular carcinoma
- Artificial Intelligence in contrast enhanced sonography

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# Role of Contrast-Enhanced Ultrasound in Liver Disease

**Jooho Lee** *CHA University*

The application of ultrasound contrast agents (UCAs) is considered essential when evaluating focal liver lesions (FLLs) using ultrasonography (US). The unique features of contrast enhanced US (CEUS) are not only noninvasiveness but also real-time assessing of liver perfusion throughout the vascular phases. The later feature has led to dramatic improvement in the diagnostic accuracy of US for detection and characterization of FLLs, including hepatocellular carcinoma (HCC) relying on the differences in echogenicity and vascularity between the FLLs and surrounding liver tissues. The UCA, SonoVue®, has been approved for use worldwide. Perfluorobutane (Sonazoid®), a second-generation contrast agent used in CEUS, is a post vascular agent taken up by Kupffer and reticuloendothelial cells. With the development of second-generation UCAs and advancement in contrast harmonic imaging, CEUS now has the capacity to sensitively and accurately show tumor vascularity.

Sonazoid®-enhanced US is considered a breakthrough imaging technology because it has drastically changed clinical practice, especially in the treatment of HCC. Sonazoid®-enhanced US imaging is divided into two phases, namely the vascular and Kupffer phases, based on the in vivo dynamics of the agent. Sonazoid®-enhanced US is extremely sensitive for the detection of intranodular blood flow in hepatic tumors, and it is superior to the sensitivity of dynamic computerized tomography. Because of limited published data, the American College of Radiology released the 2017 version of the CEUS Liver Imaging Reporting and Data System (LI-RADS) for patients at risk of HCC using pure blood–pool agents, the current version of the CEUS LI-RADS (v2017) does not address the use of perfluorobutane (Sonazoid®).

In 2018, several major guidelines for HCC were updated to include hepatobiliary contrast agent magnetic resonance imaging (MRI) and CEUS as major imaging modalities for HCC diagnosis. Furthermore, in 2022, the CEUS with Kupffer cell-specific UCA has been included as a secondary diagnostic modality of HCC by Korean Liver Cancer Association. CEUS is imaging modality with real-time imaging capability, and it is reported to be useful as a second-line modality to increase sensitivity without losing specificity for HCC diagnosis. However, until now, there is an unsolved discrepancy among guidelines on whether to accept "Kupffer phase hypointensity" as a definite diagnostic criterion for HCC or include CEUS in the diagnostic algorithm for HCC diagnosis. Furthermore, there is variability in terminology and inconsisten-

cies in the definition of imaging findings among guidelines; therefore, there is an unmet need for the development of a standardized diagnostic consensus.

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**Byung Seok Kim**

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## Self Introduction

Prof. Byung Seok Kim is a Professor of the Department of Internal Medicine, Daegu Catholic University School of Medicine.

Professor Kim served as Vice Dean for Education and Chief of Medicine at Daegu Catholic University School of Medicine.

Professor Kim graduated from Dongguk University College of Medicine and received a master's degree and doctoral degree from Yeungnam University College of Medicine.

Professor Kim currently serves as President of the Daegu-Gyeongbuk branch of the Korean Association for the Study of the Liver (2023~).

## Research Interests

Liver cirrhosis / Portal hypertension

## Representative Publications

1. Multicenter Analysis of Clinical Features and Prognosis of COVID-19 Patients with Hepatic Impairment. Gut Liver. 2021;15:606–615.
2. Changing Trends in Liver Cirrhosis Etiology and Severity in Korea: the Increasing Impact of Alcohol. J Korean Med Sci. 2021;36(21):e145.
3. Diagnostic usefulness of the spot urine sodium/potassium ratio in cirrhotic patients with ascites. PLoS ONE 2021;16(6):e0253886.
4. KASL clinical practice guidelines for liver cirrhosis: Varices, hepatic encephalopathy, and related complications. Clinical and Molecular Hepatology 2020;26:83-127.
5. Changes in Characteristics of Patients with Liver Cirrhosis Visiting a Tertiary Hospital over 15 Years: a Retrospective Multi-Center Study in Korea. Journal of Korean Medical Science 2020;35:e233.

# Endoscopic Treatments for Variceal Bleeding

**Byung Seok Kim** *Daegu Catholic University*

## Introduction

Portal hypertension, which is the most common complication of liver cirrhosis, is the main determinant in the development of varices.[1] Variceal bleeding is a major consequence of portal hypertension and causes the death of cirrhotic patients. Thus, the appropriate management of acute variceal bleeding is crucial. This review focuses on the endoscopic treatments for variceal bleeding in patients with liver cirrhosis.

## Endoscopic treatment of esophageal variceal bleeding

Endoscopy should be conducted as soon as possible, preferably within 12 hours, in cirrhotic patients with hematemesis. If variceal bleeding is suspected, endoscopic therapy should be performed. The aim of endoscopic therapy for esophageal varices is to decrease variceal wall tension through variceal obliteration.[2] The endoscopic modalities for treating esophageal variceal bleeding are endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS). EIS involves the injection of a sclerosing agent including sodium tetradecyl sulfate, ethanolamine oleate, or absolute alcohol into the variceal lumen or adjacent to the varices. Injected sclerosing agents cause injury to endothelial cells, destruct the red blood cells, and result in thrombosis of varices.[3] For complete obliteration of the varices, repeated sessions should be performed. Before EVL, EIS was the first-line treatment for esophageal variceal bleeding, as it was proven to be superior to balloon tamponade or vasoconstrictor administration in terms of bleeding control. However, EIS is no longer considered as standard treatment because it has a higher rate of treatment failure and more complications than EVL.[4,5] Currently, EVL is considered the gold standard therapy for esophageal variceal bleeding.[6] Contrary to EIS that involves chemical obliteration, EVL eradicates varices through mechanical strangulation with rubber bands. In EVL, variceal columns are sucked into a transparent cap mounted on the tip of the endoscope and ligated with rubber bands. Multiband devices are more commonly employed than the original single-band ligators because multiband devices are much simpler and quicker to use and do not need an overtube.[7] Once the varix is identified, the tip of the endoscope is pointed toward the varix, which is then continuously sucked into the transparent cap. During the suctioning of the varix into the cap, the rubber band can be fired when

a "red-out" sign appears.[8] Generally, the procedure is conducted by starting the deployment of the bands at the gastroesophageal junction and working upwards in a spiral pattern to prevent overlapping circumferential deployment of bands at the same level.[3] It is better to place at least one band on each distinct variceal column. In the presence of active bleeding, the field of vision might be restricted by the cap mounted on the tip of endoscope. Water infusion and suction can help in visualizing the bleeding focus. If possible, the rubber band should be deployed at the site of variceal bleeding. However, if the bleeding point cannot be confirmed, blind multiband ligations at the gastroesophageal junction may sufficiently reduce hemorrhage to obtain a field of vision and subsequently performing proper ligation.[8,9]

## Endoscopic treatment of gastric variceal bleeding

Compared with esophageal varices, gastric varices have lower incidence and bleeding rate.[10] However, gastric variceal bleeding is usually more massive, requires more transfusions, and is related to higher rebleeding and mortality rates than esophageal variceal bleeding.[10-12] Gastric varices are classified as gastroesophageal varices (GOVs) or isolated gastric varices (IGVs) depending on their location and relation to any esophageal varices.[10] GOVs are classified by whether they extend along the lesser curvature (GOV1s) or the gastric fundus (GOV2s). IGVs are classified as varices located in the fundus (IGV1s) and those in any other region, i.e., stomach except the fundus or duodenum (IGV2s).[10] The incidence of GOV1s is about 74%. Hemodynamically, esophageal varices and GOV1s arise from the left and right gastric veins, whereas GOV2s and IGV1s are usually supplied by the short and posterior gastric veins.[13] IGV2s are supplied by the gastroepiploic veins.[14] The risk of bleeding is significantly higher in fundal varices than in either GOV1s or IGV2s.[10]

### *1) Endoscopic treatment of GOV2 and IGV1 bleeding*

GOV2s and IGV1s are collectively called fundal varices and supplied by the short and posterior gastric veins.[13] Fundal variceal bleeding commonly occurs in large varices and is accompanied by a gastrorenal or splenorenal shunt.[15] Because fundal varices have a large volume and fast flow of blood, bleeding control is difficult and the rebleeding rate is high. Endoscopic variceal obturation (EVO) is the endoscopic treatment of choice for acute bleeding from GOV2s and IGV1s.[16-18] Gastric varices are obturated by injecting a tissue adhesive agent, such as cyanoacrylate, which leads to solidification and thrombosis in the varices.[14] Contrary to sclerosing agents used in EIS, which induce thrombosis and fibrosis of varices through endothelial damage, cyanoacrylate is rapidly transformed into a hard plastic material within varices, resulting in their solidification and thrombosis.[2] The standard protocol uses a mixture of cyanoacrylate and Lipiodol in a 1:1 ratio to delay premature hardening. The mixture of cyanoacrylate and Lipiodol is directly injected into the gastric varices at 1–2 mL each time with a needle catheter. Immediately after injection, distilled water should be passed to deliver the cyanoacrylate from the dead space of the catheter lumen to gastric varices. Before the procedure, the dead space of catheter lumen should be

checked to confirm the volume of distilled water for flushing. The needle should be promptly extracted after cyanoacrylate injection to prevent it from being embedded in the varix. After extracting the needle, distilled water should be passed into the catheter lumen at high speed for 15–20 s to prevent closure of the catheter lumen.[2] Until the varix is hard enough to touch with a needle catheter, repeated injection could be performed.[19] When deciding the site of injection, the direction of variceal blood flow and the variceal size should be considered. Huge fundal varices have a large volume and rapid flow of blood from the cardia to the fundus. Theoretically, the dome of the varix has the highest pressure and fastest blood flow. Thus, the most protruding portion of the varix should be avoided to prevent massive bleeding.[20] After EVO therapy, cyanoacrylate gradually causes an inflammatory response and eliminates vascular endothelial cells, causing variceal obliteration. The complications that could occur after EVO are infection, fever, perforation, gastric ulcer, and peritonitis.[19] Severe complications are mostly associated with distant embolic events such as pulmonary, cerebral, and splenic infarction.[21] In several studies evaluating the efficacy of EVO for acute gastric variceal bleeding, the success rate of hemostasis was 91–97% and the rebleeding rate was 17–49%.[22-24]

### *2) Endoscopic treatment of GOV1 bleeding*

GOV1s are more similar to esophageal varices than GOV2s and IGV1s in terms of size and route of portal blood flow, including having a smaller size than fundal varices as well as afferent venous drainage through the left and right gastric veins. GOV1s are closely connected with esophageal varices because obliteration of esophageal varices with EVL or EIS frequently induces resolution of gastric varices in 60–65% of patients with GOV1s.[10,25] Therefore, GOV1s are usually treated with EVL, similar to esophageal varices. However, GOV1s are present in the stomach where the overlying mucosal layer is thicker than that in the esophagus. The thick overlying mucosal layer of gastric varices could result in incomplete ligation of varices with EVL, which could induce massive hemorrhage after detaching the rubber band from the gastric mucosa.[26,27] Furthermore, bleeding from post-EVL ulcers could occur more frequently in the stomach than in the esophagus.[28] In fact, EVO seems to be superior to EVL in treating acute bleeding from GOV1s. In several randomized controlled trials and retrospective studies, the success rate of hemostasis was 85–100% with EVO and 80–90% with EVL, and the rebleeding rate was 3–26% with EVO and 14–56% with EVL.[25,28-30] In addition, a meta-analysis showed that the efficacy of EVO was superior to that of EVL in preventing rebleeding from GOV1s (OR, 0.39%; 95% CI, 0.16–0.94; $p$=0.035).[31] In summary, both EVO and EVL are available options for treating GOV1 bleeding; however, EVO is preferred over EVL.

## Conclusion

Bleeding from varices is a serious complication of portal hypertension and a major cause of mortality in patients with liver cirrhosis. If acute variceal bleeding is suspected, endoscopy should be performed as soon as possible to confirm the hemorrhagic focus and hemostasis. The two main methods of endoscopic hemostasis are EVL and EVO, and the choice between these methods is decided according to

the type of varices.

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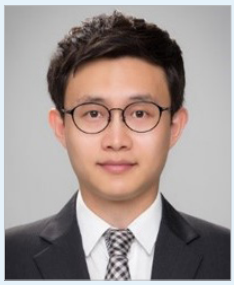

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## Self Introduction

Prof. Chu is a clinical associate professor of the Department of Radiology, Asan Medical center in Seoul.

Prof. Chu graduated from Seoul National University College of Medicine with his medical degree in 2009 and completed his internship, residency and fellowship at the Department of Radiology at Seoul National University Hospital.

Since 2019, Prof. Chu has been working as a faculty at Asan Medical Cent in Seoul, and in charge of interventional radiology such as embolization and angioplasty.

## Research Interests

Oncology, Hepatobiliary, Embolization, Vascular intervention

## Representative Publications

1. Chu HH, Gwon DI, Kim GH, Kim JH, Ko GY, Shin JH, Ko HK, Yoon HK. Balloon-occluded transarterial chemoembolization versus conventional transarterial chemoembolization for the treatment of single hepatocellular carcinoma: a propensity score matching analysis. Eur Radiol. 2023 Apr;33(4):2655-2664. doi: 10.1007/s00330-022-09284-3. Epub 2022 Dec 6.
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# Interventional Approaches for Portal Hypertension-Related Complications

**Hee Ho Chu** *University of Ulsan*

Portal hypertension refers to a syndrome caused by abnormal elevation of portal pressure and formation of portosystemic collaterals. Increased resistance to portal blood flow can occur in presinusoidal (portal vein thrombosis), sinusoidal (cirrhosis), and postsinusoidal (Budd-Chiari syndrome), the most common cause of which is cirrhosis.[1]

Varices that can occur due to portal hypertension include esophageal varices, gastric varices, and ectopic varix. Gastric varices, which occur in 30% of patients with portal hypertension, have a bleeding rate of about 10-36%, which is less than that of esophageal varices. However, once bleeding occurs, the mortality rate reaches 14-45%, making it a more dangerous complication than esophageal variceal bleeding.[2]

Treatment methods for varicose bleeding include medical drug treatment, endoscopic treatment including sclerosis and ligation, interventional procedures, and surgical shunt formation. In the case of esophageal variceal bleeding, most cases are controlled with endoscopic treatment and medical drug treatment, so interventional treatment can be used when primary medical treatment fails. In the case of gastric variceal bleeding, the frequency of rebleeding and complications with endoscopic treatment is not low, so interventional treatment is often used. [3] The treatment goal is to resolve portal hypertension or embolize varicose veins through intervention.

Procedures to reduce portal pressure include transjugular intrahepatic portosystemic shunt (TIPS), which creates a shunt, and partial splenic embolization, which reduces venous inflow. Procedures to embolize varicose veins include Balloon-occluded Retrograde Transvenous Obliteration (BRTO), which blocks the efferent vein and injects a sclerosing agent, or Plug-Assisted Retrograde Transvenous Obliteration using a Vascular plug; There are percutaneous embolization approaches using PARTO and afferent veins. Routes accessing the afferent vein include the transhepatic, transsplenic, and transparaumbilical veins.

## [Transjugular Intrahepatic Portosystemic Shunt; TIPS]

### *1. Indications and contraindications*

Indications for TIPS are (1) variceal bleeding that cannot be stopped by endoscopic treatment, especially gastric variceal bleeding, (2) uncontrolled ascites, (3) hepatorenal syndrome, (4) portal hypertensive gast-

ropathy, and (5) liver water. These include hepatic hydrothorax (6) and hepatopulmonary syndrome.[4]

Absolute contraindications include cystic liver disease, severe pulmonary hypertension, right heart failure, severe liver failure, and biliary sepsis. Relative contraindications include infection, portal vein thrombosis, severe hepatic encephalopathy, and biliary dilatation. In cases such as hepatocellular carcinoma, hemangioma, and arteriovenous malformation, TIPS can be performed if it is not located in the expected path of shunt formation.

### *2. Complications*

Complications that may arise related to the TIPS procedure include hemocholosis and premature shunt obstruction due to intrahepatic biliary puncture, gallbladder puncture, right kidney puncture, cardiac arrhythmia, hepatic artery damage, and extrahepatic portal vein puncture. Among these, the most dangerous complication is massive intra-abdominal bleeding caused by puncture of the extrahepatic portal vein and its balloon dilatation. Complications caused by portosystemic shunt include the development of hepatic encephalopathy, worsening of existing hepatic encephalopathy, or worsening of liver dysfunction.[5]

### *3. Results*

The technical success rate of the procedure is reported to be 93-100%. Typically, it is recognized that portal hypertension has been effectively decompressed when the portal vein pressure difference is less than 12 mmHg. The short-term hemostasis success rate for esophageal variceal bleeding is reported to be 81-94%. An important problem in long-term follow-up after TIPS is varicose rebleeding due to shunt occlusion or stenosis. The primary patency after TIPS is 22-66% (1 year) and 17-42% (2 years), and in long-term follow-up, the 1-year and 2-year varicose vein rebleeding rates are reported to be 20-26% and 21-32%.[6-9]

## [Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) or Plug-Assisted Retrograde Transvenous Obliteration (PARTO) for Gastric Variceal Bleeding]

BRTO or PARTO uses balloon occlusion or vascular plug to stop rapid blood flow by blocking the gastrorenal shunt, which is the outflow path of gastric varicose veins, or retrogradely injects a sclerosing agent or embolic material into the varicose vein while blocking reflux, thereby forming a blood clot inside the varicose vein.

Unlike TIPS, it helps treat hepatic encephalopathy by occluding the porto-venous shunt and has the advantage of improving liver function by increasing blood flow to the liver through the portal vein. However, it has the disadvantage of not reducing portal pressure but rather increasing it, worsening complications such as esophageal varices, portal hypertensive gastropathy, and ascites.[10,11]

### *1. Indications and contraindications*

Indications for BRTO/PARTO include (1) hemostasis of gastric variceal bleeding, (2) prevention of gastric

variceal rebleeding after successful hemostasis through endoscopy, and (3) treatment of hepatic encephalopathy.

A relative contraindication is persistent overt gastric variceal bleeding. Since BRTO/PARTO blocks the gastrorenal shunt, the pressure of the gastric varices increases during the procedure, worsening the bleeding of the gastric varices, and the sclerosing agent or embolic material does not stay inside the varicose veins but flows out. Therefore, in patients with overt gastric variceal bleeding, it is safe to perform hemostasis through medical treatment and perform interventional procedures 1 to 2 days later.

### *2. Complications*

Complications of BRTO may include mild abdominal pain, nausea, and vomiting during the procedure, and hemoglobinuria may occur after the procedure due to hemolysis caused by fever-generating ethanolamine oleate, but most cases improve on their own.

In the early stages of BRTO/PARTO treatment, ascites and portal hypertensive gastropathy may occur due to increased portal pressure, and esophageal varices may worsen.

### *3. Results*

The technical success rate is reported to be 87-100%, and in more than 95% of cases, a complete blood clot is formed inside the gastric varices after the procedure. The recurrence rate of gastric varices during follow-up is reported to be approximately 2.7-6.%. Hepatic encephalopathy improves within 1 week of the procedure.[10-12]

## [Percutaneous Transhepatic or Transsplenic Variceal Embolization]

Percutaneously puncture the liver or spleen, insert a catheter into the portal vein, perform portal angiography, confirm the location of the afferent veins and varicose veins, and occlude the afferent veins and varicose veins with an embolic material.

In patients with esophageal or gastric varices that are difficult to treat with endoscopy, percutaneous varicose embolization can be performed if it is difficult to perform TIPS or BRTO/PARTO. It is also used as a route to access the portal vein to embolize ectopic varix. If there is a lot of ascites, it is difficult to puncture the portal vein or splenic vein, and the risk of bleeding increases, so it can be performed after ascites drainage.[13]

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era? Am J Gastroenterol. 2012 Dec;107(12):1784-90.
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THE LIVER WEEK 2024

DAY 1: June 27 (Thu)

# Ultrasound Trainee Session

**Chair:**

**Moon Young Kim** (Yonsei Univ. Wonju)

**Young Chang**

*Soonchunhyang University*

## Self Introduction

Prof. Young Chang is an Assistant Professor of the Department of Internal Medicine, Soonchunhyang University College of Medicine.

Prof. Chang graduated from Seoul National University College of Medicine with her medical degree in 2011 and completed his internship and residency at the Department of Internal Medicine at Seoul National University Hospital, receiving his diploma in Internal Medicine in 2021.

Prof. Hong has been involved in a number of committees, and currently in Scientific Committee and Research Committee of the Korean Association of the Study of the Liver (2023-present), Publication Committee and Primary Liver Cancer Registry Committee of the Korean Liver Cancer Association (2023-present).

# The Beginning of Abdominal US: Anatomy of US

**Young Chang** *Soonchunhyang University*

Ultrasonography refers to the technique of using waves with frequencies higher than the audible range (20-20,000Hz), specifically between 20,000Hz to 30MHz, to create images. Ultrasonic imaging involves transmitting pulse waves into the body, which reflect off tissues with different acoustic impedances. The received signals are amplified and converted to form images. The intensity of the ultrasound, or the magnitude of the reflected waves from the medium, is displayed as brightness in B-mode imaging. M-mode shows the movement of a specific area over time, while Doppler mode compares the transmitted and received frequencies to display the speed difference, with color mode and D-mode displaying this speed as color and spectrum, respectively. Power mode solely indicates the presence of blood flow. Since the wavelength of the transmitting frequency is known, the device can measure distances and perform various measurements.

For diagnostic imaging, frequencies ranging from 1MHz to 20MHz are used, varying by organ: the heart uses 2-3MHz, the abdomen 3-5MHz, superficial organs like the thyroid and breast use 7.5-10MHz, and observing peripheral vessels or gastrointestinal tract lesions uses 12-20MHz. Ultrasound waves propagate poorly through air but well through water, making it effective for imaging organs and tissues with high water content but challenging for lungs and intestines due to gas interference. Fasting for at least 8 hours is required before an abdominal ultrasound to avoid interference from ingested food and intestinal gas.

Proper setting of ultrasound equipment is crucial for high-quality diagnostic ultrasound. Digital ultrasound equipment, which automatically adjusts resolution and has preset settings for different organs, can be fine-tuned for individual patients' body types and conditions. Key settings include:

**Gain:** Similar to monitor brightness, it adjusts the electrical signal to control image brightness. It affects the overall intensity of the received ultrasound signal but not the ultrasound's intensity itself. Proper gain adjustment is necessary to balance noise and clarity.

**STC (Sensitivity Time Control):** Adjusts gain compensation for signal attenuation at deeper body layers, allowing for sensitivity adjustments according to depth. STC is preset in devices but may require adjustment for individuals with above-average body types.

**Depth:** Sets the depth to ensure the organ of interest is adequately displayed, with standard settings for upper abdominal ultrasound around 15cm. Adjustments may be needed for patients with abdominal obesity or liver enlargement.

**Frequency:** Adjustable in 3-5 steps on ultrasound devices, with higher frequencies improving resolution but reducing penetration, and lower frequencies increasing penetration but lowering resolution. Frequency adjustments help in observing either deep or superficial lesions more effectively.

**Dynamic Range:** Defines the ratio between the maximum and minimum signal values, affecting image contrast. Increasing the dynamic range softens the image and reduces contrast, while decreasing it enhances contrast, making fine signal differences distinguishable but the image rougher and generally darker. Adjusting the dynamic range can help in observing the gallbladder more clearly by eliminating reverberation artifacts and allowing for a cleaner, thinner gallbladder wall observation (adjusting gain alongside is beneficial).


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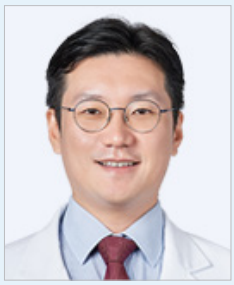

**Young Youn Cho**

*Chung-Ang University*

## Self Introduction

### *Education*

| | | |
|---|---|---|
| 2010 | Bachaler degree | Seoul National University |
| 2015 | Master degree | Seoul National University |
| 2024 | PhD degree | Seoul National University |

### *Current and Previous 4 Relevant Positions Including Academic Appointments*

| | | |
|---|---|---|
| 2011.03-2015.02 | Resident | Seoul National University Hospital |
| 2015.03-2016.07 | Fellow | Seoul National University Hospital |
| 2016.09-2018.01 | Assistant Professor | Seoul National University Hospital |
| 2018.03-2024.02 | Assistant Professor | Chung-Ang University Hospital |
| 2024.03-Current | Associate Professor | Chung-Ang University Hospital |

## Research Interests

Big data study, and microbiome study.

## Representative Publications

1. First / Gut Liver. 2020 Mar 15;14(2):225-231./ Long-term Nucleotide Analogue Treatment Has Higher Renal Toxicities than Entecavir in Patients with Chronic Hepatitis B / Cho YY, Chang Y, Nam JY, Cho H, Cho EJ, Lee JH, Yu SJ, Yoon JH, Kim YJ.
2. First/J Hepatocell Carcinoma. 2021 Jun 18;8:613-623./Clinical Characteristics of Long-Term Survivors After Sorafenib Treatment for Unresectable Hepatocellular Carcinoma: A Korean National Multicenter Retrospective Cohort Study./Cho YY, Yu SJ, Lee HW, Kim DY, Kang W, Paik YH, Sung PS, Bae SH, Park SC, Doh YS, Kim KM, Jang ES, Kim IH, Kim W, Kim YJ.
3. Co-First/ Hepatol Int. 2021 Oct;15(5):1083-1092 /Impact of tenofovir alafenamide vs. entecavir on hepatocellular carcinoma risk in patients with chronic hepatitis B./Lee HW, Cho YY, Lee H, Lee JS, Kim SU, Park JY, Kim DY, Ahn SH, Kim BK, Park SY.
4. Co-First / J Viral Hepat. 2021 Nov;28(11):1570-1578./ Effect of tenofovir alafenamide vs. tenofovir disoproxil fumarate on hepatocellular carcinoma risk in chronic hepatitis B. / Lee HW, Cho YY, Lee H, Lee JS, Kim SU, Park JY, Kim DY, Ahn SH, Kim BK, Park SY.
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# How to Get 12 Masterpiece Photos from US Scan

**Young Youn Cho** *Chung-Ang University*

## Introduction

Ultrasonography (US) plays a crucial role in liver cancer screening, particularly for early detection, which can significantly improve treatment outcomes. Finding small hepatic nodules requires improving imaging quality. In this lecture, we will discuss how to enhance the quality of ultrasonography.

## Preparation

Regular maintenance of ultrasound equipment is important. Since intestinal gas can interfere with ultrasound examinations for liver cancer screening, fasting for at least 6 hours is required.

## The 12 standard US scans

The list of the 12 standard ultrasound (US) scans is as follows. We evaluate whether anatomical structures are well visualized across the entire field, if the brightness and contrast of the images are appropriate, if depth adjustment is well managed, and if there are no artifacts. We will discuss how to improve the image quality of these scans:

(1) Transverse scan of the right hepatic lobe
(2) Intercostal scan of the right hepatic lobe
(3) Transverse scan of the left hepatic lobe
(4) Transverse scan of the left lobe of the liver.
(5) Inferior scan of the hepatic vein.
(6) Upper part of the right lobe of the liver.
(7) Coronal plane scan of the right liver and the lower pole of the kidney.
(8) Longitudinal axis scan of the gallbladder.
(9) Sagittal scan of the extrahepatic bile duct.
(10) Longitudinal axis scan of the spleen.
(11) Transverse scan of the head of the pancreas.
(12) Transverse scan of the body and tail of the pancreas.

The National Cancer Center conducts on-site mentoring for medical institutions that received inadequate judgments in liver ultrasound examinations. During these visits, experts in liver ultrasound directly visit the institutions to provide explanations regarding the previous year's evaluations, education on correcting inadequate items, and addressing concerns and deficiencies through meetings with responsible personnel. This aims to strengthen feedback on examination evaluations.

## Reference

1. National Cancer Center, Quality Guidelines of Liver Cancer Screening, 2nd edition

THE LIVER WEEK 2024

DAY 1: June 27 (Thu)

# Ultrasound Trainer Session 1

**Chair:**

**Jae Young Jang** (Soonchunhyang Univ.)

**Tae-Suk Kim**

*Kangwon National University*

## Self Introduction

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|---|---|
| 2013.03-2020.08 | Ph.D. in Clinical Medical Science Kangwon National University College of Medicine, Chuncheon-si, Korea |
| 2010.03-2012.08 | M.S. in Clinical Medical Science Kangwon National University College of Medicine, Chuncheon-si, Korea |
| 2003.03-2008.02 | M.D. in Medicine Kangwon National University College of Medicine, Chuncheon-si, Korea |
| 2016.03-2019.08 | Assistant clinical professor, Division of Gastroenterology, Department of Internal Medicine, Kangwon National University Hospital, Chuncheon, South Korea |
| 2022.03-present | Assistant Professor, Division of Gastroenterology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, South Korea |

## Research Interests

- Alcoholic liver disease
- Liver cirrhosis
- Hepatocellular carcinoma
- Abdominal US

## Representative Publications

1. Kim, Tae Suk, et al. "Metformin and dichloroacetate suppress proliferation of liver cancer cells by inhibiting mTOR complex 1." International Journal of Molecular Sciences 22.18 (2021): 10027.
2. Kim, Tae Suk, et al. "Reappraisal of sepsis-3 and CLIF-SOFA as predictors of mortality in patients with cirrhosis and infection presenting to the emergency department: A multicenter study." Clinical and molecular hepatology 28.3 (2022): 540.
3. Kim, Tae Suk, and Dae Hee Choi. "Liver Dysfunction in Sepsis." The Korean Journal of Gastroenterology= Taehan Sohwagi Hakhoe chi 75.4 (2020): 182-187.

# Ultrasound Training in Korea: Current & Future Perspective

**Tae-Suk Kim** *Kangwon National University*

Ultrasound (US) is an essential diagnostic tool in almost every medical area. However, US education for physicians has been conducted only in some university hospitals that directly perform abdominal US examinations in internal medicine, or some education is provided with the help of radiologists. US technology continues to become increasingly widespread, portable, and miniaturized. Furthermore, point-of-care US, i.e., US executed at the patient's bedside to obtain real-time objective information with diagnostic and clinical monitoring purposes or to guide invasive procedures, has been incorporated in many specialties. An educational accreditation system for trainers of ultrasonography in the internal medicine field was developed in 2018, but accredited ultrasound trainers and equipment and space for ultrasound training are lacking.

Training of Abdominal ultrasound in Korea faces four major challenges: (i) providing more specific programs and educational opportunities for residents; (ii) expansion of manpower and quality control of the certification system; (iii) training with advanced diagnostic ultrasonography; and (iv) expansion into medical student curricula.

**Hyo Jung Cho**

*Ajou University*

## Self Introduction

### *Education*

2014.03-2016.02 Ph.D. Gastroenterology, Ajou University, Suwon, Korea
2011.09-2013.08 M.S. Gastroenterology, Ajou University, Suwon, Korea
2001.03-2007.02 B.S. Medicine, Ajou University, Suwon, Korea

### *Professional Experience*

2023.03-present Associate professor Department of gastroenterology, Ajou University Hospital
2019.03-present Assistant professor Department of gastroenterology, Ajou University Hospital
2016.03-2018.02 Clinical assistant professor Department of gastroenterology, Ajou University Hospital
2016.03-2018.02 Research assistant professor Department of gastroenterology, Ajou University Hospital
2014.03-2016.02 Research Fellow Department of gastroenterology, Ajou University Hospital, Seoul, Korea

# Quality Improvement and Patient Safety in US Examination

**Hyo Jung Cho** *Ajou University*

Abdominal ultrasound is a critical diagnostic tool in gastroenterology, necessitating rigorous quality improvement (QI) to enhance accuracy and patient outcomes. The quality metrics for ultrasound evaluation include personnel, equipment, standardized quality control measures using multipurpose phantom, evaluation of ultrasound reports, and image quality of mandatory images for hepatocellular carcinoma (HCC) screening. Methodologies for quality improvement encompass the Plan-Do-Study-Act (PDSA) cycle and the Six Sigma Define-Measure-Analyze-Improve-Control (DMAIC) framework. In the QI project of ultrasound for HCC screening, the identified problems include personnel aspect and low sensitivity of early-stage HCC detection. Methods for improving personnel QI involve the implementation of an integrated certification system by a reputable society and the introduction of certification exams. QI project methodologies for enhancing the sensitivity of early HCC detection include the adoption of a standardized reporting system (such as the LI-RADS visualization score) and personalized screening approaches based on this system. The implementation of structured training, stringent equipment standards, and systematic QI methodologies is expected to significantly enhance the quality of abdominal ultrasound. Continuous monitoring and re-education are essential to maintaining high diagnostic standards, ultimately improving patient safety and outcomes.


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DAY 1: June 27 (Thu)

# Ultrasound Trainer Session 2

**Chair:**

**Soon Koo Baik** (Yonsei Univ. Wonju)
**Young Seok Kim** (Soonchunhyang Univ.)

**Hye Won Lee**

*Yonsei University*

## Self Introduction

Dr. Hye Won Lee graduated from Ewha Womans University College of Medicine and received her Ph.D. degree from Yonsei University College of Medicine. She completed her residency and fellowship at Severance hospital, where she continues to work as an Assistant Professor at Yonsei University College of Medicine. She visited the Chinese University of Hong Kong as a vising scholar for two years. She has continued to conduct her research on chronic liver disease, especially NASH and HBV. She has won several awards and grants from various institutions and academies. She is recognized as one of the outstanding young physicians in Korea.

## Research Interests

- Chronic liver disease including NASH and viral hepatitis
- Hepatocellular carcinoma

## Representative Publications

1. H Lin, HW Lee, TCF Yip, E Tsochatzis, S Petta, et al. Vibration-controlled transient Elastography scores to predict liver-related events in Steatotic liver disease. JAMA. 2024 Mar 21:e241447.
2. Lee HW, Kim KH, Ahn SH, Lee HC, Choi J. The associations between fibrosis changes and liver-related events in patients with metabolic dysfunction-associated steatotic liver disease. Liver Int. 2024 Mar 15.
3. Lee HW, Yip TC, Wong VW, Lim YS, Chan HL, Ahn SH, Wong GL, Choi J. CAMP-B score predicts the risk of hepatocellular carcinoma in patients with chronic hepatitis B after HBsAg seroclearance. J Gastroenterol Hepatol. 2024 Feb 15
4. Lee HW, Kim H, Park T, Park SY, Chon YE, Seo YS, Lee JS, Park JY, Kim DY, Ahn SH, Kim BK, Kim SU. A machine learning model for predicting hepatocellular carcinoma risk in patients with chronic hepatitis B. Liver Int. 2023 Aug;43(8):1813-1821.
5. Lee DH, Jee JJ, Lee YS, Kim DY, Bang JY, Lee HW, Koh H, Bae SH. Fecal microbiota transplantation improves hepatic fibro-inflammation via regulating oxidative stress in experimental NASH. Dig Liver Dis. 2023 Nov;55(11):1521-1532

# What is the Role of US and Elastography in the MASLD Era?

**Hye Won Lee** *Yonsei University*

Liver fibrosis is a determinant of the long-term prognosis of chronic liver diseases. To accurately assess liver fibrosis, a liver biopsy is required. However, liver biopsy is an invasive procedure and is not suitable for all patients with liver diseases. Elastography, a tool for assessing liver fibrosis based on ultrasound, comprises three main techniques: transient elastography (TE), point shear wave elastography (pSWE), and two-dimensional shear wave elastography (2D-SWE). TE is not included in ultrasound imaging machines and uses mechanically induced impulses from the skin surface. By contrast, SWE uses conventional ultrasound machines to measure the propagation speed of shear waves transmitted through the liver from the transducer. pSWE generates a single shear wave at a single frequency, whereas 2D-SWE uses various frequencies to generate multiple waves.

For metabolic dysfunction-associated steatotic liver disease (MASLD), the diagnostic AUC of TE for advanced liver fibrosis ranged from 0.65 to 0.98, with cutoff values of 6.6 to 10.4 kPa, and the AUC for cirrhosis diagnosis ranged from 0.94 to 0.97, with cutoff values of 10.3 to 17.0 kPa, indicating high diagnostic performance. Recent multicenter cohort studies have proposed the FibroScan-AST (FAST) score, which reflects TE values, CAP values, and AST values, and the AGILE score system based on elastography. AGILE 3+ calculates scores based on age, sex, AAR, platelet count, presence of type 2 diabetes, and TE values, with a lower cutoff of 0.451, an upper cutoff of 0.679, an AUC of 0.86, and a positive predictive value of 72% for diagnosing advanced liver fibrosis. For cirrhosis, AGILE 4 had a lower cutoff of 0.251, an upper cutoff of 0.565, an AUC of 0.93, and a positive predictive value of 73%, thereby exceeding the positive predictive values of FIB-4, NFS, and ELF, and demonstrating high diagnostic performance.

In patients with MASLD, the diagnostic AUC of pSWE for significant liver fibrosis was > 0.8. Specifically, pSWE showed high diagnostic performance for advanced liver fibrosis, with a sensitivity of 100% and a specificity of 91%. In a domestic single-center cohort study, the diagnostic AUC of pSWE for advanced liver fibrosis was 0.86, with a cutoff value of 1.395. However, as the degree of hepatic steatosis increased from mild to moderate to severe, the AUC decreased to 0.91, 0.85, and 0.69, respectively. Meta-analyses have shown that pSWE has diagnostic performance similar to TE. In a prospective study involving 231 patients diagnosed with NAFLD by liver biopsy, the diagnostic AUC of 2D-SWE for advanced liver fibrosis was 0.920, comparable to the values of magnetic resonance elastography and TE.

In conclusion, non-invasive elastography techniques—including TE, pSWE, and 2D-SWE—are highly accurate alternatives to liver biopsy for assessing liver fibrosis in patients with MASLD. Each technique has shown excellent diagnostic performance, and their sensitivities and specificities vary according to the degree of hepatic steatosis. These advanced techniques for elastography are valuable tools and their use can enhance the management and prognosis of chronic liver diseases.


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**Janghan Jung**

*Hallym University*

## Self Introduction

### *Education*

2000.3-2006.2 M.D., Konyang University, College of Medicine, Daejeon, Korea
2009.9-2011.2 M.S., Graduate School of Medicine, Konyang University, Daejeon, Korea
2019.9-present Ph.D student, Dept. of Internal Medicine, Yonsei University, College of Medicine, Seoul, Korea

### *Professional Experience*

2006.3-2007.2 Intern Trainee, Konyang University Hospital, Daejeon, Korea
2007.3-2011.2 Resident Trainee in Internal Medicine, Konyang University Hospital, Daejeon, Korea
2015.5-2017.2 Clinical and Research Fellowship, Division of Gastroenterology, Department of Internal Medicine, Yonesi University Severance Hospital, Seoul, Korea
2017.3-2019.8 Clinical Assistant Professor, Division of Gastroenterology & Hepatology, Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Korea
2019.9-present Assistant Professor, Division of Gastroenterology & Hepatology, Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Korea

## Research Interests

1. Viral hepatitis
2. Nonalcoholic fatty liver disease
3. Alcohol liver disease
4. Hepatocellular carcinoma

## Representative Publications

1. Jang TY, Liang PC, Jun DW, Jung JH, Toyoda H, Wang CW, Yuen MF, Cheung KS, Yasuda S, Kim SE, Yoon EL, An J, Enomoto M, Kozuka R, Chuma M, Nozaki A, Ishikawa T, Watanabe T, Atsukawa M, Arai T, Hayama K, Ishigami M, Cho YK, Ogawa E, Kim HS, Shim JJ, Uojima H, Jeong SW, Ahn SB, Takaguchi K, Senoh T, Buti M, Vargas-Accarino I E, Abe H, Takahashi H, Inoue K, Yeh ML, Dai CY, Huang JF, Huang CF, Chuang WL, Nguyen MH, Yu ML. Mortality in patients with chronic hepatitis B treated with tenofovir or entecavir: A multinational study. J Gastroenterol Hepatol. 2024 Mar 13. doi: 10.1111/jgh.16537. Epub ahead of print. PMID: 38480009.
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# Clinical Practice Guidelines for the Management of Benign Neoplasm of Liver

**Janghan Jung** *Hallym University*

The widespread use of imaging has increased the identification of incidental lesions in the liver in asymptomatic patients. Benign tumors of the liver that can be observed incidentally include the following types.

Hepatic hemangiomas are the most common primary liver tumors. Hemangiomas are present in 0.4–20% of the general population and are typically discovered incidentally during evaluation of non-specific abdominal complaints. Hemangioma can be diagnosed in all age groups but are more frequently diagnosed in women between 30–50 years. Reported female to male gender ratios are variable, ranging from as low as 1.2:1 and as high as 6:1. Hepatic hemangiomas are frequently small (< 4 cm) and solitary, although they can reach 20 cm in diameter. Focal nodular hyperplasia (FNH) accounts for the second most frequent benign tumor of the liver. There is a marked female preponderance (up to 90%), with the average age at presentation between 35 and 50 years. In most cases FNH is solitary and smaller than 5 cm. FNH are multiple in 20–30% of cases and associated with liver hemangioma in 20% of cases. Hepatocellular adenoma (HCA) is a benign neoplasm that arises de novo and may potentially have several risk factors. In select cases it may be stimulated by a metabolic or hormonal abnormality in the individual. HCA is approximately 10 times less common than FNH. HCA is frequently diagnosed in women aged 35–40 years, with a reported female:male ratio of 10:1. Nodular regenerative hyperplasia (NRH) has a prevalence of over 5.3% in individuals > 80 years old. The general population presents with NRH at a lower frequency of 2.1–2.6%. No apparent relationship is found between NRH and gender. Simple hepatic cysts are postulated to be congenital exclusions of hyperplastic bile duct rests that lack a communication with biliary ducts. They are composed of an outer layer of fibrous tissue and are lined by a cuboidal, columnar epithelium that continually produces cystic fluid. Simple hepatic cysts are usually < 1 cm and can grow up to 30 cm. Simple hepatic cysts are uncommon before the age of 40 years and have a female predilection of 1:4. Biliary cystadenomas (BCs) are congenitally derived, aberrant bile duct remnants composed of three layers of tissue. The outer layer of thick collagen and mixed connective tissue surrounds a middle layer of mesenchymal smooth muscle cells and fibroblasts, and an inner lining of cuboidal / columnar epithelium that typically secretes mucin. Grossly, BCs have a heterogeneous interior with septations forming multiple loculations filled with mucinous (95%) or serous (5%) material.

Some BCs have papillary projections that form thick, compact septa. BCs are reported to constitute up to 1–5% of total hepatic cysts, and up to 10% of cysts > 4 cm. There are no known associations with the use of oral contraceptives, although the 1:4 female predilection suggests a possible hormonal involvement.

Although the vast majority are benign liver tumors, such incidental detection of liver nodules is a source of anxiety in patients. Accordingly, this lecture aims to comprehensively review practical guidelines for benign liver tumors. By synthesizing various practical guidelines, we can come up with the following brief plans. If a typical hemangioma less than 3 cm in size is observed among hyperechoic lesions, no additional follow-up or additional tests are required. But if findings of 3 cm or more or an atypical hemangioma are observed, additional contrast enhanced imaging studies such as CT/MRI and biopsy will be performed, and measures appropriate for each diagnosis will be necessary. In the case of hypoechoic or isoechoic lesions, contrast enhanced imaging studies should be performed to make a diagnosis and, if necessary, biopsy should be performed. In the case of anechoic lesions, no additional examination or follow-up is necessary if it is a typical simple hepatic cyst. However, in the case of atypical cysts, diagnosis should be made through contrast enhanced imaging studies and, if necessary, active treatment such as surgery will be necessary.

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## Research Interests

1. Abdominal ultrasonography
2. HCC, NAFLD

## Representative Publications

1. Hepatocellular carcinoma incidence is decreasing in Korea but increasing in the very elderly. Chon YE, Park SY, Hong HP, Son D, Lee J, Yoon E, Kim SS, Ahn SB, Jeong SW, Jun DW. Clin Mol Hepatol. 2023 Jan;29(1):120-134. doi: 10.3350/cmh.2021.0395. Epub 2022 Aug 12.
2. The diagnostic value of circulating tumor DNA in hepatitis B virus induced hepatocellular carcinoma: a systematic review and meta-analysis. Young Chang, Soung Won Jeong, Jae Young Jang, Hyuksoo Eun, Young Sun Lee, Do Seon Song, Su Jong Yu, Sae Hwan Lee, Won Kim, Hyun Woong Lee, Sang Gyune Kim, Seongho Ryu, Suyeon Park. J Liver Cancer. 2022;22(2):167-177.
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# Liver Doppler: When and How to Use It?

**Soung Won Jeong** *Soonchunhyang University*

## Introduction

Doppler ultrasonography (US) is the useful modality for evaluating blood flow in major hepatic vessels including portal vein (PV), hepatic vein (HV), and hepatic artery (HA). As liver disease shows the characteristic waveforms based on each flow dynamics, the understanding of blood flow in doppler examinations is required.

## Doppler ultrasonography in portal vein, hepatic vein, and hepatic artery

### *1) Portal vein*

The normal portal venous waveform always remain above the baseline and should undulate gently. The peak portal velocity corresponds to systole, and the trough velocity corresponds to end diastole. The primary influence on variation in portal venous pressure is atrial contraction, which occurs at end diastole. Atrial contraction, toward end diastole, transmits back pressure, first through the hepatic veins, then to the hepatic sinusoids, and ultimately to the portal circulation, where forward portal venous flow is consequently decreased. In summary, the portal venous waveform is normally anterograde and phasic. Abnormal portal venous flow usually manifests in one of four ways as follows [1. Increased pulsatility (pulsatile waveform), 2. Slow portal venous flow, 3. Hepatofugal (retrograde) flow, 4. Absent (aphasic) portal venous flow]. For imaging, the patient is in a supine position and performed a breath-hold at the end of normal expiration. The mean portal vein velocity in cirrhotic patients is relatively low compared with that in healthy subjects because of increased intrahepatic vascular resistance. However, portal blood velocity and flow may differ between patients with similar portal pressures because of significant variability in portosystemic collateral patterns.[1-3] The spectral waveform is used to measure the maximum (Vmax) and minimum (Vmin) velocity of blood in the portal veins. Venous pulsatility index (VPI) defined as (Vmax – Vmin) / Vmax. In some studies, the portal VPI showed the ability to diagnose patients with significant fibrosis in NAFLD, making it an accurate noninvasive biomarker.[4,5]

### *2) Hepatic vein*

The doppler HV waveform in healthy subjects is triphasic (two negative waves and one positive), and

this pattern is the consequence of variations in the central venous pressure because of the cardiac cycle. In patients with cirrhosis, the presence of abnormal biphasic or monophasic HV waveforms has been indisputably demonstrated by a number of studies. For doppler HV examination, HV can be easily visualized along its longitudinal axis by color flow mapping at the supine position. The flow in HV displays the blue color in color flow mapping because it is away from the ultrasonic probe. Thereafter, doppler shift signals are obtained from the HV at a distance of 3–6 cm from the junction of the vein with the inferior vena cava. The monophasic waveform was associated with severe portal hypertension (hepatic venous pressure gradient,HVPG >15 mmHg) with relatively high sensitivity and specificity in cirrhotic patients who experienced variceal bleeding.[6] Assessment of damping index (DI) allows the quantification of the extent of the abnormal HV waveform (loss of pulsatility). The DI is calculated by dividing the minimum velocity by the maximum velocity of the HV waveform. DI significantly correlated with the grade of HVPG, i.e. with higher HVPG, an increase in DI was observed.[7]

### *3) Hepatic artery*

During standard doppler US examinations, arteries have a physiologic tendency to favor either a low- or a high-resistance state. Arteries that normally have low resistance in resting include the internal carotid arteries, hepatic arteries, renal arteries, and testicular arteries. The postprandial mesenteric vessels also have low resistance. Arteries that normally have high resistance in resting patients include the external carotid arteries, extremity vessels, and fasting mesenteric arteries. The most frequently used index in the hepatic arteries is the resistive index (RI), which is calculated as RI = (PSV - EDV)/(PSV); PSV = peak systolic velocity, EDV = end diastolic velocity. The HA is a low-resistance vessel, with an expected RI ranging from 0.55 to 0.7. In summary, the hepatic arterial waveform is normally pulsatile with low resistance. Liver disease may manifest in the hepatic artery as abnormally elevated (RI >0.7) or decreased (RI<0.55) resistance. Any measured RI above or below the normal range may represent disease. A high RI is not specific for liver disease; therefore, it is less meaningful as an isolated finding than is a low RI. An RI that is too high may be the result of the postprandial state, old age, or diffuse distal microvascular disease, which has a wide variety of causes including chronic liver disease due to cirrhosis or chronic hepatitis. An RI that is too low may be the result of proximal stenosis or distal vascular shunting (arteriovenous or arterioportal fistulas), as seen in severe cirrhosis; trauma (including iatrogenic injury); or Osler-Weber-Rendu syndrome.[8,9] In NAFLD, several studies have shown that HARI has a stronger relationship than portal VPI with NAFLD.[10,11] However, the effect of cirrhosis on hepatic arterial microcirculation is complex and variable. Arterial resistance has been shown to be decreased, normal, or increased in cirrhotic patients by hepatic arterial buffer response (compensatory small artery proliferation and increased numbers of arteriolar beds) and arteriovenous shunting.[12] It has been shown that HARI is not useful for diagnosing cirrhosis or predicting its severity.[12,13]

## Conclusion

The portal VPI can be measured to diagnose patients with significant fibrosis in NAFLD, although portal vein indices exhibit some limitations. Hepatic vein wave form and DI can serve as a useful adjunct in the management of patients with cirrhosis. In addition, HARI showed stronger relationship than portal VPI with NAFLD in some studies. A predictive model using these doppler parameters is expected for the useful modality to diagnose the liver disease.

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Prof. Soo Young Park is a Professor of the Department of Internal Medicine, Kyungpook National University College of Medicine and is currently holding a position of Chief of Department of Gastroenterology in Kyungpook National University Hospital.

Prof. Pakr graduated from Kyungpook National University College of Medicine with his medical degree in 1999 and completed his internship and residency at the Department of Internal Medicine at the same University Hospital.

Since 2011, Prof. Hong has been performing interventional procedures in hepatology including liver biopsy, RFA, cryotherapy and microwave ablation. Prof. Park has published over 180 papers and interests of research includes translational research, interventional oncology and clinical research. Recently he builds his carreer in artificial intelligence research combining multiple modalities.

# Case-Based Approach of RFA

**Soo Young Park** *Kyungpook National University*

Radiofrequency ablation (RFA) is an effective treatment modality in the curative treatment of early-staged hepatocellur carcinoma (HCC). Along with well-trained skill in interventional procedure, proper selection of patients for treatment indication, appropriate pre-procedural preparation, and post-treatment management will improve effectiveness of RFA, thereby improving the survival of patients with HCC.

Careful selection of patients for local ablation for HCC should be made after considering multiple factors that affects the effectiveness and safety of the treatment. These factors include tumor size and number; tumor staging; image guidance method; liver function reservoir; overall performance status and severity of underlying disease; and availability of other treatment options. An individualized approach could lead to better treatment outcomes.

Ultrasound (US) imaging guidance is most widely accepted method for the identification of the location of hepatic tumors and deploying ablation devices in real-time and this real-time assessment of the ablation area based on highly echogenic bubbles during thermal procedures is very helpful for creating optimal ablation zone. Thus, US is an effective imaging guidance technique for local percutaneous ablation. The Korean survey results revealed that 74.3% of the operators always used US as an image-guiding technique during local ablation. However, US cannot distinguish some tumors from the surrounding liver parenchyma as it may be obscured by the base of the lung or intestines or poor visibility owing to poor sonic windows. CT or fluoroscopic imaging can be used as a guiding technique in such cases to enable the procedure to be performed on tumors that are not clearly visible on US.

Under contrast enhanced ultrasound (CEUS) study, US contrast agents highlight enhancement of HCC in contrast to liver parenchyma in arterial phase. Furthermore, they can display the hemodynamic characteristics of tumors in real-time, thereby assisting in local ablation procedures under certain circumstance. Many operators perform CEUS when necessary.

There are many limitations for successful RFA. The tumor with poor conspicuity in US is the most common cause of technically. In these cases, CEUS could be to enhance the conspicuity of index tumor. If the tumor is located close to the adjacent organs, the collateral thermal injury can develop. One of

most vulnerable organs is the colon, resulting to septic peritonitis. Other organs include diaphragm, gallbladder, main bile duct. To minimize thermal injury to the gastrointestinal tract and diaphragm, we can create artificial ascites to separate the dangerous organ from the ablation zone. Artificial ascites assisted RFA is widely performed for the tumor located located below hepatic surface as artificial ascites can improve the sonic window as well as decrease the thermal injury by displacing the liver downward. To minimize thermal injury to the main bile duct during ablation, biliary cooling through a naso-biliary catherter could be tried. If the tumor is exophytic growing, it is hard to find appropriate route for RF. In these cases, It would be a better choice to take alternative treatment strategy such as TACE because the direct puncture of exophytic tumor can increase the risk of tumor seeding.

Electrodes ranging from 15–17G are commonly used for RFA, with thicker electrodes increasing the ablation range. The length of the uninsulated electrode tip determines the ablation zone, ranging from 1–3 cm, enabling the operator to adjust the ablation range by selecting the thickness and length of the active tip and the number of electrodes inserted. The electric current used ranges from 30–200 W, depending on the experience of the operator. The electrodes can be repositioned after each ablation session to perform additional ablation, if necessary. The ablation duration varies depending on the size and number of tumors.

In conclusion, RFA is the most popular non-surgical technique for treating early stage HCC because of its excellent local tumor control and safety. Treatment outcome is superior to that of PEI in terms of local tumor control and survival. Overall survival of RFA is comparable to surgical resection in a selected patients with smaller tumors. The advantages of RFA are the minimal invasiveness, favorable local tumor control effect, and promising long-term survival gain. In the future, RFA will keep its role of main stream of curative treatment of HCC as a local ablative method in the era of multi-modality treatment of HCC.

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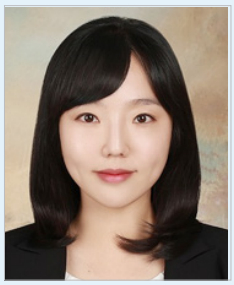

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The Korean Association for the Study of the Liver
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## Research Interests

Hepatocellular carcinoma, Liver cirrhosis, viral hepatitis, MASLD

## Representative Publications

1. Impact of metabolic factors on risk of cardiovascular disease in nondiabetic metabolic dysfunction-associated fatty liver disease. Hepatol Int 2023;17:626-635.
2. Tissue Circular RNA_0004018 and 0003570 as Novel Prognostic Biomarkers for Hepatitis B-Related Hepatocellular Carcinoma. Genes (Basel) 2023;14.
3. A multidisciplinary approach with immunotherapies for advanced hepatocellular carcinoma. J Liver Cancer 2023;23:316-329.

# Complications during Liver Intervention

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Diagnosis and treatment of HCC require several liver interventions, including liver biopsy, radiofrequency ablation (RFA), and transarterial chemoembolization (TACE), which are crucial for improving patient survival rates and quality of life. These procedures are generally safe but can lead to various complications.

Liver biopsy is performed by inserting a needle into a specific part of the liver, guided by ultrasound or CT imaging. This method provides an accurate diagnosis and detailed cellular analysis, crucial for planning treatment. The overall complication rate for liver biopsy procedures is 2.3%. The incidence of major complications is 1.3%. Major complications include bleeding, bile leakage, and peritonitis. Higher complication rates are observed in older patients and those with more severe disease. Particular caution is necessary for patients at higher risk of bleeding.

RFA uses an electrode to deliver high-frequency currents directly to the tumor site, causing thermal ablation. It is minimally invasive and effective for small tumors, generally less than 3 cm. Common complications include hepatic injuries such as liver infarction, liver abscess, bile duct injury, and biloma; hemorrhage; extrahepatic organ injuries involving the lungs, gastrointestinal tract, and gallbladder; and skin burns.

TACE aims to deliver chemotherapy directly to the liver tumor and block its blood supply to induce tumor necrosis. This method increases the effectiveness of chemotherapy while reducing systemic side effects. However, there is a higher risk of complications in patients with impaired liver function, and there is potential for post-embolization syndrome, characterized by fever, abdominal pain, and/or leukocytosis within the first few days after treatment. Additionally, hepatobiliary complications such as liver infarction, liver abscess, ischemic biliopathy, and cholecystitis, as well as access site injuries like hematoma, can occur.

Liver interventions are essential in diagnosing and treating HCC, with each method selected based on the patient's condition and tumor characteristics. Liver interventions are generally safe, but it is important to be aware of potential complications and be prepared to manage them effectively. Recognizing these complications and addressing them promptly is crucial for improving patient outcomes.

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## Research Interests

1. Basic and clinical research of non-alcoholic fatty liver disease and liver fibrosis
2. Immune cell therapy for liver cancer
3. Regenerative medicine for liver fibrosis and cirrhosis

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1. Shin SK, Oh S, Chun SK, Ahn MJ, Lee SM, Kim K, Kang H, Lee J, Shin SP, Lee J, Jung YK. Immune signature and therapeutic approach of natural killer cell in chronic liver disease and hepatocellular carcinoma. J Gastroenterol Hepatol. 2024 May 27. doi: 10.1111/jgh.16584
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# Overview in AI Applications to US Imaging

**Seung Kak Shin** *Gachon University*

Artificial intelligence (AI) has been applied in the medical fields of hepatology including prediction of the occurrence and prognosis for hepatocellular carcinoma (HCC), diagnosis or differentiating malignant from benign disease, and identifying patients at high risk for disease progression.[1,2]

One of the most significant applications of AI in ultrasound (US) imaging is automated image interpretation. AI algorithms, particularly those based on deep learning (DL), can analyze ultrasound images and provide diagnostic insights with high accuracy. Automated image interpretation reduces the workload of radiologists or physicians, enabling them to focus on more complex cases and improving overall diagnostic efficiency.[3]

Radiomics involves the extraction of quantitative features related to texture, shape, and intensity from medical images, which can then be analyzed using machine learning (ML) and DL to uncover patterns and correlations that may not be discernible to the human eye.[4] These features can provide critical insights into tissue characteristics and pathology.[5] For instance, in liver imaging, radiomics can help quantify liver texture and identify patterns associated with liver fibrosis, steatosis, and cirrhosis. Similarly, radiomics features can aid in differentiating malignant from benign lesions, thus enhancing diagnostic accuracy.[6,7]

Recently, we also developed US-based deep learning model for detection and classification of focal liver lesions. In this lecture, AI applications to US imaging will be discussed.

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DAY 2: June 28 (Fri)

# KASL Symposium 1

## Tailoring Hepatitis Management: From Antiviral Therapy to Post-Cure Surveillance

**Chairs:**

**Man-Fung Yuen** (The Univ. of Hong Kong, Hong Kong)
**Jong Eun Yeon** (Korea Univ.)

**Hyung Joon Yim**

*Korea University*

## Self Introduction

Dr. Yim graduated from Korea University Medical College in 1994. He received internship, residency, and fellowship training at Korea University Medical Center. He also had research fellowship training periods in 2005-2006 at University of Michigan, Ann Arbor, MI, USA under the supervisor, Dr. Anna Lok. He earned Ph.D. degree at Korea University Graduate School from Dr. Kwan Soo Byun.

Currently, Dr. Yim has been taking a number of roles, including the Chairman of the viral hepatitis study group under the KASL, the director of external affairs boards of KSG, and the director of research committee of KUSA.

Following are Dr. Yim's previous and current position at the Korea University Ansan Hospital.

| | |
|---|---|
| 2017.06-2021.12 | Korea University Ansan Hospital, Director of Health Promotion Center |
| 2017.034-2020.02 | Korea University Ansan Hospital, Director of Department of Internal Medicine |
| 2016.02-2018.02 | Korea University Ansan Hospital, Chief of Division of Gastroenterolgy and Hepatology |
| 2014.02-2015.06 | National Institute of Health, Bethesda, MD, USA, Visiting Professor |
| 2006.03-present | Korea University Ansan Hospital, Professor of Gastroenterolgy and Hepatology |

## Research Interests

Dr. Yim's research interests are viral hepatitis, complication of portal hypertension, alcoholic liver diseases, and hepatocellular carcinoma.

## Representative Publications

1. Yim HJ, Kang SH, Jung YK, Ahn SH, Kim W, Yang JM, Jang JY, Kweon YO, Cho YK, Kim YJ, Hong GY, Kim DJ, Sohn JH, Lee JW, Park SJ, Yim SY, Park JK, Um SH. Reduced Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Receiving Long-Term Besifovir Therapy. Cancers (Basel). 2024 Feb 22;16(5):887.
2. Yim HJ, Kang SH, Jung YK, Ahn SH, Kim W, Yang JM, Jang JY, Kweon YO, Cho YK, Kim YJ, Hong GY, Kim DJ, Sohn JH, Lee JW, Park SJ, Yim SY, Park JK, Um SH. Reduced Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Receiving Long-Term Besifovir Therapy. Cancers (Basel). 2024 Feb 22;16(5):887.
3. Yim HJ, Kim TH, Suh SJ, Yim SY, Jung YK, Seo YS, Kang SH, Kim MY, Baik SK, Kim HS, Kim YS, Park SY, Kim BI, Park JY, Heo J, Sohn JH, Heo NY, Han KH, Um SH. Response-Guided Therapy With Cefotaxime, Ceftriaxone, or Ciprofloxacin for Spontaneous Bacterial Peritonitis: A Randomized Trial: A Validation Study of 2021 AASLD Practice Guidance for SBP Am J Gastroenterol. 2023 Apr 1;118(4):654-663.
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# Standardized and Individualized Criteria for Cessation of Antiviral Therapy in Chronic Hepatitis B

**Hyung Joon Yim** *Korea University*

Nucleos(t)ide analogues (NAs) are preferred antiviral therapeutics for patients with chronic hepatitis B (CHB) due to convenience, minimal side effects, and potent antiviral activities of the drugs. However, the duration of the therapy is unclear, thus indefinite treatment is often necessary.[1] In the past, HBeAg seroconversion was considered as the endpoint of the treatment of HBeAg positive chronic hepatitis B. However, hepatitis B virus (HBV) relapsed in more than 50% of patients, and HBeAg reverted during long-term follow-up.[2,3] For HBeAg negative chronic hepatitis B, it was also previously considered to withhold NAs if HBV DNA is not detected for a long-term period. However, the relapse rate reached over 50% during 5-year follow-up periods.[4,5] Notably, relapse was rarely observed after cessation of the NAs in case of HBsAg loss.[4,6] In addition, HBsAg loss is associated with improvement of liver transplant-free survival and reduces incidence of hepatocellular carcinoma.[6,7] Hence, HBsAg loss is suggested as an optimal endpoint of antiviral therapy for chronic hepatitis B and it is considered a standard criteria for cessation of treatment in the absence of advanced liver cirrhosis .[1]

Although HBsAg loss is considered a functional cure, the frequency is very low.[6] Therefore, continuous use of antiviral agent until HBsAg loss seems to take a very long time. In recent years, efforts have been made to find an appropriate compromise, and it has been proposed to use a quantitative value of HBsAg rather than the qualitative value.[8-10] Multivariate analyses have shown that low HBsAg level at the time of cessation of NAs was the strongest parameter for free of relapse.[9,10] Furthermore, the cut-off of the HBsAg level that can predict the persistent virologic response or loss of HBsAg after cessation of therapies has been suggested as 2 log IU/mL.[8-10] A more recent multicenter study showed different HBsAg cut-off according to ethnicity; in Whites with < 1000 IU/mL and Asians with < 100 IU/mL. With these cut-offs, HBsAg loss occurred in more than 30% of the patients during follow-up.[11]

More recently, role of new biomarkers such as hepatitis B core-related antigen (HBcrAg) and HBV RNA were applied for prediction of HBV relapse after cessation of antiviral therapy.[12] A cut-off HBcrAg > 4 log U/mL was a good predictor of relapse.[13] Combination of HBcrAg < 4 log U/mL and HBsAg < 20 IU/mL was related to reduced risk of HBV relapse and increased HBsAg loss rate.[13] Also, HBsAg <100 IU/mL and negative HBV RNA at the end of therapy was a good predictor for identifying patients with low risk of off-treatment relapse in HBeAg positive patients.[14] These cut-offs may be utilized for cessation of antivi-

ral therapy as an individualized criteria.

Before the cessation of the NAs, peginterferon has been tried to achieve HBeAg seroconversion or HBsAg clearance in several clinical studies.[15,16] However this strategy was not widely spread due to the side effects and the limited efficacy. Currently, new therapeutics such as siRNA or antisense oligonucleotides are under investigation to facilitate achieving the HBsAg loss.[17,18]

In conclusion, HBsAg loss is currently the standard criteria of the NA therapy, but a decrease of HBsAg level below the certain cut-off by quantification assay would be a good alternative for finite NA therapy for individual patients. Multimodality treatment with new therapeutics is warranted for stopping NA therapy and achieving a functional cure.

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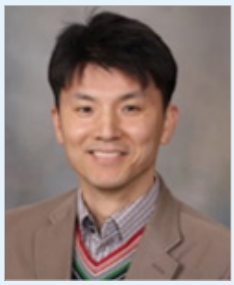

**Jeong Won Jang**

*The Catholic University of Korea*

## Self Introduction

Dr. Jang is a Professor of Internal Medicine at The Catholic University of Korea. He received his medical degree from The Catholic University of Korea, and completed his Internal Medicine Residency and Hepatology/Gastroenterology Fellowship at Seoul St. Mary's Hospital in Seoul. He has been a faculty member of The Catholic University of Korea since 2005, and has been working at affiliated hospitals, Incheon St. Mary's Hospital (2005-2012) and Seoul St. Mary's Hospital (2013 ~ present). Between 2014 and 2015, he has worked as a Visiting Scientist at Center for Basic Research in Digestive Diseases, Mayo Clinic, Minnesota, USA.

Dr. Jang is currently a board member of The Korean Liver Cancer Study Group and has served as a board member of the Korean Association for the Study of Liver Diseases. He has authored and co-authored over 150 articles and two books, and is the editorial board member of four international liver journals.

## Research Interests

Research interest: (1) HBV direct oncogenic potential and integration into the host genome, (2) the reactivation and immunology of hepatitis B, and (3) genomic alterations and biomarker discovery in liver diseases and hepatocarcinogenesis.

## Representative Publications

1. Han JW, .. Jang JW. A Machine Learning Algorithm Facilitates Prognosis Prediction and Treatment Selection for Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma. Clin Cancer Res 2024 Apr 19. doi: 10.1158/1078-0432. [Online ahead of print.]
2. Nam H, Lee J, .. Jang JW. Analysis of Immune-Related Adverse Events of Atezolizumab and Bevacizumab in Patients with Hepatocellular Carcinoma: A Multicenter Cohort Study. Liver Cancer 2024 [In press].
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4. Nam HC, Lee SW, .. Jang JW. Prediction of Hepatocellular Carcinoma by On-Therapy Response of Non-Invasive Fibrosis Markers in Chronic Hepatitis B. Am J Gastroenterol 2021;116:1657-1666.
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# Monitoring and Prevention of Reactive and Progressive Properties of Occult Hepatitis B Virus Infection

**Jeong Won Jang** *The Catholic University of Korea*

Occult hepatitis B virus (HBV) infection (OBI) is characterized by the presence of HBV DNA in the liver, with or without detectable HBV DNA in the blood, in individuals who test negative for hepatitis B surface antigen (HBsAg). OBI can be antibody positive (anti-HBc alone or with anti-HBs) (seropositive OBI) or antibody negative (seronegative OBI). This condition poses a significant challenge due to its complex biological nature and its debated virological and clinical relevance. Although asymptomatic, OBI carries risks of HBV transmission, reactivation, and liver disease progression, necessitating effective prevention and monitoring strategies. OBI can transmit HBV through blood transfusion or liver transplantation and is often linked to HBV reactivation, particularly with strong immunosuppressive therapy. Over time, OBI may contribute to chronic liver damage and cirrhosis, especially in the presence of coexisting liver diseases, and is considered a risk factor for hepatocellular carcinoma due to its pro-oncogenic properties. Monitoring strategies for OBI in high-risk patients include liver function tests, HBV DNA levels, and serological markers like anti-HBc and anti-HBs. Advanced tests for detecting low-level HBV DNA or HBsAg can help identify at-risk patients. Repeated HBV DNA quantification and anti-HBc assays are required in high-risk situations to guide appropriate medical interventions. Antiviral prophylaxis with nucleos(t)ide analogues is recommended for HBsAg-negative/anti-HBc-positive patients undergoing B cell-targeting therapies or hematopoietic stem cell transplantation to prevent HBV reactivation. Preventing and monitoring OBI require a comprehensive approach, including vaccination, rigorous screening, and advanced diagnostics. Ongoing research is vital to refine these strategies and improve outcomes for those at risk of or living with OBI.

**Tatsuya Kanto**

*National Center for Global Health and Medicine, Japan*

## Self Introduction

Tatsuya Kanto is a researcher and hepatologist/physician who expertise immunology in the field of liver diseases. He got PhD degree at Osaka University and worked as a research associate for dendritic cell biology in University of Pittsburgh, USA from 1998 to 2001. He worked as an Associate Professor in Osaka University from 2003 to 2013 and moved to National Center for Global Health and Medicine (NCGM). His current position is Director General, The Research Center for Hepatitis and Immunology, NCGM. He has been working with the Ministry of Health, Labor and Welfare to promote Hepatitis Action Plan in Japan. His field of interest is the clarification of the pathogenesis of liver disease for the development of immune-based therapy against viral hepatitis, liver cirrhosis and cancer. He has published more than 230 papers and invited review articles in peer-reviewed journals, such as Hepatology, Journal of Hepatology, Immunity, Journal of Immunology and Gastroenterology.

## Research Interests

Viral Hepatitis, Liver Cancer, Immunology, Hepatitis Countermeasures, Hepatitis Policy

## Representative Publications

1. Mori T, Yoshio S, Yoshikawa S, et al. Toll-like receptor 7 agonist, GS-986, is an immune-stimulant inducing follicular helper T cells and expanding HBs antigen-specific B cells in vitro. Liver Int, 2023 Jun;43(6):1213-1224.
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# Precision Strategy for HCC Surveillance after Curing Hepatitis C: Debates across Guidelines

**Tatsuya Kanto** *National Center for Global Health and Medicine, Japan*

Hepatitis C is one of the largest infectious diseases in the world, and viral hepatitis-related deaths are reported to eventually surpass deaths from the three major infectious diseases. The introduction of DAAs to the clinics has made HCV an eliminable disease and proved effective in preventing the development of cirrhosis and liver cancer[1]. Extrahepatic organ diseases caused by HCV infection are improved as well in some cases after attaining the SVR. However, it is reported that HCV induces epigenomic modifications in hepatocytes and immune cells and these remain in patients after HCV clearance. Such "epigenetic scarring" attracts much research attention as a mechanism of post-SVR hepatocarcinogenesis and residual dysfunction of immune cells. Liver cirrhosis, advanced liver fibrosis and metabolic factors (e.g. diabetes, alcohol consumption, obesity) are well-known risks for post-SVR HCC. It is thus desirable to stratify patients according to their liver cancer risk after achieving SVR and provide an efficient follow-up based on the tailored decision of monitoring schedules.

Since 2017, we have been developing clinical indicators (CIs) for viral hepatitis and cirrhosis care at regional core centers for the management of liver disease as a part of the Policy Research for Hepatitis Measures of the Ministry of Health, Labor and Welfare in Japan. We have performed nationwide survey using these indicators to assess the changes in the quality of care for liver disease across the country[2]. The survey regarding 29 CIs (hepatitis CIs) was conducted with 72 regional core centers from 2018 to 2023. The hepatitis CIs consisted of 6 categories (general liver disease, hepatitis C, hepatitis B, cirrhosis and subsidy systems). Based on the results of our survey over the past five years, we evaluated the trends of each indicator over time. In this survey, most of CIs in six categories showed the rate of achievement more than 80% of the relevant target values. However, six indicators, including resistance-associated substitutions testing for HCV DAA failure, failed to meet their goals. Hepatitis CIs related to SVR, such as the follow-up using fibrosis indicators (APRI/FIB-4), regular imaging tests and tumor marker measurement, were also progressing at high indicator values. These results show that post-SVR monitoring for HCC surveillance is well established in the real-word settings in Japan[3].

The duration of HCC surveillance after SVR is controversial. Both AASLD and EASL guidelines (GLs) state "indefinitely" for cirrhosis (F4), but for patients in stage F3, "indefinitely" for EASL and unspecified for AASLD, respectively. The JSH GLs does not state the required duration of post-SVR follow-up[4], and it

depends on clinical decisions by attending physicians. It is expected that new biomarkers and indicators will be developed in the future, enabling individualized surveillance methods. From the cost effectiveness points of view, it is arguably necessary to identify patient groups for whom surveillance can be discontinued at some points after SVR.

In this presentation, I will share the status of viral hepatitis treatment and follow-up based on the nationwide CI survey in Japan and discuss the future of an HCC surveillance system after SVR.

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**Maria Buti**

*University of Barcelona, Spain*

## Self Introduction

Maria Buti is Consultor Senior and Professor of Medicine at the Hospital General Universitari Valle Hebron, Barcelona. She was graduated at University of Barcelona in 1979. Dr Butí has worked in viral hepatitis for the last 25 years, particularly in diagnosis and therapy of hepatitis B and C. She has been published more than 500 papers in the field of liver disease in peer review journals such as The New England Journal of Medicine, The Lancet, Journal of Hepatology and numerous contributions to books with and Hirsch Index of 95 and the number of citations 51.405.

Dr Butí was President of the Spanish Association for the Study of Liver Diseases, and an active member of the EASL, and the AASLD and various professional societies. Currently she is the chair of public Health and Policy at European Association for the study of the liver (EASL) member of EASL governing board and associate editor of Journal of Hepatology, the journal with the highest Impact factor in liver diseases. She is one the experts of the Spanish National Plan on Hepatitis C elimination and also on the WHO guidelines for hepatitis B as well as EASL guidelines for hepatitis B and D.

## Research Interests

Hepatitis B, C , D and E

## Representative Publications

1. Buti M, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, Aguilar Schall R, Flaherty JF, Martins EB, Charuworn P, Kitrinos KM, Subramanian GM, Gane E, Marcellin P. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B infection. DIGESTIVE DISEASES AND SCIENCES: 2015 60 (5), 1457-1464
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# Experimental Drugs and Therapeutic Endpoints of Chronic Hepatitis D

**Maria Buti** *University of Barcelona, Spain*

Chronic hepatitis D virus infection is the most severe form of viral hepatitis. Antiviral treatment is urgently needed to prevent patients from developing end stage liver disease or hepatocellular carcinoma. Treatment options were limited to off-label use of pegylated interferon alfa until conditional approval of bulevirtide by the EMA (European Medicines Agency) in July 2020. Virus entry inhibitor bulevirtide has received in 2023 the final approval by the European Medicines Agency. Bulevirtide is a subcutaneous drug which appears to be safe. Its antiviral efficacy increases with treatment duration. Bulevertide can be given in monotherapy as a long-term treatment or in combination with pegINF as a finite therapy duration. Combining bulevirtide with pegIFN has the highest antiviral efficacy short-term. The prenylation inhibitor lonafarnib prevents hepatitis D virus assembly. Prenylation inhibitor lonafarnib have finished the phase 3 study with disappointing results and it is associated with dose-dependent gastrointestinal toxicity and is better used with ritonavir which increases liver lonafarnib. Combining lonafarnib/ritonavir with pegIFN has superior antiviral efficacy. Nucleic acid polymers are amphipathic oligonucleotides whose effect appears to be a consequence of phosphorothioate modification of internucleotide linkages. These compounds led to HBsAg clearance in a sizable proportion of patients. PegIFN lambda is associated with less IFN typical side effects. However the pahse 3 study was stopped for liver toxicity.

Several other antiviral compounds against hepatitis B such as siRNAs are currently investigated as monotherfapy or in combination with monoclonal antibodies and represent promising agents for the treatment of chronic HDV infection.

The goal of therapy is to achieve HDV eradication, with the very best treatment being one that would achieve clearance of both HDV and hepatitis B surface antigen (HBsAg), yielding a functional cure of both HDV and HBV. However, another goal for development drugs is more than 2 log reduction in HDV-RNA combined with normal ALT levels. This end-points is also an endpoint for long-term treatment duration in Bulevertide studies.


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June 27-29, 2024 | Walkerhill, Seoul, Korea

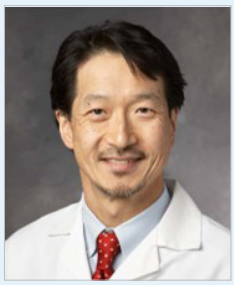
THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# Commemorative Lecture

**Chair:**

**Young Oh Kweon** (Kyungpook National Univ.)



**W. Ray Kim**

*Stanford University, USA*

## Self Introduction

W. Ray Kim, MD is Professor and Chief in the Division of Gastroenterology and Hepatology at Stanford University School of Medicine. Dr. Kim earned his medical diploma at Seoul National University. After moving to the US, he received his GI and hepatology training at Mayo Clinic College of Medicine. He rose through the ranks to be a Professor of Medicine at Mayo. In 2013, he assumed his current position at Stanford.

He is currently serving as President of the American Association for the Study of Liver Disease.

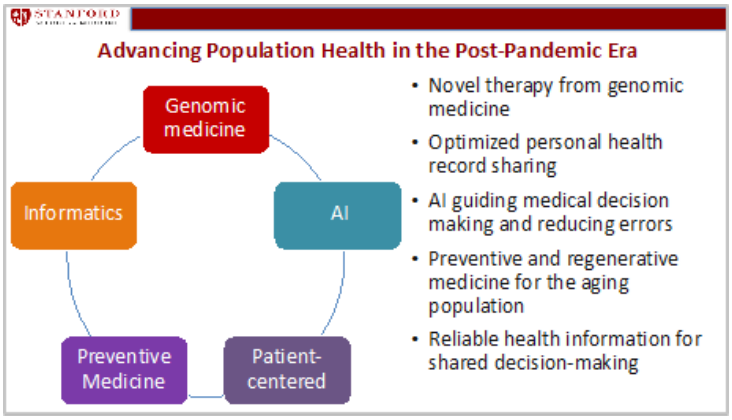
## Research Interests

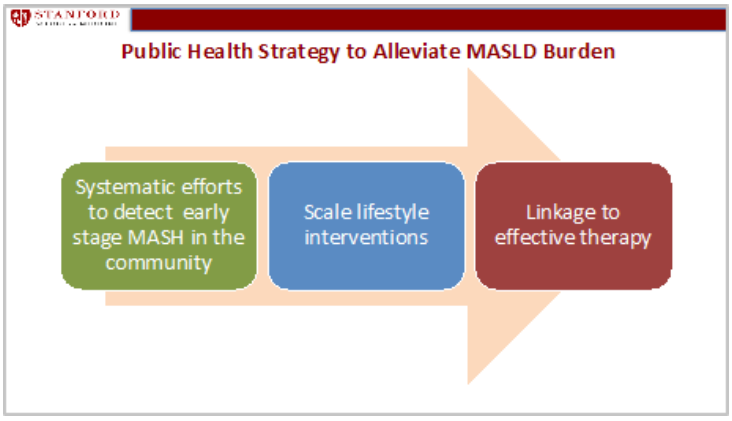
Dr. Kim's research interest has been in outcomes modeling in chronic liver disease. His research accomplishments include development of the Model for End Stage Liver Disease (MELD) and the Steatosis-Associated Fibrosis Estimator (SAFE) score. His research has produced >250 original publications to date with an h-index of >90.

# The Journey of a Hepatologist

**W. Ray Kim** *Stanford University, USA*

The COVID-19 pandemic brought numerous fundamental changes in health care. It clearly had an enormous impact on mortality, morbidity and direct and indirect healthcare costs; however, it also prompted and accelerated innovations in bioscience and medical care. Figure 1 illustrates some of those examples, including genomic medicine, artificial intelligence and medical informatics, leading to strong emphases on patient-centered care and preventive medicine to improve overall health outcomes on the population level.



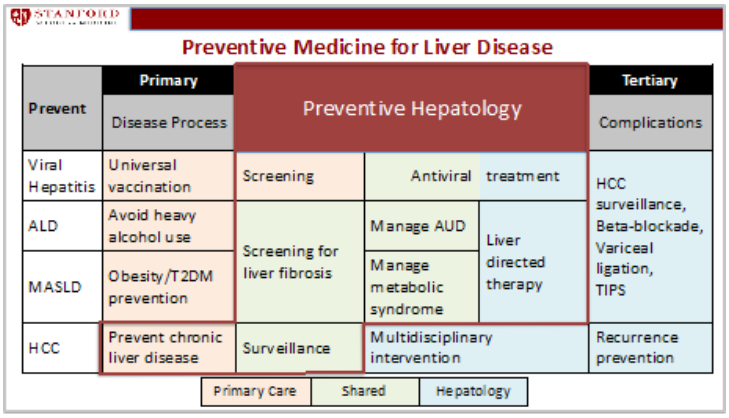




The public health impact of chronic liver disease has been increasing globally including Asia and the US. Figure 2 represents a plan by which the burden of major liver diseases such as metabolic dysfunction-associated liver disease (MASLD) may be reduced by public health interventions. Long before liver directed therapy is contemplated, coordinated efforts to detect early-stage disease are needed on the community level. For MASLD, a consequence of overwhelmingly prevalent metabolic conditions amenable to lifestyle changes, systemic, widespread interventions to address obesity and metabolic dysfunction are essential.

In fact, preventive medicine is a key necessary ingredient for the control of liver disease on the population level. In Figure 3, strategic interventions may be developed for specific liver disease etiologies, which require leadership and collaboration among generalists in primary care and specialists in

hepatology. A prerequisite for such an approach is a functioning healthcare delivery system, promoting partnership between the generalist and specialist.

As we look forward to the future in which the worldwide burden of liver disease is mitigated by preventive efforts on all levels, advancing global leadership among Asian physicians will make a critical difference. Concerted efforts to build leadership capacity among young hepatologists should start with development of essential leadership abilities and incorporate skills to harness individual personality traits and tranform cultural expecations and norms to effective leadership qualities.




THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# KASL-AASLD Joint Symposium

## HCC Evolution: Understanding Risks and Therapeutic Approaches

**Chairs:**

**W. Ray Kim** (Stanford Univ., USA)
**Si Hyun Bae** (The Catholic Univ. of Korea)

**Ju Hyun Shim**

*University of Ulsan*

## Self Introduction

### *Employment*

Professor,
Department of Gastroenterology, Asan Medical Center, Seoul, Korea

### *Post Graduate Training*

| | |
|---|---|
| 2020.03- | Professor, Dept of Gastroenterology & Liver Center, Asan Medical Center |
| 2015.03-2020.02 | Associate Professor, Dept of Gastroenterology & Liver Center, Asan Medical Center |
| 2010.03-2015.02 | Assistant Professor, Dept of Gastroenterology & Liver Center, Asan Medical Center |
| 2008.03-2010.02 | Fellowship, Dept of Gastroenterology, Asan Medical Center |
| 2007.03-2008.02 | Public Health Doctor, National Cancer Center, Goyang, Korea |
| 2001.03-2005.02 | Residency, Seoul National University Hospital, Seoul, Korea |
| 2000.03-2001.02 | Internship, Seoul National University Hospital, Seoul, Korea |

### *Education*

| | |
|---|---|
| 2009.03-2011.02 | Doctor's degree, University of Ulsan College of Medicine, Seoul, Korea |
| 2003.03-2005.02 | Master's degree, College of Medicine, Seoul National University, Seoul, Korea |

# Temporal and Spatial Cancer Evolution of Dysplastic Nodules in the Liver

**Ju Hyun Shim** *University of Ulsan*

Hepatocellular carcinoma (HCC) is a prevalent and aggressive malignancy that imposes a significant burden on global health. With over 900,000 cases annually, HCC ranks as the sixth most common cancer worldwide and is the third leading cause of cancer-related deaths. The high prevalence of hepatitis B, hepatitis C, chronic alcohol consumption, and hepatic steatosis contributes to the development of chronic liver diseases and subsequently HCC, through a multistep and long-term process.

HCC often arises in the context of liver cirrhosis, typically preceded by precancerous lesions known as dysplastic nodules (DNs), which include low-grade dysplastic nodules (LGDNs) and high-grade dysplastic nodules (HGDNs). DNs are identifiable upon gross examination of liver specimens, exhibiting distinct nodular lesions with cytological and/or architectural atypia in histology. However, the presence of DNs alone is insufficient for an HCC diagnosis. Annual progression rates to HCC are reported at 20% for patients with HGDNs and 10% for those with LGDNs, underscoring HGDNs as precursors of HCC. Notably, some HGDNs contain malignant foci, referred to as "nodule-in-nodule," definitively indicating the precursor role of the surrounding HGDN to the HCC within.

Genetic alterations are believed to trigger the progression from HGDN to early HCC. Despite this, the genetic differences between HGDN and HCC remain not fully understood. Spatial transcriptomics, which provides a comprehensive view of transcriptional heterogeneity within the tumor microenvironment, has been mainly utilized to investigate the spatial heterogeneity of various cancers and their evolutionary process. In my talk, I will introduce the results of spatial transcriptomics by lesion to investigate nodule-in-nodule samples in order to identify key factors and mechanisms driving liver cancer development.

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**Yujin Hoshida**

*University of Texas Southwestern Medical Center, USA*

## Self Introduction

Dr. Hoshida is Professor of Internal Medicine, Director of Liver Tumor Translational Research, H. Ray and Paula Calvert Chair in Gastroenterology Oncology, CPRIT Scholar in Cancer Research at Division of Digestive & Liver Diseases and Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center.

He is a physician scientist trained in clinical hepatology, diagnostic pathology, diagnostic and interventional radiology, biostatistics, genomics, and systems biology. His research focus is liver cancer risk prediction and chemoprevention in patients with chronic liver diseases. He has led multiple international collaborative projects on cancer risk prediction, disease classification, and chemoprevention target discovery and clinical trials with support from NIH, DOD, European Union, and other funding agencies. He also serves for study sections at NIH, DOD, and other national/international agencies. He serves as Associate Editor of Hepatology, served as editorial board member for Gastroenterology and other GI and cancer journals.

## Research Interests

Liver cancer, Cirrhosis, Biomarker, Chemoprevention, Disease classification

## Representative Publications

1. Fujiwara N, Kubota N, Crouchet E, Koneru B, Marquez CA, Jajoriya AK, Panda G, Qian T, Zhu S, Goossens N, Wang X, Liang S, Zhong Z, Lewis S, Taouli B, Schwartz ME, Fiel MI, Singal AG, Marrero JA, Fobar AJ, Parikh ND, Raman I, Li QZ, Taguri M, Ono A, Aikata H, Nakahara T, Nakagawa H, Matsushita Y, Tateishi R, Koike K, Kobayashi M, Higashi T, Nakagawa S, Yamashita YI, Beppu T, Baba H, Kumada H, Chayama K, Baumert TF, Hoshida Y. Molecular signatures of long-term hepatocellular carcinoma risk in nonalcoholic fatty liver disease. Sci Transl Med. 2022 Jun 22;14(650):eabo4474.
2. Qian T, Fujiwara N, Koneru B, Ono A, Kubota N, Jajoriya AK, Tung MG, Crouchet E, Song W, Marquez CA, Panda G, Hoshida A, Lewis C, Yopp AC, Rich N, Singal AG, Nakagawa S, Goossens N, Higashi T, Koh AP, Bian CB, Hoshida H, Tabrizian P, Gunasekaran G, Florman SS, Schwartz ME, Hiotis S, Nakahara T, Aikata H, Murakami E, Beppu T, Baba H, Warren A, Bhatia S, Kobayashi M, Kumada H, Rwema SH, Nair V, Patel M, Kim-Schulze S, Corey KE, O'Leary JG, Klintmalm GB, Thomas DL, Dibas M, Rodriguez G, Zhang B, Friedman SL, Baumert TF, Fuchs BC, Chayama K, Zhu S, Chung RT, Hoshida Y. Molecular signature predictive of long-term liver fibrosis progression to inform anti-fibrotic drug development. Gastroenterology. 2022.
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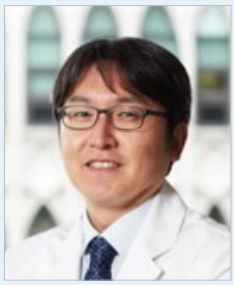
# Genomic and Epigenetic Clues to Persistent Risk of HCC after Curing Hepatitis C

**Yujin Hoshida** *University of Texas Southwestern Medical Center, USA*

With the widespread use of DAAs, the number of patients who achieve SVR has been sharply increasing. While the subsequent HCC incidence is significantly reduced after SVR, the risk of HCC development persists for up to a decade in a subset of patients. Thus, it is critical to elucidate the underlying molecular aberrations to identify at-risk patients and to develop interventions to mitigate this risk. Studies have suggested the involvement of various genetic and epigenetic mechanisms that may drive post-SVR hepatocarcinogenesis. Candidate molecular targets with potential clinical relevance will be overviewed.



**Do Young Kim**

*Yonsei University*

## Self Introduction

Do Young Kim is now a professor of Internal Medicine at Yonsei University College of Medicine, Seoul, Korea, and a hepatologist in the Severance Hospital where he has been a faculty member since 2007. He graduated Yonsei University at 1996, and completed training course in Severance Hospital from 1996 to 2001. He studied proteomics and microRNA in hepatocellular carcinoma (HCC) at Fred Hutchinson Cancer Research Center as a research associate between 2011 and 2012.

## Research Interests

- HCC
- Hepatitis C

## Representative Publications

1. Cho KJ, …, Kim DY. [Corresponding author] YAP/TAZ suppress drug penetration into hepatocellular carcinoma via stromal activation. Hepatology 2021;74:2605-2621.
2. Kim BH, …, Kim DY. [Corresponding author] Expert consensus on the management of adverse events in patients receiving lenvatinib for hepatocellular carcinoma. J Gastroenterol Hepatol [Epub ahead of print].
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# Clinical and Subclinical Risk Factors of Non-Viral HCC: Is It Preventable?

**Do Young Kim** *Yonsei University*

The etiology and epidemiology of hepatocellular carcinoma (HCC) is changing over the world. While the incidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) related HCC is decreasing, non-viral HCC including non-alcoholic fatty liver disease (NAFLD) associated HCC is increasingly prevalent even in Asian countries.

Diabetes mellitus (DM) or obesity is important risk factor of non-viral HCC. Although the precise mechanism underlying hepatocarcinogenesis in these metabolic diseases are imcompletely understood, multi-steps from simple steatosis to non-alcoholic steatohepatitis (NASH) finally resulting hepatic fibrosis would be involved.

Recently, promising anti-obesity and anti-diabetic drugs such as glucagon like peptide-1 (GLP-1) receptor agonist and sodium/glucose cotransporter 2 (SGLT 2) inhibitor exert potent efficacy in patients with metabolic diseases. Also, the impact of these drugs on the development of HCC is being studied in patients with obesity or diabetes.

In this talk, the major clinical and subclinical risk factors in non-viral HCC will be introduced and discussed.

**Grace L. Su**

*University of Michigan, USA*

## Self Introduction

Undergraduate- Yale University
Medical School- University of Chicago, Pritzker School of Medicine
GI Fellowship- University of Pittsburgh
President-Elect, American Association for the Study of Liver Diseases
Professor of Medicine and Surgery, University of Michigan Medical School
Associate Chief, Medicine Service, VA Ann Arbor Healthcare System
Chief, Gastroenterology and Hepatology, VA Ann Arbor Healthcare System
Director of the Morphomics analysis group, University of Michigan

## Research Interests

- Analytic Morphomics for the diagnosis, treatment, and risk stratification of chronic liver disease.
- Novel methods for delivering subspecialty care and improving access.
- Digital biomarkers in cancer

## Representative Publications

1. Su GL, Zhang P, Belancourt PX, Youles B, Enchakalody B, Perumalswami P, Waljee A, Saini S. Incorporation of quantitative imaging data using artificial intelligence improves risk prediction in veterans with liver disease. Hepatology. 2023 Dec 29. doi: 10.1097/HEP.0000000000000750. Epub ahead of print. PMID: 38156985.
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# Guidelines and Evidence-Based Recommendations for Sequential Systemic Therapy of HCC

**Grace L. Su** *University of Michigan, USA*

The framework of systemic therapy for hepatocellular carcinoma (HCC) has experienced significant evolution recently, thanks to breakthroughs in therapeutic options. Sorafenib, the foundational multi-kinase inhibitor, had long held the monopoly as the first-line systemic therapy for advanced HCC based on the seminal SHARP trial,[1] which demonstrated significant gains in overall and progression-free survival compared to placebo. However, the landscape remained unchanged for a considerable duration as no subsequent trials showed superior efficacy over sorafenib in the first-line setting, until the approval of lenvatinib. This shift came with the REFLECT trial's outcomes, presenting non-inferiority to sorafenib and offering an alternative first-line treatment option.[2]

Nonetheless, the paradigm saw a more dramatic alteration with the introduction of immune checkpoint inhibitors, alone or in combination with anti-VEGF/VEGFR antibodies. Paradigm-shifting studies such as the IMbrave150 trial positioned atezolizumab plus bevacizumab as a new benchmark in first-line HCC management due to its superiority over sorafenib, followed by impressive results from the HIMALAYA study evaluating the efficacy of durvalumab in combination with tremelimumab. These regimens have quickly been integrated into the latest clinical guidelines.[3-6]

With the increasing arsenal of systemic therapies, sequential therapy has become an emerging paradigm in hepatocellular carcinoma (HCC) treatment. There is a significant knowledge gap with second line treatments after immunotherapy as most trials were performed with sorafenib as the comparator. This lecture will seek to review the current guidelines and evidence-based recommendations for the utilization of sequential systemic therapy.

As we navigate these emerging territories, new horizons in neoadjuvant and adjuvant approaches that integrate systemic therapy with loco-regional interventions and surgery are unfolding. These advancements promise to revolutionize the therapeutic landscape further. The focus of this presentation will be on current guidelines and evidence-based practices, with the goal of optimizing and personalizing the management of HCC in light of these novel paradigms. The talk emphasized the critical need for a dynamic application of knowledge in tailoring treatment sequences based on individual patient factors and the latest evidence to provide the best possible outcomes.

## References


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2. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-73.
3. Korean Liver Cancer A, National Cancer Center K. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. J Liver Cancer. 2023;23(1):1-120.
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6. Su GL, Altayar O, O'Shea R, Shah R, Estfan B, Wenzell C, et al. AGA Clinical Practice Guideline on Systemic Therapy for Hepatocellular Carcinoma. Gastroenterology. 2022;162(3):920-34.

THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# KASL Symposium 2

## Comprehensive Approaches in Alcohol-Related Liver Disease: From Genetics to Therapy

**Chairs:**

**Ki Tae Suk** (Hallym Univ.)
**Won Hyeok Choe** (Konkuk Univ.)

**Jean-Charles Nault**

*Sorbonne Université, France*

## Self Introduction

Jean-Charles Nault received is MD and PhD from Paris Descartes University. He is currently professor in the liver unit of the Avicenne Hospital in Bobigny, France with a high priority on early detection of primary liver tumors and on therapeutic innovation. He is also an active member of the laboratory of "functional genomics of solid tumors" in Cordeliers Research Center.

## Research Interests

His research is dedicated to translational research, in particular the identification of new driver genes in hepatocellular adenoma and hepatocellular carcinoma, of new therapeutic targets and of the molecular determinants of hepatocellular carcinoma's prognosis. He has discovered the role of mutation in the promoter of telomerase in liver carcinogenesis, identified a new virus responsible (adeno associated virus type 2) of development of HCC on normal liver and new therapeutic targets in advanced HCC.

## Representative Publications

1. Molecular-based targeted therapies in patients with hepatocellular carcinoma and hepato-cholangiocarcinoma refractory to atezolizumab/bevacizumab. Limousin W, Laurent-Puig P, Ziol M, Ganne-Carrié N, Nahon P, Ait-Omar A, Seror O, Sidali S, Campani C, Blanc P, Lermine A, Marisa L, Zucman-Rossi J, Nault JC. J Hepatol. 2023 Dec;79(6):1450-1458.
2. Body weight changes and duration of estrogen exposure modulate the evolution of hepatocellular adenomas after contraception discontinuation. Demory A, Péron JM, Calderaro J, Selves J, Mokrane FZ, Amaddeo G, Paradis V, Ziol M, Sutter O, Blaise L, Ganne-Carrié N, Vilgrain V, Cauchy F, Zucman-Rossi J, Ronot M, Nault JC. Hepatology. 2023 Feb 1;77(2):430-442.
3. Systemic Treatments with Tyrosine Kinase Inhibitor and Platinum-Based Chemotherapy in Patients with Unresectable or Metastatic Hepatocholangiocarcinoma. Gigante E, Hobeika C, Le Bail B, Paradis V, Tougeron D, Lequoy M, Bouattour M, Blanc JF, Ganne-Carrié N, Tran H, Hollande C, Allaire M, Amaddeo G, Regnault H, Vigneron P, Ronot M, Elkrief L, Verset G, Trepo E, Zaanan A, Ziol M, Ningarhari M, Calderaro J, Edeline J, Nault JC. Liver Cancer. 2022 Jun 14;11(5):460-473
4. Percutaneous radiofrequency ablation for hepatocellular carcinoma developed on non-alcoholic fatty liver disease. Nguyen N, Rode A, Trillaud H, Aubé C, Manichon AF, Hocquelet A, Paisant A, Dao T, Nahon P, Ganne-Carrié N, Blaise L, Cauchy F, Sutter O, Séror O, Nault JC. Liver Int. 2021 Dec 11.
5. Clinical impact of genomic diversity from early to advanced hepatocellular carcinoma. Nault JC, Martin Y, Caruso S, Hirsch TZ, Bayard Q, Calderaro J, Charpy C, Copie-Bergman C, Ziol M, Bioulac-Sage P, Couchy G, Blanc JF, Nahon P, Amaddeo G, Ganne-Carrie N, Morcrette G, Chiche L, Duvoux C, Faivre S, Laurent A, Imbeaud S, Rebouissou S, Llovet J, Seror O, Letouzé E, Zucman-Rossi J. Hepatology. 2020 Jun 17.

# Genetic Vulnerabilities of Alcohol-Related Hepatitis and HCC in the East and West

**Jean-Charles Nault** *Sorbonne Université, France*

Genome-wide association studies (GWAS) in the field of liver diseases have revealed previously unknown pathogenic loci and generated new biological hypotheses. Various genetic variants have been implicated in predisposing individuals to alcohol-related liver disease (ALD). Notable among these are variants in genes such as PNPLA3, TM6SF2, MBOAT7, and HSD17B13, which have shown strong associations with ALD-related outcomes including cirrhosis, and hepatocellular carcinoma. These genes influence liver fat metabolism thereby contributing to disease pathogenesis. More recently, single nucleotide polymorphisms in TERT and WNT3A/WNT9A were involved in the development of alcohol related HCC without promoting the development of the underlying liver disease. However, individual genetic loci may have limited predictive value in clinical practice. Therefore, additional genome-wide studies (to identify frequent variants) and exome-wide studies (to identify rare variants) are necessary to identify new variants associated with cancer to better explain the heritability of these phenotypes. This approach warrants also evaluation in prospective cohorts to enhance the treatment of ALD.

**Pierre-Emmanuel Rautou**

*Université Paris-Cité, France*

## Self Introduction

### *Titles and Diplomas*

| | |
|---|---|
| 2015 | Research direction accreditation ("Habilitation de direction de recherches") |
| 2011.06 | PhD. in vascular biology, summa cum laude, University of Paris 7, Paris, France. Supervisor: Dr. Chantal M. Boulanger |
| 2009 | Completion of clinical training in Hepatology, Paris Hospitals, France |
| 2008.06 | Doctor of Medicine (MD), summa cum laude, University of Paris 7. Hepatology. Supervisor: Prof. Dominique Valla |
| 2007 | Master Degree. University of Paris 7, Paris, France |

### *Current Positions*

| | |
|---|---|
| 2019-present | Inserm team leader, Inserm UMR-1149, Research Center on Inflammation, Paris https://www.rautoulab.com/ |
| 2016-present | Full Professor, Hepatology Department, Beaujon Hospital, Clichy, and Université Paris-Cité |
| 2012-present | Head of the Liver Hemodynamic Laboratory, Beaujon Hospital, Clichy, France http://hupnvs.aphp.fr/hemodynamique-hepatique/ |

## Representative Publications

1. Vion AC*, Kheloufi M*, Hammoutene A, Poisson J, Lasselin J, Devue C, Pic I, Dupont N, Busse J, Starke K, Lafaurie-Janvore J, Barakatf AI, Loyer X, Souyri M, Viollet B, Julia P, Tedgui A, Codogno P, Boulanger CM*, Rautou PE*. Autophagy is required for endothelial cell alignment and atheroprotection under physiological blood flow. Proc Natl Acad Sci U S A. 2017 Oct 10;114(41):E8675-E8684 (OA; impact factor 2022: 11.1)
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3. Hammoutene A, Biquard L, Lasselin J, Kheloufi M, Tanguy M, Vion AC, Mérian J, Colnot N, Loyer X, Tedgui A, Codogno P, Lotersztajn S, Paradis V, Boulanger CM, Rautou PE. A defect in endothelial autophagy occurs in patients with nonalcoholic steatohepatitis and promotes inflammation and fibrosis. J Hepatol 2020 Mar;72(3):528-538. (OA; impact factor 2022: 25.7)
4. Poisson J, Tanguy M, Davy H, Camara F, El Mdawar MB, Kheloufi M, Dagher T, Devue C, Lasselin J, Plessier A, Merchant S, Blanc-Brude O, Souyri M, Mougenot N, Dingli F, Loew D, Hatem SN, James C, Villeval JL, Boulanger CM, Rautou PE. Erythrocyte-derived microvesicles induce arterial spasms in JAK2V617F myeloproliferative neoplasm. J Clin Invest. 2020 May 1;130(5):2630-2643. (OA; impact factor 2022: 15.9)
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# Biomarkers in Alcohol-Related Liver Diseases

**Pierre-Emmanuel Rautou** *Université Paris-Cité, France*

**Young Kul Jung**

*Korea University*

## Self Introduction

### *Education*

| | | |
|---|---|---|
| 1999.02 | Korea University, College of Medicine, Seoul, Korea | Bachelor |
| 2004.02 | Korea University, Graduate School of Medicine, Seoul, Korea | Master |
| 2012.02 | Korea University, Graduate School of Medicine, Seoul, Korea | PhD |

### *Professional Experience*

| | | |
|---|---|---|
| 1999-2004 | Intern, Resident | Korea University Medical Center, Seoul, Korea |
| 2004-2007 | Public health service | Ganghwa Public health center, Incheon. |
| 2007-2009 | Fellowship | Guro Hospital Korea University Medical Center, Seoul, Korea |
| 2009-2014 | Assistant Professor | Gachon University of Medicine and Science Gil Medical Center |
| 2014-2019 | Associate Professor | Ansan Hospital Korea University Medical Center, |
| 2018 -2019 | Visiting Professor | Kyoto University iPS cell research center |
| 2019-present | Professor | Ansan Hospital Korea University Medical Center, |

## Research Interests

- Cirrhosis, viral hepatitis, alcoholic hepatitis, ACLF, HCC
- iPS cell, regeneration medicine

## Representative Publications

1. Yim HJ, Kim TH, Suh SJ, Yim SY, Jung YK, Seo YS, Kang SH, Kim MY, Baik SK, Kim HS, Kim YS, Park SY, Kim BI, Park JY, Heo J, Sohn JH, Heo NY, Han KH, Um SH. Response-Guided Therapy With Cefotaxime, Ceftriaxone, or Ciprofloxacin for Spontaneous Bacterial Peritonitis: A Randomized Trial: A Validation Study of 2021 AASLD Practice Guidance for SBP. Am J Gastroenterol. 2023 Apr 1;118(4):654-663.
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4. Shin SK, Oh S, Chun SK, Ahn MJ, Lee SM, Kim K, Kang H, Lee J, Shin SP, Lee J, Jung YK. Immune signature and therapeutic approach of natural killer cell in chronic liver disease and hepatocellular carcinoma. J Gastroenterol Hepatol. 2024 May 27.
5. Kim TH, Jung YK, Yim HJ. Correspondence on Letter regarding "Impacts of muscle mass dynamics on prognosis of outpatients with cirrhosis". Clin Mol Hepatol. 2023 Jan;29(1):173-175.

# Principles of and Debates on Indication and Duration of Use of Corticosteroids in Severe Alcoholic Hepatitis

**Young Kul Jung** *Korea University*

Severe alcoholic hepatitis (SAH) remains a formidable challenge in hepatology, with a high mortality rate despite therapeutic advancements. SAH is characterized by a profound inflammatory response driven by chronic alcohol consumption. Ethanol metabolism produces acetaldehyde and reactive oxygen species (ROS), which induce hepatocyte damage and apoptosis. This cellular injury triggers the activation of Kupffer cells and hepatic stellate cells, leading to the release of pro-inflammatory cytokines such as TNF-$\alpha$, IL-1$\beta$, and IL-6. Advanced molecular studies have identified the involvement of danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) in perpetuating the inflammatory milieu. Additionally, recent research has highlighted the role of gut-liver axis dysbiosis and microbial translocation in exacerbating liver inflammation.

Corticosteroids, predominantly prednisolone, have been the cornerstone of SAH treatment due to their potent anti-inflammatory and immunosuppressive properties. The anti-inflammatory effects are mediated through the inhibition of NF-$\kappa$B and suppression of cytokine synthesis. Clinical trials, including the landmark STOPAH trial, have demonstrated improved 28-day survival rates with corticosteroid therapy. However, the benefit in long-term survival remains equivocal, with recent meta-analyses indicating no significant mortality reduction at 90 days and one year.

Despite their efficacy, corticosteroids pose substantial risks, particularly in immunocompromised SAH patients. The risk of severe infections, such as spontaneous bacterial peritonitis and sepsis, is markedly elevated, necessitating vigilant monitoring. Additionally, corticosteroid therapy can precipitate hyperglycemia, gastrointestinal bleeding, and muscle wasting. The identification of non-responders, using tools such as the Lille model, is critical in optimizing patient outcomes and minimizing unnecessary exposure to steroid-associated complications.

The limitations of corticosteroids have catalyzed the exploration of alternative therapeutic avenues. Pentoxifylline, an anti-TNF agent, has shown some benefit in reducing renal complications but lacks consistent efficacy in improving overall survival. Biological agents targeting specific cytokines, such as anakinra (IL-1 receptor antagonist) and infliximab (anti-TNF antibody), are under investigation. Additionally, the modulation of the gut microbiota with probiotics and fecal microbiota transplantation represents a novel therapeutic strategy aimed at restoring intestinal barrier integrity and reducing systemic

inflammation.

While corticosteroids remain the mainstay of therapy for SAH, their use is fraught with challenges and limited by significant adverse effects. The quest for more effective and safer treatments is ongoing, with promising research focusing on targeted biological therapies and gut-liver axis modulation. A multidisciplinary approach, incorporating early diagnosis, stringent infection control, and consideration of liver transplantation, is paramount in improving the prognosis of SAH patients.

**Keywords:** Severe alcoholic hepatitis, corticosteroids, prednisolone, inflammatory pathways, gut-liver axis, biological therapies, Lille model.


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**Julie K. Heimbach**

*Mayo Clinic, USA*

## Self Introduction

Dr. Julie Heimbach is a Professor of Surgery and the Director of the William von Liebig Center for Transplantation at Mayo Clinic in Rochester, Minnesota. She is an abdominal transplant surgeon who has focused on living donor liver transplantation and liver transplantation for hilar cholangiocarcinoma. Dr. Heimbach has also been very active in organ allocation policy development at the national level, having served as the chair of the OPTN/UNOS Liver Committee. She has also served on the board of the American Society of Transplant Surgeons and the governing board of the AASLD. In addition, Dr. Heimbach serves as an Associate Editor of the Journal of Hepatology.

## Research Interests

- Liver transplant for malignancy
- Obesity and liver transplant
- Living donor liver transplantation

## Representative Publications

1. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, Jou JH, Kulik LM, Agopian VG, Marrero JA, Mendiratta-Lala M, Brown DB, Rilling WS, Goyal L, Wei AC, Taddei TH.Hepatology. 2023 Dec 1;78(6):1922-1965. doi: 10.1097/HEP.0000000000000466. Epub 2023 May 22.PMID: 37199193
2. Liver Transplantation as a New Standard of Care in Patients With Perihilar Cholangiocarcinoma? Results From an International Benchmark Study. Breuer E, Mueller M, Doyle MB, Yang L, Darwish Murad S, Anwar IJ, Merani S, Limkemann A, Jeddou H, Kim SC, López-López V, Nassar A, Hoogwater FJH, Vibert E, De Oliveira ML, Cherqui D, Porte RJ, Magliocca JF, Fischer L, Fondevila C, Zieniewicz K, Ramírez P, Foley DP, Boudjema K, Schenk AD, Langnas AN, Knechtle S, Polak WG, Taner CB, Chapman WC, Rosen CB, Gores GJ, Dutkowski P, Heimbach JK, Clavien PA
3. MELD 3.0: The Model for End-Stage Liver Disease Updated for the Modern Era. Kim WR, Mannalithara A, Heimbach JK, Kamath PS, Asrani SK, Biggins SW, Wood NL, Gentry SE, Kwong AJ.Gastroenterology. 2021 Dec;161(6):1887-1895.e4. doi: 10.1053/j.gastro.2021.08.050. Epub 2021 Sep 3.
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# Optimal Timing of Liver Transplantation in Severe Alcoholic Hepatitis

**Julie K. Heimbach** *Mayo Clinic, USA*

Alcohol associated liver disease is currently the most common indication for liver transplantation (LT) in the United States, surpassing HCV in 2016 and remaining ahead of MASLD, despite the obesity epidemic.[1] In 2022, 37.5% of adult liver transplant waitlisted candidates in 2022 had alcohol-associated liver disease; this represents a 66.0% increase since 2012. In Asia, as in all regions of the world, alcohol-related liver disease is also on the rise. The standard approach to LT in the setting of alcohol-associated liver disease has been under significant scrutiny following the landmark publication by Mathurin et al in 2011 demonstrating the survival benefit of LT for selected patients with alcohol-associated hepatitis (AH) without a prolonged period of abstinence.[2] However, key questions remain, given that a proportion of patients will successfully recover from AH without LT and uncertainty remains regarding the optimal way to selection patients to optimize survival while reducing the risk of selection patients who will have sustained relapse of alcohol use post LT. Expanding indications for LT must always be carefully considered, given the continued critical shortage of available grafts for LT and the risk of waitlist mortality (death or removal from the list for being too ill to undergo LT). In the most recent analysis of waitlist outcomes in the United States, about 30% of patients listed for LT and followed for 3 years die or are removed from the list, primarily due to becoming too sick for transplant.[1]

The spectrum of alcohol-related liver disease ranges from hepatic steatosis and steatohepatitis to cirrhosis, and patients with cirrhosis are at further risk of the development of hepatocellular carcinoma, in addition to the risks of decompensated liver disease.[3] Acute alcohol associated hepatitis (AH) is a clinical syndrome which includes jaundice, prolonged INR, hypoalbuminemia, with mild-to-moderate elevation of transaminases and usually accompanies by fatigue, anorexia, and nausea, and this can develop potentially at all stated of alcohol-related liver disease.[4,5] Patients with high-risk alcohol consumption ( >28 g alcohol per day for women and >42 g alcohol per day for men in the past 12 months) have significant risk of developing steatosis. In fact, 80-90% of patient undergoing biopsy with high-risk alcohol consumption develop steatosis within 3-8 days and of these, nearly 30% develop AH.[3] A recent analysis by Melenger et al has demonstrated that alcohol associated liver disease is on the rise in the United States, and similar increase in the burden of liver disease due to alcohol has been reported world-wide.[6,7] With the onset of the COVID-19 pandemic, mortality due to cirrhosis increased markedly (quarterly age-stan-

dardized all-cause mortality due to ALD increased during the pandemic at a rate of 11.2% versus a pre-COVID increase of 1.1% per quarter), mainly attributable to ALD.[8]

In addition to being the most common indication for listing for liver transplant, alcohol-associated liver disease was the primary diagnosis for 40.8% of transplants performed in the US in 2022.[1] Additionally, the percentage of centers in the US which currently offer LT for acute alcohol related hepatitis is now 85% compared to 0% in 2005.[9] Since the initial report by Mathiern et al, there have been 4 additional studies of LT for AH, ranging from a single center series of 9 patients reported by Im et al in 2014, to 147 patients reported in a multi-center US study by Lee et al.[12-16] Post-transplant outcomes in all four series, including the most recent multi-center report from Italy (N=16), were identical to those transplanted with prolonged (> 6 months) of abstinence, and far superior to survival for patients with AH who did not undergo LT. Selection tools to identify which patients have a low chance of spontaneous recovery and therefore are best served with LT are needed, and recent data have shown that MELD score may be the best predictor of mortality, compared to the Maddrey discriminant function score.[17-19] Additionally, identifying which patients are at risk of sustained, high-dose alcohol use post LT are needed, given this cohort is at risk for mortality post LT. Determining whether interventions, such as incorporating addiction treatment into the early post-transplant phase may also improve survival is also an essential area of future study.[19-24]

In summary, rates of ALD and AH are rising, and LT is being increasing utilized at a treatment strategy. The outcomes reported so far, including relatively small multi-center, case-control studies, are favorable, when comparing post LT survival outcomes for patients undergoing LT for AH with a brief period of abstinence to those undergoing LT for ALD with prolonged abstinence. Key questions related to the optimal selection of patients with low likelihood of spontaneous recovery and a low chance of return to harmful drinking post LT are still being developed.

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2. Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365(19):1790–1800.
3. Simonetto DA, Shah VH, Kamath PS. Outpatient management of alcohol-related liver disease. Lancet Gastroenterol Hepatol. 2020 May;5(5):485-493. doi: 10.1016/S2468-1253(19)30415-7. PMID: 32277901; PMCID: PMC8074849.
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18. Lee BP, Vittinghoff E, Hsu C, Han H, Therapondos G, Fix OK, et al. Predicting low risk for sustained alcohol use after early liver transplant for acute alcoholic hepatitis: the sustained alcohol use post-liver transplant score. Hepatology 2019;69(4):1477–1487.
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20. Carrique L, Quance J, Tan A, Abbey S, Sales I, Lilly L, et al. Results of early transplantation for alcohol-related cirrhosis: integrated addiction treatment with low rate of relapse. Gastroenterology 2021;161(6):1896–1906.e2.
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# Meet the Editor

## CMH & AASLD Journals

**Chairs:**

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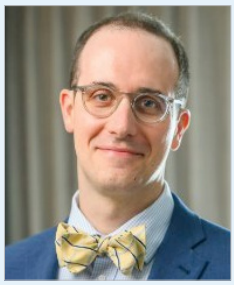


## Elliot B. Tapper

*University of Michigan, USA*


## Self Introduction

Elliot Tapper MD is Associate Professor at University of Michigan where he directs the Michigan Cirrhosis Program. He is editor-in-chief of Hepatology Communications. His research program is focused on improving quality of life in patients with cirrhosis. He trained in medicine, gastroenterology, and transplant hepatology at Beth Israel Deaconness in Boston.

## Research Interests

1. Patient reported outcomes. Research seeks to define unmet needs and deploy clinical trials which improve symptom burden.
2. Hepatic encephalopathy. Previous work defined epidemiology, developed risk scores for incident HE, and created models to improve hospital readmissions. Currently leading a multicenter trial of primary prophylaxis of HE.

## Representative Publications


1. Tapper EB, Parikh ND. Diagnosis and Management of Cirrhosis and Its Complications: A Review. Jama. 2023 May 9;329(18):1589-602.
2. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. bmj. 2018 Jul 18;362.
3. Tapper EB, Lok AS. Use of liver imaging and biopsy in clinical practice. New England Journal of Medicine. 2017 Aug 24;377(8):756-68.
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# Tips for Getting an Acceptance from AASLD Journals

**Elliot B. Tapper** *University of Michigan, USA*

Elliot Tapper MD, editor-in-chief of *Hepatology Communications* and editorial board member for *Hepatology*, provides advice on how to get accepted to an AASLD journal. The core lessons he will impart relate to presentation and design. He will give advice on how to prepare a paper that 'looks the part' and inspires interest in the topic. This involves structuring the introduction and discussion carefully, designing thoughtful tables, and beautiful figures. He gives advice on specific study designs which carry pitfalls that result in desk-rejection.

**Won Kim**

*Seoul National University*

## Self Introduction

I graduated from Seoul National University College of Medicine in 1997 and earned a master's degree in 2002 and a doctoral degree in 2005 at the same College. I'm currently an Associate Professor of the department of internal medicine of Seoul National University College of Medicine.

1) President (2023- ), KASL-Alcohol-Related Problem Study Group
2) Director of Research & Project committee (2021-2023) & Director of Publication committee (2024-), Korean Association of Study of Liver disease (KASL)
3) Director of Research (2018-2019), Korean Liver Cancer Association (KLCA)
4) Editor-in-chief (2024- ), Clinical Molecular Hepatology
5) EASL-AASLD NAFLD Nomenclature Revision Committee member

## Research Interests

- Integrated multi-omics approach for precision medicine in MASLD
- New drugs and biomarkers discovery for MASLD

## Representative Publications

1. Outcomes of Various Classes of Oral Antidiabetic Drugs on Nonalcoholic Fatty Liver Disease. JAMA Internal Medicine. (2024)
2. Metabolic dysfunction-associated steatotic liver disease increases the risk of incident cardiovascular disease: a nationwide cohort study. EClinicalMedicine (2023)
3. Myosteatosis, but not sarcopenia, predisposes NAFLD subjects to early steatohepatitis and fibrosis progression. Clin. Gastroenterol. Hepatol (2023)
4. Disease-specific eQTL screening reveals an anti-fibrotic effect of AGXT2 in non-alcoholic fatty liver disease. Journal of Hepatology (2021)
5. Distinct signatures of gut microbiome and metabolites associated with significant fibrosis in non-obese NAFLD. Nature Communication (2020)

# Tips for Getting an Acceptance from CMH

**Won Kim** *Seoul National University*


## Yujin Hoshida

*University of Texas Southwestern Medical Center, USA*


## Self Introduction

Dr. Hoshida is Professor of Internal Medicine, Director of Liver Tumor Translational Research, H. Ray and Paula Calvert Chair in Gastroenterology Oncology, CPRIT Scholar in Cancer Research at Division of Digestive & Liver Diseases and Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center.

He is a physician scientist trained in clinical hepatology, diagnostic pathology, diagnostic and interventional radiology, biostatistics, genomics, and systems biology. His research focus is liver cancer risk prediction and chemoprevention in patients with chronic liver diseases. He has led multiple international collaborative projects on cancer risk prediction, disease classification, and chemoprevention target discovery and clinical trials with support from NIH, DOD, European Union, and other funding agencies. He also serves for study sections at NIH, DOD, and other national/international agencies. He serves as Associate Editor of Hepatology, served as editorial board member for Gastroenterology and other GI and cancer journals.

## Research Interests

Liver cancer, Cirrhosis, Biomarker, Chemoprevention, Disease classification

## Representative Publications


1. Fujiwara N, Kubota N, Crouchet E, Koneru B, Marquez CA, Jajoriya AK, Panda G, Qian T, Zhu S, Goossens N, Wang X, Liang S, Zhong Z, Lewis S, Taouli B, Schwartz ME, Fiel MI, Singal AG, Marrero JA, Fobar AJ, Parikh ND, Raman I, Li QZ, Taguri M, Ono A, Aikata H, Nakahara T, Nakagawa H, Matsushita Y, Tateishi R, Koike K, Kobayashi M, Higashi T, Nakagawa S, Yamashita YI, Beppu T, Baba H, Kumada H, Chayama K, Baumert TF, Hoshida Y. Molecular signatures of long-term hepatocellular carcinoma risk in nonalcoholic fatty liver disease. Sci Transl Med. 2022 Jun 22;14(650):eabo4474.
2. Qian T, Fujiwara N, Koneru B, Ono A, Kubota N, Jajoriya AK, Tung MG, Crouchet E, Song W, Marquez CA, Panda G, Hoshida A, Lewis C, Yopp AC, Rich N, Singal AG, Nakagawa S, Goossens N, Higashi T, Koh AP, Bian CB, Hoshida H, Tabrizian P, Gunasekaran G, Florman SS, Schwartz ME, Hiotis S, Nakahara T, Aikata H, Murakami E, Beppu T, Baba H, Warren A, Bhatia S, Kobayashi M, Kumada H, Rwema SH, Nair V, Patel M, Kim-Schulze S, Corey KE, O'Leary JG, Klintmalm GB, Thomas DL, Dibas M, Rodriguez G, Zhang B, Friedman SL, Baumert TF, Fuchs BC, Chayama K, Zhu S, Chung RT, Hoshida Y. Molecular signature predictive of long-term liver fibrosis progression to inform anti-fibrotic drug development. Gastroenterology. 2022.
3. Crouchet E, Bandiera S, Fujiwara N, Li S, El Saghire H, Fernández-Vaquero M, Riedl T, Sun X, Hirschfield H, Jühling F, Zhu S, Roehlen N, Ponsolles C, Heydmann L, Saviano A, Qian T, Venkatesh A, Lupberger J, Verrier ER, Sojoodi M, Oudot MA, Duong FHT, Masia R, Wei L, Thumann C, Durand SC, González-Motos V, Heide D, Hetzer J, Nakagawa S, Ono A, Song WM, Higashi T, Sanchez R, Kim RS, Bian CB, Kiani K, Croonenborghs T, Subramanian A, Chung RT, Straub BK, Schuppan D, Ankavay M, Cocquerel L, Schaeffer E, Goossens N, Koh AP, Mahajan M, Nair VD, Gunasekaran G, Schwartz ME, Bardeesy N, Shalek AK, Rozenblatt-Rosen O, Regev A, Felli E, Pessaux P, Tanabe KK, Heikenwälder M, Schuster C, Pochet N, Zeisel MB, Fuchs BC, Hoshida Y, Baumert TF. A human liver cell-based system modeling a clinical prognostic liver signature for therapeutic discovery. Nat Commun. 2021 Sep 17;12(1):5525.
4. Fujiwara N, Kobayashi M, Fobar AJ, Hoshida A, Marquez CA, Koneru B, Panda G, Taguri M, Qiang T, Raman I, Li Q, Hoshida H, Sezaki H, Kumada H, Tateishi R, Yokoo T, Yopp AC, Chung RT, Fuchs BC, Baumert TF, Marrero JA, Parikh ND, Zhu S, Singal AG, Hoshida Y. A blood-based prognostic liver secretome signature and long-term hepatocellular carcinoma risk in advanced liver fibrosis. Med. 2021;2(7):836-850.

# Hepatology Editor's Picks: Noticeable Publications in 2023-2024

**Yujin Hoshida** *University of Texas Southwestern Medical Center, USA*

Korea is an important source of high-quality publications in Hepatology. We will overview noticeable publications from Korean institutions in 2023-2024 on diverse topics, including liver pathophysiology, viral hepatitis, liver cancer, and steatohepatitis.

**Seung Up Kim**

*Yonsei University*

## Self Introduction

Seung Up Kim, M.D., Ph.D. is a Professor of Yonsei University College of Medicine. He is a member of Korean Association of the Study of the Liver and Korean Liver Cancer Study Group. He has more than 300 SCI(E) original, peer reviewed publications as primary or corresponding author. He is a invited referee for more than 10 SCI(E) journals including Gastroenterology, Hepatology, Journal of Hepatology, etc. His major research interests include viral hepatitis, liver fibrosis, and liver cancer. He acts as an Editor-in-Chief, Emeritus of Clinical and Molecular Hepatology, an Editorial Board member of Clinical Gastroenterology and Hepatology, an academic editor of PLoS One, an Associate editor of World Journal of Gastroenterology, and Associate Editor of Gut and Liverr, and editorial board member of Journal of Gastroenterology and Hepatology.

## Research Interests

'Molecular biology of hepatitis B virus', 'Immunogenetics of hepatitis virus infection', 'Noninvasive assessment of liver fibrosis', and 'Diagnosis and treatment for viral hepatitis and liver cancer'.

## Representative Publications

1. Kim SU (Co-first), Seo YS, Lee HA, Kim MN, Lee YR, Lee HW, Park JY, Kim DY, Ahn SH, Han KH, Hwang SG, Rim KS, Um SH, Tak WY, Kweon YO, Kim BK, Park SY. A multi-center study of entecavir vs. tenofovir on prognosis of treatment-naïve chronic hepatitis B in the Republic of Korea. J Hepatol 2019; 71: 456-464.
2. Lee YH, Jung KS, Kim SU, Yoon HJ, Yun YJ, Lee BW, Kang ES, Han KH, Cha BS. Sarcopenia is associated with NAFLD independently of obesity and insulin resistance: nationwide surveys (KNHANES 2008-2011). J Hepatol 2015;63:486-93.
3. Kim BK, Kim SU (Corresponding), Kim KA, Chung YE, Kim MJ, Park MS, Park JY, Kim DY, Ahn SH, Kim MD, Park SI, Won JY, Lee DY, Han KH. Complete response at the first chemoembolization is still the robust predictor for favorable outcome in hepatocellular carcinoma. J Hepatol 2015 2015; 62: 1304-1310.
4. Kim MN, Kim SU (Co-corresponding), Kim BK, Park JY, Kim DY, Ahn SH, Song KJ, Park YN, Han KH. Increased risk of hepatocellular carcinoma in chronic hepatitis B patients with transient elastography-defined subclinical cirrhosis. Hepatology 2015 2015; 61: 1851-1959.

# CMH Editor's Picks: Noticeable Publications in 2023-2024

**Seung Up Kim** *Yonsei University*

Clinical and Molecular Hepatology (CMH) has entered a new era of its journey at the end of 2019, when CMH was indexed in the Science Citation Index Expanded (SCIE). The recent impact factor increased up to 3.9 in 2020 and is estimated around 8.9 in 2022. CMH has taken another leap toward a premier journal in the field of hepatology, a home for quality research, reviews, and commentaries.

During 2023-2024, CMH has published around 30 interesting papers. Of these, I will introduce three papers with a high number of citations, entitled "Hepatocellular carcinoma incidence is decreasing in Korea but increasing in the very elderly" by Chon et al., "Global burden of primary liver cancer and its association with underlying aetiologies, sociodemographic status, and sex differences from 1990-2019: A DALY=based analysis of the Global Burden of Disease 2019 study" by Choi et al., and "Assessing the performance of ChatGPT in answering questions regarding cirrhosis and hepatocellular carcinoma" by Yeo et al.


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June 27-29, 2024 | Walkerhill, Seoul, Korea

THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# KLCA Symposium 1

## Cutting-Edge Translational Tools for HCC

**Chairs:**

**Hyunchul Rhim** (Sungkyunkwan Univ.)
**Young Nyun Park** (Yonsei Univ.)

**Junil Kim**

*Soongsil University*

## Self Introduction

Prof. Junil Kim is a Professor of the Department of Bioinformatics, Soongsil University College of Natural Science and is currently holding a position of Director of the Institute for Biological Systems.

Prof. Kim graduated from Interdisciplinary Graduate Program in Bioinformatics at Seoul National University with his master's degree in 2008 and received his Ph.D. degree in systems biology from Korea Advanced Institute of Sciencd and Technology (KAIST) in 2014.

Since 2022, Prof. Kim has been taking a number of roles, including committee member of the Korean Society of Bioinformatics (2022-Present), the Korean Society of Molecular and Cellular Biology (2022-2023), Korea Genome Organization (2023-Present), and the Korean Society for Biochemistry and Molecular Biology (2024-Present).

## Research Interests

- Piecing together jigsaw puzzle and single cell dynamics in time-space continuum using AI.
- Evolutionary design principle of biomolecular regulatory networks
- Predicting phenotypes of the bio-organisms from genomic information and their interactions

## Representative Publications

1. Junil Kim*, Michaela Mrugala Rothová*, Esha Madan*, et al., "Neighbor-specific gene expression revealed from physically interacting cells during mouse embryonic development", PNAS (IF: 12.777), Vol. 120, Issue 2, e2205371120, 3 Jan. 2023 (*co-fist author)
2. Dongha Kim*, Junil Kim*, Young Suk Yu, Yong Ryoul Kim, Sung-hee Baek, Kyoung-Jae Won, "Systemic approaches using single cell transcriptome reveal that C/EBP $\gamma$ regulates autophagy under amino acid starved condition", Nucleic Acids Research (IF: 19.160), Vol. 50, Issue 13, 7298-7309, 22 July 2022 (*co-fist author)
3. Guangzheng Weng, Junil Kim †, and Kyoung Jae Won †, "VeTra: a tool for trajectory inference based on RNA velocity", Bioinformatics (IF: 6.931), Vol. 37, Issue 20, p3509-3513, 15 Oct. 2021. ( † co-corresponding author)
4. Junil Kim, Simon T. Jakobsen, Kedar N. Natarajan, Kyoung Jae Won, "TENET: Gene network reconstruction using transfer entropy reveals key regulatory factors from single cell transcriptomic data", Nucleic Acids Research (IF: 19.160), Vol. 49, Issue 1, e1-e1, 11 Jan. 2021.
5. Junil Kim, Diana E. Stanescu, and Kyoung Jae Won, "CellBIC: Bimodality-based top-down clustering of single-cell RNA sequencing data reveals hierarchical structure of the cell type", Nucleic Acids Research (IF: 19.160), Vol. 46, Issue 21, e124, 30 Nov. 2018.

# Current and Future Perspective of Spatial Omics in HCC

**Junil Kim** *Soongsil University*

Many clinical researchers have developed targeted therapy and immunotherapy for the case of advanced stage of hepatocellular carcinoma (HCC). However, the molecular mechanisms of HCC development still need to be investigated to improve the response rate of those therapies. In this talk, I will present two of my recent studies.

First, I will present a single nucleus RNA sequencing analysis obtained from HCC patients. The snRNA-seq data were generated from biopsy samples of six patients with Barcelona Clinic Liver Cancer (BCLC) advanced C stage. I first found that the gene expression heterogeneity in hepatocytes were mainly dissected by vascular invasion. To identify the key regulators of malignant progression of hepatocytes, I applied TENET, a gene regulatory network (GRN) inference tool based on pseudotime-ordered single cell expression. TENET predicts that two novel transcription factors, which regulates many targets and regulates each other. This finding was comprehensively validated by overexpression and knockdown of those two regulators in various HCC cell lines. This study suggested that GRN analysis with single cell transcriptomics may provide new therapeutic targets for HCC.

My second presentation topic is Pan-cancer spatial transcriptomics analysis obtained from publicly available large-scale datasets including single cell RNAseq of 2,054,005 cells and Visium of 228 slides and 539,664 spots. These large and multimodal datasets were integrated using variational inference-based deep learning method. The integrative analysis of these two types of transcriptomics data enables to compare multiple cancer types in terms of spatial correlation of various cell types including cancer cell, T cells, B cell, myeloid cells, fibroblasts and endothelial cells. Spatial correlation of cell types in HCC showed that T cells, B cells and myeloid cells were co-localized compared to other cancer types. These Pan-cancer spatial transcriptomics approach enables to compare differential spatial compositions of cancer cells and TMEs in multiple cancer types.

**Sun Young Yim**

*Korea University*

## Self Introduction

### *Education*

| | |
|---|---|
| 2001-2007 | Korea University College of Medicine (Bachelor's degree) |
| 2007-2011 | Korea University College of Medicine Department of Internal Medicine (Master's degree) |
| 2012-2015 | Korea University College of Medicine Department of Internal Medicine (PhD) |

### *Professional Experience*

| | |
|---|---|
| 2008-2012 | Residency: Department of Internal Medicine, Korea University Hospital |
| 2012-2016 | Clinical instructor: Division of Gastroenterology and Hepatology, Korea University Hospital |
| 2016-2018 | Research Fellow, MD Anderson Cancer Center, Houston |
| 2017-2020 | Clinical assistant professor: Division of Gastroenterology and Hepatology, Korea University Hospital |
| 2020-2021 | Assistant professor: Division of Gastroenterology and Hepatology, Korea University Hospital |
| 2021- | Associate professor: Division of Gastroenterology and Hepatology, Korea University Hospital |

## Research Interests

Hepatocellular carcinoma, HCC biomarker, Hepatitis B

## Representative Publications

1. Yim SY, Ha J, Karagozian R. Mortality and Liver-Related Events in Lean Versus Non-Lean Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2023.
2. Yim SY, Lee SH, Jeong YS, et al. Consensus subtypes of hepatocellular carcinoma associated with clinical outcomes and genomic phenotypes. Hepatology 2022.
3. Yim SY, Chun HS, Lee JS, et al. Transarterial Radioembolization for Unresectable Hepatocellular Carcinoma: Real-Life Efficacy and Safety Analysis of Korean Patients. Cancers 2022;14(2):385
4. Yim SY, Jung J, Park S, Jang Y, Lee SH, Jeong YS, et al. Clinical Significance of Glycolytic Metabolic Activity in Hepatocellular Carcinoma. Cancers (Basel). 2022;15(1)
5. Yim SY, Lee JS. An Overview of the Genomic Characterization of Hepatocellular Carcinoma. J Hepatocell Carcinoma 2021;8:1077-1088.
6. Yim SY, Kang SH, Shin JH, et al. Low ARID1A Expression is Associated with Poor Prognosis in Hepatocellular Carcinoma. Cells 2020;9.
7. Yim SY, Seo CG, Um SH, et al. Survival according to recurrence patterns after resection for transplantable hepatocellular carcinoma in HBV endemic area: Appraisal of liver transplantation strategy. Clin Res Hepatol Gastroenterol 2020;44:532-542.

# Precision Medicine for Designing Future Clinical Trials for Immuno-Oncology Treatment

**Sun Young Yim** *Korea University*

The huge change in HCC landscape is not only associated with the incorporation of several treatments but also to the improvement in the management of underlying liver disease. Both factors, and the questioned dogma about HCC development in patients cured of hepatitis C and the incremental incidence in patients with noncirrhotic HCC adding complexity for the HCC clinical trial design as well as clinical decision-making process. One of the main considerations when designing a clinical trial are to select a well-defined target patient population (i.e., inclusion and exclusion criteria) and prespecify clear endpoints (primary and secondary) and a data analysis plan.

Stratification is critical in randomized studies to warrant balanced comparisons. Unlike other solid tumors such as breast, lung, colon, and others, where therapeutic decisions are driven by an understanding of a patient given molecular features, in HCC "one-size-fits-all" is still the usual approach to patients. This applies to all therapies so far accepted in guidelines, except for ramucirumab. Biomarkers provide the distinct possibility of supplementing existing anatomic and/or pathologic information to provide a more accurate assessment of prognosis (to be used for patient stratification) and/or to identify individuals who are more likely to respond to specific therapy (predictive of response). Molecular studies comparing the pretreatment and posttreatment tissue provide an opportunity to understand the effects of therapeutics on relevant pathways in the tumor. These studies can provide critical information that could guide a patient selection strategy in conventional efficacy studies.

Primary endpoint OS can be confounded by sequential therapies received by patients after tumor progression. Also, in the case of immune checkpoint inhibitors, tumor response can have a longer lag time compared to other molecular therapies and can even mimic progression shortly after treatment initiation (i.e., pseudoprogression). This has led to the development of immune-related response criteria, which require confirmation of progression at least 4 weeks after progressive disease is first documented. The lack of a reliable correlation between PFS and OS could be due to tumor cell plasticity. Tumor cell plasticity is involved in the clinical behavior of the cancer (indolent vs. aggressive), acquisition of tumor heterogeneity, and the sensitivity/response to treatment. The imbalance in the proportion of "indolent" versus "aggressive HCC" between arms or the underestimation/overestimation of HCC behavior at baseline in single-arm clinical trial could be associated with clinical trial failure or under-overestima-

tion of trial results.

Precision medicine has exploited next-generation sequencing and matched targeted therapy/immunotherapy deployment in effort to overcome the above limitations in clinical trials. Clinical trials have evolved, shifting from tumor type-centered to gene-directed and histology-agnostic trials, with innovative adaptive designs and personalized combination treatment strategies tailored to individual biomarker profiles. Tumor and liquid biopsy genomic profiling and transcriptomic, immunomic, and proteomic interrogation are applied to optimize therapy. However, biomarker guided therapeutic trials in HCC are lacking compared to other cancers. The attempts of incorporating biomarkers in clinical care and trials will be discussed.


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**Hyungjin Rhee**

*Yonsei University*

## Self Introduction

Prof. Hyungjin Rhee is an associate professor in the Department of Radiology at Yonsei University College of Medicine. Prof. Rhee graduated from Yonsei University College of Medicine with his medical degree in 2007 and completed his internship and residency at the Department of Radiology at Severance Hospital, receiving his diploma in Radiology in 2012.

He obtained his Ph.D. in the physician-scientist program from the Department of Pathology at Yonsei University College of Medicine by 2017. Since 2018, he has been serving as a faculty member in the Department of Radiology at Yonsei University College of Medicine.

## Research Interests

Imaging diagnosis and characterization of primary liver cancers

## Representative Publications

1. Molecular and radiopathologic spectrum between HCC and intrahepatic cholangiocarcinoma, Hepatology. 2023 Jan 1;77(1):92-108
2. Ezetimibe combination therapy with statin for non-alcoholic fatty liver disease: an open-label randomized controlled trial (ESSENTIAL study), BMC Med. 2022 Mar 21;20(1):93.
3. Gadoxetic acid-enhanced MRI of macrotrabecular-massive hepatocellular carcinoma and its prognostic implications, J Hepatol. 2021 Jan;74(1):109-121
4. Gross type of hepatocellular carcinoma reflects the tumor hypoxia, fibrosis, and stemness-related marker expression, Hepatol Int. 2020 Mar;14(2):239-248
5. Dynamics of genomic, epigenomic, and transcriptomic aberrations during stepwise hepatocarcinogenesis, Cancer Res. 2019 Nov 1;79(21):5500-5512

# Radiogenomics and Radiomics in Liver Cancers

**Hyungjin Rhee** *Yonsei University*

The radiomics is emerging methods of quantitative analysis of medical imaging. The radiomic analysis consists of several steps: (1) image acquisition and preprocessing, (2) identification and segmentation of the volume (or region) of interest, (3) extraction of descriptive features from the volume (or region), (4) model development to predict outcomes. Radiomic features include semantic feature and agnostic feature, with agnostic features further categorized as shape, first-order, second-order, and higher-order features. An increasing number of publications indicate that radiomic analysis is beneficial for characterizing and prognosticating liver cancers. However, the complexity of radiomic analysis and the labor-intensive segmentation process limit its clinical feasibility. Additionally, radiomic features are heavily influenced by the imaging equipment and acquisition parameters, leading to reproducibility issues in radiomic analysis.

Recently, the use of deep learning, including convolutional neural networks, in tumor imaging analysis has been increasing. Unlike radiomics, deep learning automates both feature extraction and model development. Therefore, deep learning often requires a larger number of cases for training compared to radiomics, and models created with deep learning tend to be difficult to interpret, akin to a black box. On the other hand, radiomics uses human-defined features, allowing for effective models to be created with relatively fewer cases, and the resulting models can often be interpreted. Recently, to enhance the performance of radiomics models, various filters have been frequently applied during radiomic feature extraction, and deep learning has been used when creating radiomics models, leading to the creation of radiomic models that are difficult to interpret.

Radiogenomics is a field of study that investigates the correlations between semantic or agnostic imaging features and genomic characteristics. Through radiogenomics, it is possible to analyze the tumor character and heterogeneity using voxel-by-voxel analysis of the entire tumor. This approach is expected to be less invasive and more cost-effective for determining genetic characteristics than traditional genetic analysis. There have been reports of attempts to use radiogenomics to identify IDH1 and ATRX mutations, MGMT methylation in glioma or glioblastoma, and EGFR and KRAS mutations and ALK rearrangement in lung cancer. However, there are few published papers in liver cancer, and little is known about its clinical utility.

**Hye Won Lee**

*Yonsei University*

## Self Introduction

Dr. Hye Won Lee graduated from Ewha Womans University College of Medicine and received her Ph.D. degree from Yonsei University College of Medicine. She completed her residency and fellowship at Severance hospital, where she continues to work as an Assistant Professor at Yonsei University College of Medicine. She visited the Chinese University of Hong Kong as a vising scholar for two years. She has continued to conduct her research on chronic liver disease, especially NASH and HBV. She has won several awards and grants from various institutions and academies. She is recognized as one of the outstanding young physicians in Korea.

## Research Interests

- Chronic liver disease including NASH and viral hepatitis
- Hepatocellular carcinoma

## Representative Publications

1. H Lin, HW Lee, TCF Yip, E Tsochatzis, S Petta, et al. Vibration-controlled transient Elastography scores to predict liver-related events in Steatotic liver disease. JAMA. 2024 Mar 21:e241447.
2. Lee HW, Kim KH, Ahn SH, Lee HC, Choi J. The associations between fibrosis changes and liver-related events in patients with metabolic dysfunction-associated steatotic liver disease. Liver Int. 2024 Mar 15.
3. Lee HW, Yip TC, Wong VW, Lim YS, Chan HL, Ahn SH, Wong GL, Choi J. CAMP-B score predicts the risk of hepatocellular carcinoma in patients with chronic hepatitis B after HBsAg seroclearance. J Gastroenterol Hepatol. 2024 Feb 15
4. Lee HW, Kim H, Park T, Park SY, Chon YE, Seo YS, Lee JS, Park JY, Kim DY, Ahn SH, Kim BK, Kim SU. A machine learning model for predicting hepatocellular carcinoma risk in patients with chronic hepatitis B. Liver Int. 2023 Aug;43(8):1813-1821.
5. Lee DH, Jee JJ, Lee YS, Kim DY, Bang JY, Lee HW, Koh H, Bae SH. Fecal microbiota transplantation improves hepatic fibro-inflammation via regulating oxidative stress in experimental NASH. Dig Liver Dis. 2023 Nov;55(11):1521-1532

# Discovery of Blood Biomarkers for Immune-Based Treatments of HCC: Protein vs. cfDNA/snRNA

**Hye Won Lee** *Yonsei University*

Biomarkers, objectively measurable indicators of biological processes or responses to therapeutic interventions, are important in the management of hepatocellular carcinoma (HCC). Traditionally, the serum $\alpha$-fetoprotein (AFP) level is used as a biomarker for HCC, aiding in detection, surveillance, diagnosis, and prognosis assessment. In the IMbrave150 and CheckMate-040, underscore the evolving landscape of biomarker utilization in HCC treatment. In IMbrave150 trial, the serum AFP response at 6 weeks was investigated as a potential surrogate biomarker for prognosis in patients receiving atezolizumab plus bevacizumab. Similarly, a baseline AFP level $< 400$ $\mu$g/L in CheckMate-040 was correlated with prolonged overall survival compared to a level $\geq 400$ $\mu$g/L, highlighting the prognostic value of AFP.

Liquid biopsy—which encompasses circulating tumor cells, circulating cell-free tumor DNA (ctDNA), and extracellular vesicles—shows promise as an alternative biomarker strategy in HCC. Notably, ctDNA profiling in patients treated with atezolizumab plus bevacizumab revealed associations between a high cell-free DNA (cfDNA) level and a diminished response rate and reduced survival. Additionally, the presence of TERT promoter mutations in ctDNA was correlated with improved overall survival, indicating that ctDNA has potential as a prognostic biomarker.

Beyond protein-based biomarkers, non-coding RNAs (ncRNAs), which constitute a significant portion of the transcriptome, have much potential. However, although ncRNAs, which include small nuclear RNAs (snRNAs), show promise as biomarkers, their prevalence and utility in HCC, particularly in the era of immunotherapy, are unclear. Single-nucleus RNA sequencing data collected from a longitudinal series of patient samples are needed to provide insight into mechanisms of treatment resistance and enable real-time assessment of the need for treatment modifications. Single-nucleus RNA sequencing (snRNA-seq) allows characterization of the cellular microenvironment. The discovery of disease-associated hepatocytes (daHeps) as a highly predictive biomarker will facilitate the triage of patients with liver disease into low and high-risk groups. However, data are lacking on snRNA as a biomarker in patients with HCC; therefore, further investigations are warranted.

In conclusion, although traditional protein biomarkers such as AFP are valuable, the emergence of liq-

uid biopsy and other techniques will facilitate the discovery of biomarkers of HCC. Further research is needed to evaluate the clinical utility and integration of these biomarkers into routine practice, which has the potential to revolutionize the management of HCC in the era of immune-based therapies.

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THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# KLCA-JLCA Joint Symposium

## Paving the Way Forward: Novel Immunotherapy Strategies for HCC

**Chairs:**

**Jong Young Choi** (The Catholic Univ. of Korea)
**Michiie Sakamoto** (Keio Univ., Japan)

**Yong-Han Paik**

*Sungkyunkwan University*

## Self Introduction

| | |
|---|---|
| 1988-1994 | Yonsei University College of Medicine |
| 1995-1999 | Resident, Dept of Medicine, Severance Hospital, Seoul, Korea |
| 1999-2001 | Clinical Fellow, Dept of Medicine, Yonsei University College of Medicine, Seoul, Korea |
| 2001-2003 | Research Fellow, Dept of Medicine, University of North Carolina at Chapel Hill, NC, USA |
| 2003-2011 | Associate Professor, Dept of Medicine, Yonsei University College of Medicine, Seoul, Korea |
| 2008-2010 | Research Scientist, Dept of Medicine, University of California, San Diego, CA, USA |
| 2015-Present | Professor, Dept of Medicine, Sungkyunkwan University College of Medicine, Seoul, Korea |
| 2023-Present | Director, Liver Cancer Center, Samsung Medical Center |

## Research Interests

The goal of my research is to investigate the molecular mechanism and novel therapeutics for hepatic fibrosis and liver cancer. Specifically, I have been studying the mechanism of liver cancer development from the background fibrotic liver, exploring the interaction between nonparenchymal cells including hepatic stellate cells present in fibrotic liver and malignant transformation of hepatocytes.

## Representative Publications

1. Sohn W, Kang DB, Kang M, Guallar E, Cho JH, Paik YH. Impact of nationwide hepatocellular carcinoma surveillance on the prognosis in patients with chronic liver disease. Clin Mol Hepatol 2022 Oct;28(4):851-863.
2. Hong JY, Cho HJ, Sa JK, Liu X, Ha SY, Lee T, Kim H, Kang W, Sinn DH, Gwak GY, Choi MS, Lee JH, Koh KC, Paik SW, Park HC, Kang TW, Rhim H, Lee SJ, Cristescu R, Lee J, Paik YH, Lim HY. Hepatocellular carcinoma patients with high circulating cytotoxic T cells and intra-tumoral immune signature benefit from pembrolizumab: results from a single-arm phase 2 trial. Genome Med 2022 Jan 6;14:1-15
3. Goh MJ, Oh JH, Park Y, Kim J, Kang W, Sinn DH, Gwak GY, Paik YH, Choi MS, Lee JH, Koh KC, Paik SW. Efficacy and Safety of Lenvatinib Therapy for Unresectable Hepatocellular Carcinoma in a Real-World Practice in Korea. Liver Cancer 2021 Feb;10:52-62
4. Kim J, Kang W, Kang SH, Park SH, Kim JY, Yang S, Ha SY, Paik YH. Proline-rich tyrosine kinase 2 mediates transforming growth factor-beta-induced hepatic stellate cell activation and liver fibrosis. Sci Rep 2020 Dec 3;10(1):21018
5. Sohn W, Cho JY, Kim JH, Lee JI, Kim HJ, Woo MA, Jung SH, Paik YH. Risk score model for the development of hepatocellular carcinoma in treatment-naïve patients receiving oral antiviral treatment for chronic hepatitis B. Clin Mol Hepatol. 2017 Jun;23(2):170-178.

# Trailblazing First-Line Therapies: Which Immuno-Oncology Therapy Would be the Best for Advanced HCC?

**Yong-Han Paik** *Sungkyunkwan University*

Advanced hepatocellular carcinoma (HCC) remains a leading cause of cancer-related deaths worldwide, with increasing incidence and mortality rates globally. Advanced HCC presents a significant therapeutic challenge, necessitating the exploration of novel and effective first-line treatments. Immuno-oncology therapies, particularly immune checkpoint inhibitor (ICI) containing regimens, have emerged as promising candidates in the treatment of advanced HCC. This lecture aims to evaluate the efficacy and safety profiles of various ICI-based therapies for advanced HCC, with a particular focus on the atezolizumab plus bevacizumab (Atezo/Bev) regimen, as well as the durvalumab plus tremelimumab (Durva/Trem; STRIDE) regimen, highlighting their advantages and limitations.

The combination of atezolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, and bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody, has emerged as a promising treatment for patients with advanced HCC. Atezo/Bev combination has demonstrated superior overall survival (OS) and progression-free survival (PFS) compared to sorafenib. In the IMbrave150 trial, patients receiving Atezo/Bev had a median OS of 19.2 months, significantly longer than the 13.4 months observed in patients treated with sorafenib (HR=0.58, $P$<0.001). The median PFS was 6.8 months for the combination therapy compared to 4.3 months for sorafenib. The combination benefits from a dual mechanism of action: atezolizumab reactivates the immune system to target cancer cells, while bevacizumab inhibits angiogenesis, thereby restricting tumor growth. This synergistic approach not only enhances therapeutic efficacy but also offers the potential for durable responses and improved patient outcomes. However, the Atezo/Bev regimen is not without its challenges. Immune-related adverse effects, ranging from mild to severe, can occur and require vigilant monitoring and management. Bevacizumab, an anti-angiogenic agent, is associated with specific adverse events such as hypertension, proteinuria, and an increased risk of bleeding. Bleeding risk is a particularly significant concern in HCC patients due to the frequent presence of cirrhosis and esophageal varices, necessitating careful patient selection and close monitoring for hemorrhagic events. Additionally, the development of anti-drug antibodies (ADAs) against atezolizumab can occur, potentially reducing the drug's efficacy. These antibodies may neutralize the therapeutic effect of atezolizumab or accelerate its clearance from the body, leading to suboptimal treatment outcomes.

The durvalumab plus tremelimumab (STRIDE) regimen has also shown promising results in the treatment of advanced HCC. In the HIMALAYA trial, the combination of a single priming dose of tremelimumab with durvalumab regimen achieved a median OS of 16.4 months, compared to 13.8 months with sorafenib (HR=0.78, $p$=0.004). This combination leverages the complementary actions of durvalumab, a PD-L1 inhibitor, and tremelimumab, a CTLA-4 inhibitor, to enhance anti-tumor immune responses. The STRIDE regimen demonstrated a favorable safety profile with minimal bleeding risk, further supporting its potential as a first-line therapy. Regarding anti-drug antibody, HIMALAYA showed the rates of ADAs to either tremelimumab or durvalumab were low.

Despite these strengths, the STRIDE regimen also has its limitations. Similar to atezolizumab, immune-related adverse effects can occur and necessitate vigilant monitoring. The combined use of PD-L1 and CTLA-4 inhibitors can lead to increased immune activation, which may result in the immune-related toxicities.

The future perspectives of immuno-oncologic treatment in the first-line therapy of advanced HCC are evolving rapidly, driven by ongoing research and clinical trials. The CheckMate 9DW trial investigated the combination of nivolumab (an anti-PD-1 therapy) with ipilimumab (an anti-CTLA-4 therapy) as a first-line treatment for advanced HCC. The dual combination therapy of nivolumab plus ipilimumab demonstrated a statistically significant improvement in OS compared to investigator's choice of sorafenib or lenvatinib. Exploring new targets beyond PD-1/PD-L1 and CTLA-4 pathways can enhance the efficacy of immunotherapies. These include inhibitors targeting LAG-3, TIM-3, and TIGIT. The Morpheus-liver study is a phase Ib/II trial evaluated the efficacy of adding tiragolumab, an anti-TIGIT agent, to the standard regimen of Atezo/Bev. The study involved patients with unresectable, locally advanced, or metastatic HCC. Results demonstrated a notable improvement in the objective response rate (ORR) with the triplet therapy, achieving an ORR of 42.5%. Furthermore, the median PFS was significantly extended to 11.1 months with the triplet regimen, compared to 4.2 months with the doublet therapy. Building on the Morpheus-Liver findings, the IMbrave 152 study is undergoing to confirm the benefits of adding tiragolumab to the Atezo/Bev combination.

In conclusion, while both atezolizumab plus bevacizumab and durvalumab plus tremelimumab regimens represent substantial advancements in the first-line treatment of advanced HCC, their implementation requires a balanced consideration of their strengths and weaknesses. The integration of new IO agents targeting different immune checkpoints, such as PD-1, CTLA-4, and TIGIT, appears to enhance anti-tumor responses and improve clinical outcomes, marking a significant step forward in the management of advanced HCC.

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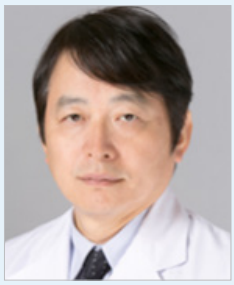

**Masatoshi Kudo**

*Kindai University, Japan*

## Self Introduction

| | |
|---|---|
| 1978 | Graduated from Kyoto University Graduate School of Medicine |
| 1978 | Kyoto University Hospital |
| 1979 | Kobe City General Hospital |
| 1987 | University of California, Davis Medical Center |
| 1997-present | Professor and Chairman, Kindai University Faculty of Medicine, Department of Gastroenterology and Hepatology |
| 2001-present | Secretary General, JLCA |
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## Research Interests

Hepatocellular carcinoma, Viral hepatitis, MASH,MASLD

## Representative Publications

1. Kudo M*, Ueshima K, Saeki I, Ishikawa T, Inaba Y, Morimoto N, Aikata H, Tanabe N, Wada Y, Kondo Y, Tsuda M, Nakao K, Ito T, Hosaka T, Kawamura Y, Kuzuya T, Nojiri S, Ogawa C, Koga H, Hino K, Ikeda M, Moriguchi M, Hisai T, Yoshimura K, Furuse J, Arai Y: A Phase 2, prospective, multicenter, single-arm trial of transarterial chemoembolization therapy in combination strategy with lenvatinib in patients with unresectable Intermediate-stage hepatocellular carcinoma: TACTICS-L trial. Liver Cancer 13:99-112, 2024. https://doi.org/10.1159/000531377
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3. Abou-Alfa G †, Lau G †, Kudo M †, Chan SL †, Kelley RK, Furuse J, Sukeepaisarnjaroen W, Kang YK, Tu DV, De Toni E, Rimassa L, Breder V, Vasilyev A, Heurgue A, Tam V, Mody K, Thungappa SC, Ostapenko Y, Yau T, Azevedo S, Varela M, Cheng AL, Qin S, Galle P, Ali S, Marcovitz M, Makowsky M, Pharm D, He P, Kurland JF, Negro A, Sangro B: Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. New Engl J Med Evidence, 2022. († Shared 1st authors) DOI: 10.1056/EVIDoa2100070
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5. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 391:1163-1173, 2018.

# Navigating the Post-Immunotherapy: Second-Line Options for HCC

**Masatoshi Kudo** *Kindai University, Japan*

Essential factors in post-immunotherapy treatment are selecting agents with a high response rate and selecting agents that are likely to be effective against tumors that have not responded to immunotherapy in the first-line setting. Lenvatinib provides FGF inhibition in addition to VEGF inhibition. In hepatocellular carcinoma, the cancer produces FGF19, which binds to FGFR4 expressed on the cancer cells, forming an autocrine loop that activates the FGF19 and FGFR4 pathways, which transmit signals and are responsible for cancer cell growth. Therefore, inhibiting the FGF19 and FGFR4 pathways in treating hepatocellular carcinoma is essential. FGF also contributes to the mechanism of resistance to anti-VEGF therapy. This may be because bevacizumab induces hypoxia, which activates HIF-1$\alpha$, increases FGFR1, and enhances angiogenesis. It is also known that about 30% of hepatocellular carcinomas have $\beta$-catenin mutations and that high levels of $\beta$-catenin mutations decrease intratumoral T cells. It has been reported that activation of immune $\beta$-catenin activity results in poor PFS and OS. In response to this, selecting an effective secondary drug in $\beta$-catenin mutated HCC is necessary. Lenvatinib is known to be effective both in patients with and without CTNNB1 mutations. It is also known that the expression level of $\beta$-catenin correlates with FGFR4 expression. FGFR4 promotes the activation of glycogen synthase kinase 3B (GSK3B), and activated GSK3B decreases $\beta$-catenin and promotes nuclear transfer of $\beta$-catenin. Therefore, it is known that FGFR4 is extensively involved in the expression and activation of $\beta$-catenin. It is also known that lenvatinib is better for FGFR4-positive cases, especially in response rate and PFS than negative cases.

For these reasons, lenvatinib is the most recommended second-line therapy. In some trials, lenvatinib after immunotherapy is also known to have a better response rate and PFS rather than being used for first-line therapy, making it the best choice as a second-line agent.

In Japan, lenvatinib is used as second-line therapy in more than 70-90% of cases. There also exists an immunotherapy called rechallenge therapy. It is known that the administration of atezolizumab plus bevacizumab or durvalumab plus tremelimumab after lenvatinib as second-line therapy or regorafenib or cabozantinib as third-line therapy has shown promising results. It is also known that rechallenge therapy can be effective even in the advanced stage HCC if the intratumoral microenvironment changes after LEN-TACE. Therefore, considering the above, we believe that lenvatinib, LEN-TACE, or cabozantinib should be considered at least once for 2nd line after immunotherapy, followed by immunotherapy rechallenge therapy.

**Pil Soo Sung**

*The Catholic University of Korea*

## Self Introduction

### *Education*

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| 2007.02 | M.D. | Medicine | College of Medicine, The Catholic University of Korea, Seoul, Korea |
| 2011.08 | M.S. | Internal Medicine | College of Medicine, The Catholic University of Korea, Seoul, Korea |
| 2016.02 | Ph.D. | Immunology | Graduate School of Medical Science & Engineering, KAIST, Daejeon, Korea |

### *Professional Experience*

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| 2007-2008 | Rotating Internship-Catholic Medical Center, The Catholic University of Korea, Seoul, Korea |
| 2008-2012 | Residency-Department of Internal Medicine, Seoul St. Mary's hospital, The Catholic University of Korea, Seoul, Korea |
| 2012-2016 | Researcher and teaching assistant, Graduate School of Medical Science & Engineering, KAIST, Daejeon, Korea |
| 2016-2018 | Clinical Fellowship, Department of Internal Medicine, Seoul St. Mary's hospital, The Catholic University of Korea, Seoul, Korea |
| 2018-2020 | Clinical Assistant Professor, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea |
| 2020-2022 | Assistant Professor, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea |
| 2022- Present | Associate Professor, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea |

## Research Interests

HCC, liver fibrosis, NAFLD, alcoholic liver disease, AIH

## Representative Publications

1. Intrahepatic immunoglobulin A complex induces polarization of cancer-associated fibroblasts to matrix phenotypes in the tumor microenvironment of hepatocellular carcinoma (corresponding author)
   Hepatology 2024, e-puib
2. Intrahepatic inflammatory IgA+PD-L1high monocytes in hepatocellular carcinoma development and immunotherapy. (first author) J Immunother Cancer. 2022 May;10(5):e003618. doi: 10.1136/jitc-2021-003618.
3. Crosstalk between tumor-associated macrophages and neighboring cells in hepatocellular carcinoma. (sole author)
   Clin Mol Hepatol. 2021 Oct 19. doi: 10.3350/cmh.2021.0308. Online ahead of print.
4. EpCAM-high liver cancer stem cells resist natural killer cell-mediated cytotoxicity by upregulating CEACAM1. (corresponding author)
   J Immunother Cancer. 2020 Mar;8(1):e000301. doi: 10.1136/jitc-2019-000301.
5. IFNL3-adjuvanted HCV DNA vaccine reduces regulatory T cell frequency and increases virus-specific T cell responses. (first author)
   J Hepatol. 2020 Jul;73(1):72-83. doi: 10.1016/j.jhep.2020.02.009. Epub 2020 Feb 21.

# Overcoming Resistance and Relapse against HCC Immunotherapy

**Pil Soo Sung** *The Catholic University of Korea*

Hepatocellular carcinoma (HCC) is the fourth-leading cause of cancer-related deaths and the most common primary liver cancer. The causes of HCC include hepatitis C virus, hepatitis B virus, fatty liver diseases such as non-alcoholic steatohepatitis (NASH), and alcoholic liver disease.[1] Surgical resection has a high recurrence rate, while chemotherapy including multi-tyrosine kinase inhibitors has shown limited efficacy in improving the overall prognosis of patients with HCC. Recently, immunotherapy has revolutionized HCC treatment.[2] In particular, a combination of atezolizumab and bevacizumab has been shown to improve overall survival rates compared with those of sorafenib, leading to FDA approval.[3] Despite these advancements, prognosis remains uncertain, and therapeutic limitations still exist.[4]

In recent years, the tumor microenvironment (TME) has gained significant attention because of its crucial role in tumor immune suppression, metastasis, and targeted therapy response.[5] The TME is composed of various immune cells, such as T lymphocytes, macrophages, neutrophils, and dendritic cells, and non-immune components, such as fibroblasts, endothelial cells of the blood and lymph vessels, and the extracellular matrix.[6] The TME promotes the invasive growth of tumors and the colonization of distant organs. Cancer-associated fibroblasts (CAFs) participate in various stages of tumor development via multiple pathways. CAFs can support cancer cells directly or indirectly by producing multiple cytokines, chemokines, and growth factors.[7] They can induce the inhibition of immune effector cell activity and recruit immune-suppressive cells, enabling cancer cells to evade immune surveillance.

Previous study indicates the presence of CAF dynamics with different characteristics in the TME, and an improved understanding of heterogeneity and dynamics allows us to explain how CAFs contribute to the complexity of the TME.[8] A recent study identified various CAF dynamics in HCC.[9] However, the dynamics and heterogeneity of CAFs in HCC remain poorly understood, and the interactions between cancer cells and the specific dynamics of CAFs remain largely unknown.

Immunoglobulin A (IgA) neutralizes pathogens and prevents infections in mucosal sites.[10] However, in the human liver, IgA exacerbates inflammation and disrupts anti-tumor immunity.[11] Previous studies have demonstrated that increased serum IgA levels in patients with HCC upregulate programmed death-ligand 1 (PD-L1) expression in monocytes/macrophages and induce intrahepatic

and intratumoral infiltration in the inflamed liver and TME of patients with HCC.[12] Recent research has established that IgA secreted by intestinal B cells plays a pivotal role in activating monocyte-derived macrophages and fostering fibrosis during HCC development.[13] Additionally, research had been conducted on the correlation between IgA complexes and specific immune cell types, such as plasma cells and intrahepatic and intratumoral monocytes/macrophages.[11, 12] However, to date, no studies have investigated the correlation between IgA and fibroblasts. Our study proposes a novel role for the IgA complex in the TME. Increased intrahepatic IgA levels in HCC increase the proportion of mCAFs among the CAF subpopulations. Furthermore, our study confirmed that an increase in mCAFs enhances immunosuppression. Specifically, elevated intrahepatic IgA levels result in increased binding between CD71 on the CAFs and the IgA complex, subsequently inducing their differentiation into mCAFs. Increased PD-L1 expression in these induced mCAFs leads to immunosuppression.[14]

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## Takahiro Kodama

*Osaka University, Japan*


## Self Introduction

I am an assistant professor in the Department of Gastroenterology and Hepatology at Osaka University Graduate School of Medicine since 2016. I received an M.D. degree in 2002 and a Ph.D. degree in 2011 at Osaka University. From 2012 to 2016, I served as a postdoctoral associate at The Methodist Hospital Research Institute. I am a board-certified member of the Japanese Society of Hepatology, Gastroenterology, and Internal Medicine as well as a councilor of the Japanese Cancer Association and an active member of the American Association of Cancer Research (AACR) and the American Association for the Study of Liver Diseases (AASLD). I have published over 120 peer-reviewed papers and over 20 first-author papers including 2 JCI, 2 Gastroenterology, 3 HEPATOLOGY, 1 Journal of Hepatology, 1 Clinical Cancer Research, and 4 PNAS. I have obtained several national grants as a principal investigator. I am an editorial board member of HEPATOLOGY and serve as an associate journal editor of Scientific Reports, Frontiers in Oncology, and Frontiers in Pharmacology.

## Research Interests

My research interests include biomarkers for HCC pharmacotherapy, biology and therapeutics for hepatobiliary-pancreatic cancer and steatotic liver disease.

## Representative Publications


1. Shiode Y*, Kodama T*, Shigeno S, Murai K, Tanaka S, Newberg JY, Kondo J, Kobayashi S, Yamada R, Hikita H, Sakamori R, Suemizu H, Tatsumi T, Eguchi H, Jenkins NA, Copeland NG, Takehara T. Traf3 inactivation promotes the development of intrahepatic cholangiocarcinoma via NIK-mediated hepatocyte transdifferentiation. Hepatology. 2023 Feb 1;77(2):395-410. doi: 10.1002/hep.32317. Epub 2022 Feb 1. PMID: 34995376 (* These authors contributed equally)
2. Murai H*, Kodama T*, Maesaka K, Tange S, Motooka D, Suzuki Y, Shigematsu Y, Inamura K, Mise Y, Saiura A, Ono Y, Takahashi Y, Kawasaki Y, Iino S, Kobayashi S, Idogawa M, Tokino T, Hashidate-Yoshida T, Shindou H, Miyazaki M, Imai Y, Tanaka S, Mita E, Ohkawa K, Hikita H, Sakamori R, Tatsumi T, Eguchi H, Morii E, Tatsumi T, Takehara T. Multiomics identifies the link between intratumor steatosis and the exhausted tumor immune microenvironment in hepatocellular carcinoma. Hepatology 2023 Jan 1;77(1):77-91. doi: 10.1002/hep.32573. Epub 2022 Jun 17. PMID: 35567547 (* These authors contributed equally)
3. Kozumi K*, Kodama T*, Murai H, Sakane S, Govaere O, Cockell S, Motooka D, Kakita N, Yamada Y, Kondo Y, Tahata Y, Yamada R, Hikita H, Sakamori R, Kamada Y, Daly AK, Anstee QM, Tatsumi T, Morii E, Takehara T. Transcriptomics Identify Thrombospondin-2 as a Biomarker for Nonalcoholic Steatohepatitis and Advanced Liver Fibrosis. Hepatology. 2021 Nov;74(5):2452-2466. doi: 10.1002/hep.31995. Epub 2021 Aug 21. PMID: 34105780 (* These authors contributed equally)
4. Myojin Y*, Kodama T*, Maesaka K, Motooka D, Sato Y, Tanaka S, Abe Y, Ohkawa K, Mita E, Hayashi Y, Hikita H, Sakamori R, Tatsumi T, Taguchi A, Eguchi H, Takehara T. ST6GAL1 is a Novel Serum Biomarker for Lenvatinib-susceptible FGF19-driven Hepatocellular Carcinoma. Clin Cancer Res. 2021 Feb 15;27(4):1150-1161. doi: 10.1158/1078-0432.CCR-20-3382. Epub 2020 Dec 7. (* These authors contributed equally)
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# Predictive Biomarker Research of Combination Immunotherapy: Current Status and Future Perspectives

**Takahiro Kodama** *Osaka University, Japan*

Hepatocellular carcinoma (HCC) is a dismal disease with the third highest mortality rate among all cancer types. Pharmacotherapy for unresectable HCC has entered a new era with the advent of immunotherapy. Treatment options have shifted from conventional therapy centered on multi-kinase inhibitors (MKIs) to combined immunotherapy centered on immune checkpoint inhibitors (ICIs). Currently, both anti-PD-L1/anti-VEGF antibody combination therapy and anti-PD-L1/anti-CTLA-4 antibody combination therapy are recommended as first-line therapy in the guidelines, while the other regimens including various MKIs such as Lenvatinib and Sorafenib are positioned as second-line or later. On the other hand, responses to any of these regimens are achieved in up to 30% of patients, and immunotherapy is associated with a certain frequency of severe irAEs. Appropriate use of these regimens may be important to prolong the prognosis of patients with uHCC, but there are no clear biomarkers to guide the optimal use of these regimens. In this lecture, I would like to summarize the current status of predictive biomarker research of combination immunotherapy for uHCC. First, I will briefly touch on the basics of cancer immunity and mode of action (MoA) of two combination immunotherapies, especially from the perspective of cancer immunity cycle. Then, I would like to introduce biomarker candidates for HCC immunotherapy. Factors reported to predict response to ICI in many cancer types are PD-1/PD-L1 expression, TMB and MSI-H, but their usefulness in HCC seems to be limited. Meanwhile, tumor microenvironment analysis-derived factors such as intratumoral CD8+ T-cell infiltration and/or gene expression profiling-based molecular signatures have been reported as predictors of response in HCC. I would also like to introduce our studies focusing on liquid biopsy such as serum cytokines and ctDNA as well as clinical factors such as neutrophil-lymphocyte ratio (NLR), pretreatment antibiotic use, and MRI imaging findings as predictors of response and prognosis in combined immunotherapy. Lastly, I would like to briefly touch on the future perspective of biomarker research of combination immunotherapy in HCC.


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# KLCA Symposium 2

## Epoch-Making Changes for HCC Care

**Chairs:**

**Jinsil Seong** (Yonsei Univ.)
**Jin Wook Chung** (Seoul National Univ.)

**Pyoung Jae Park**

*Korea University*

## Self Introduction

Pyoung-Jae Park is a Professor of the Department of Surgery, Korea University College of Medicine and is a Chief of division of Transplant and Vascular surgery  Korea University Guro Hospital.

Prof. Park graduated from Korea University College of Medicine with his medical degree in 2001 and completed his internship and residency at the Department of Surgery at Korea University Anam Hospital, receiving his diploma in General Surgery in 2006. Moreover, he worked and trained as clinical fellow of division of Liver transplantation and hepatobiliary surgery in the Asan Medical center.

### *Education*

| | |
|---|---|
| 1995.03-2001.02 | College of Medicine, Korea University, Seoul, Korea(B.S., M.D. degree) |
| 2002.09-2005.02 | M.S. degree of medical science, Korea University, Seoul, Korea |
| 2011.03-2014.02 | Ph. D course of medical science, Ulsan University, Seoul, Korea |

### *Postgraduate Professional Training*

| | |
|---|---|
| 2002.03-2006.02 | Medical Residency in Surgery, Korea University Medical Center, Seoul, Korea |
| 2009.05-2011.02 | Clincal Fellowhip in Liver Transplantion and Hepatobiliary Surgery, Asan Medical Center, Seoul, Korea |
| 2011.05-2012.02 | Clinical Research Fellowship in Department of Surgery, Division of Transplantation, University of Illinois at Chicago Medical Center, Chicago, IL |
| 2012.03-2014.02 | Clinical Associate Professor in Division of Hepatobilliary and Pancreas sugery, Department of Surgery, Korea University Guro Hospital, Seoul, Korea |
| 2014.03-2021.08 | Clinical Associate Professor in Division of Transplant and Vascular Surgery, Department of Surgery, Korea University Guro Hospital, Seoul, Korea |
| 2021.09-Present | Professor in Division of Transplant and Vascular Surgery, Department of Surgery, Korea University Guro Hospital, Seoul, Korea |

## Research Interests

Liver transplantation; Hepatobiliary surgery; Transplant surgery

## Representative Publications

1. Multicenter study of prognostic factors in paraaortic lymph node dissection for metastatic colorectal cancer
2. Prevalence and clinical significance of pancreatic cystic lesions in immunosuppressed patients following solid organ transplantation
3. Single-port versus conventional laparoscopic distal pancreatectomy: a propensity score matched analysis and a learning curve of single-port approach
4. Single-Center Experience Using Marginal Liver Grafts in Korea
5. Liver transplantation for acute-on-chronic liver failure from erythropoietic protoporphyria.

# Maximizing Indication and Safety in Living Donor Liver Transplantation for HCC

**Pyoung Jae Park** *Korea University*

Advanced hepatocellular carcinoma (HCC) poses a significant therapeutic challenge due to limited treatment options and poor prognosis. However, a multidisciplinary approach that combines various therapeutic modalities has shown promise in downstaging tumors and ultimately enabling liver transplantation, offering a potentially curative option for select patients. This lecture will explore the medical rationale, clinical evidence, and key references supporting the integration of diverse therapies in the management of advanced HCC.

Recent clinical trials have demonstrated the efficacy of multidisciplinary approaches in advanced HCC. Studies investigating the atezolizumab-bevacizumab regimen have shown significant tumor response rates and prolonged survival in patients with unresectable HCC. Furthermore, successful downstaging of tumors has expanded the pool of liver transplant candidates, leading to improved post-transplant outcomes and long-term survival.

Liver Transplantation as a Curative Strategy: Liver transplantation represents a curative option for carefully selected patients with advanced HCC. Criteria for transplant candidacy include tumor size and number, vascular invasion, and absence of extrahepatic spread. Downstaging tumors through systemic therapy can improve transplant eligibility and outcomes. However, close monitoring and stringent patient selection are crucial to minimize the risk of disease recurrence post-transplant.

A multidisciplinary approach integrating systemic therapy, locoregional treatments, and liver transplantation offers a promising strategy for the management of advanced HCC. By leveraging diverse therapies and tailoring treatment plans to individual patients, clinicians can achieve downstaging of tumors and provide potentially curative treatment options for this challenging disease.

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**Hyo-Cheol Kim**

*Seoul National University*

## Self Introduction

Dr. Hyo-Cheol Kim is a clinical professor at the Seoul National University Hospital, in Seoul, South Korea. Dr. Kim completed his residency in diagnostic radiology at the Seoul National University Hospital (1999–2003) and is board- certified in radiology. In 2008, he finished his fellowship training in interventional radiology at the Seoul National University Hospital and has been a professor of interventional radiology there since then.

Dr. Kim has published 107 articles in various peer-reviewed journals, including Nature Communications, Radiology, and JVIR, as a first or corresponding author. He also serves as associate editor of JVIR and section editor of KJR.

## Research Interests

Dr. Kim's clinical interests include chemoembolization and radioembolization for hepatocellular carcinoma. He has performed animal research focused on intra-arterial therapy of a rat liver tumor model.

## Representative Publications

1. Choi JW, Suh M, Paeng JC, Kim JH, Kim HC. Radiation Major Hepatectomy Using Ablative Dose Yttrium-90 Radioembolization in Patients with Hepatocellular Carcinoma 5 cm or Larger. J Vasc Interv Radiol. 2024 Feb;35(2):203-212.
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# Making an Impact with Radioembolization for HCC Management

**Hyo-Cheol Kim** *Seoul National University*

Hepatocellular carcinoma (HCC) remains a formidable challenge in oncology due to its aggressive nature and the complexities associated with underlying liver disease. As an interventional radiologist, the advent of radioembolization has significantly revolutionized the approach to HCC management. This innovative technique not only exemplifies the potential of interventional radiology in cancer therapy but also provides a targeted, effective treatment option that aligns with the goals of precision medicine.

Radioembolization, or selective internal radiation therapy (SIRT), involves the intra-arterial administration of yttrium-90 (Y-90) microspheres directly into the hepatic artery supplying the tumor. This method ensures high-dose radiation delivery to the tumor while sparing healthy liver parenchyma. From an interventional radiologist's perspective, the precision and control offered by radioembolization are unparalleled. The ability to directly target hepatic tumors while minimizing systemic exposure aligns perfectly with the core principles of interventional radiology: precision, minimally invasive techniques, and enhanced patient outcomes.

One of the primary impacts of radioembolization is its efficacy in controlling tumor growth. By delivering radiation internally, radioembolization induces significant tumor necrosis and reduces tumor burden. This localized approach is particularly beneficial for patients with intermediate to advanced HCC who are not candidates for surgical resection or liver transplantation. The ability to provide an effective palliative treatment that can stabilize disease progression or even shrink tumors to operable sizes is a game-changer.

For interventional radiologists, the technical execution of radioembolization is both challenging and rewarding. It requires meticulous planning, including detailed imaging studies and careful mapping of the hepatic vasculature to ensure optimal delivery of the radioactive microspheres. The procedure itself, although complex, showcases the advanced skills and expertise of interventional radiologists, highlighting the crucial role they play in the multidisciplinary management of HCC.

Moreover, radioembolization offers a significant quality of life advantage. Compared to systemic chemotherapy, which often comes with a high burden of side effects, radioembolization is typically well-tolerated. Patients can often resume normal activities shortly after the procedure, with fewer dis-

ruptions to their daily lives. This minimally invasive nature, combined with a relatively quick recovery time, underscores the patient-centered approach that interventional radiologists strive to achieve.

The potential for radioembolization to serve as a bridge to curative therapies further amplifies its impact. By downsizing tumors, it can convert patients from being ineligible to eligible for liver transplantation or surgical resection. This bridging capability not only expands treatment options but also offers renewed hope for patients and their families, which is profoundly gratifying for those involved in their care.

In terms of outcomes, emerging data suggest that radioembolization can improve overall survival rates, particularly when integrated into a comprehensive treatment plan that may include other modalities such as transarterial chemoembolization (TACE) or systemic therapies. The strategic combination of these treatments can lead to synergistic effects, enhancing overall efficacy and offering a multidisciplinary approach to tackling HCC.

In conclusion, from an interventional radiologist's perspective, radioembolization represents a pivotal advancement in HCC management. Its ability to deliver targeted, high-dose radiation with precision, coupled with its role in bridging patients to curative therapies and maintaining quality of life, underscores its transformative impact. As the field continues to evolve with ongoing research and technological advancements, radioembolization is set to remain a cornerstone in the interventional radiologist's armamentarium against HCC.


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**Jeong Il Yu**

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## Self Introduction

Prof. Jeong Il Yu is an Associate Professor of the Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine.

Prof. Hong graduated from CHA University College of Medicine with his medical degree in 2005 and completed his internship and residency at the Department of Radiation Oncology, at Samsung Medical Center, receiving his diploma in Radiation Oncology in 20100.

## Research Interests

- Gastro-Intestinal Radiation Oncology
- Radiation Immune-modulation

## Representative Publications

1. Seo SH, Yu JI, Park HC, et al. Proton Beam Radiotherapy as a Curative Alternative to Radiofrequency Ablation for Newly Diagnosed Hepatocellular Carcinoma. Anticancer Res. 2024 May;44(5):2219-2230.
2. Goh MJ, Park HC, Yu JI, et al. Impact of Intrahepatic External Beam Radiotherapy in Advanced Hepatocellular Carcinoma Patients Treated with Tyrosine Kinase Inhibitors. Liver Cancer. 2023 Feb 10;12(5):467-478.
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# Harnessing the Power of Radiotherapies for HCC Treatment

**Jeong Il Yu** *Sungkyunkwan University*

Although radiation therapy (RT) is one of the most efficient loco-regional modalities in oncologic fields[1], the application of RT has been hesitated for a considerable period of time, and it's use has even been actively discouraged in several guidelines, because of the limitations in RT dose delivery to achieve local control and at the same time do not cause liver function deterioration, historically[2].

With the introduction of these advanced RT techniques that enable high-precision, high-dose radiation delivery while minimizing the impact on the normal liver, especially SABR or PBT is being implemented with curative purpose in patients unsuitable for the application of existing standard curative local treatment, including resection or ablation. The oncologic outcomes, including local control, overall survival and adverse events of recent retrospective or prospective comparative studies between SABR or PBT and standard managements including radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) for HCC are presented below (Table 1)[3-9]. In most studies, SABR or PBT showed superior or at least non-inferior outcomes in terms of local control (LC) rate compared to TACE or RFA. In the randomized controlled phase III trials[3,8], furthermore, no statistically significant differences were identified between the two groups in terms of toxicity and overall survival (OS). Also in retrospective studies, no difference in OS was detected between the two groups after inverse probability of treatment weighting (IPTW) or propensity score matching (PSM), controlling for other confounding variables[4-7,9]. Based on these results, SABR or PBT can be considered as an effective curative treatment alternative for early liver cancer that is not indicated for existing standard curative treatments.

Although recommended treatment for HCC of BCLC C stage, especially in the case of HCC accompanied by extrahepatic metastasis is systemic agents, effective combination treatment methods remain controversial in cases with the intrahepatic tumor invades major blood vessels or is extensive and rapid intrahepatic tumor control is essential to maintain liver function. Several retrospective studies have reported that in these patients, combination RT for intrahepatic tumors is more effective than sorafenib or lenvatinib alone, which were previous standard systemic treatments[10-12]. Recently, the NRG/RTOG-1112 randomized phase III trial reported the superior outcomes of sorafenib after SABR for locally advanced HCC compared to sorafenib alone[13]. It will be necessary to evaluate its usefulness and safety through prospective trials on the combination of RT and systemic treatment based on immune checkpoint in-

hibitors, which are currently recommended as first line treatment in advanced HCC.

In addition, reports and expectations are growing for patients cured through active local treatment in oligometastatic conditions in various primary tumors[14]. Especially, the need for immunotherapy, shows a durable disease control when responding to treatment, is increasingly emphasized, and this is also true for HCC, where immunotherapy is recently recommended as first line treatment in those patients. In fact, retrospective and prospective studies have been reported on the treatment effects of RT in these HCC patients[15-17]. In addition, a randomized study was recently published showing that preemptive palliative RT can improve overall treatment outcomes in the case of metastatic lesions that can cause local problems even if there are no symptoms[18], so there may be a need to consider its application in HCC patients in similar condition as well.

**Table 1.** Recent retrospective or prospective studies using SABR or PBT for HCC

| Author | Year | Study design | Intervention comparator | n | ≥Gr3 AE | LC (%) | OS (%) |
|---|---|---|---|---|---|---|---|
| Wahl et al. | 2016 | Retro<br>IPTW | SABR<br>RFA | 63<br>161 | 5%<br>11% | 83.8(2 yr)<br>80.2(2 yr)<br>*P*=0.029 | 46.3(2 yr)<br>52.9(2 yr)<br>*P*=NS |
| Hara et al. | 2019 | Retro<br>PSM | RT<br>RFA | 374 | 37% | 94.7(3 yr)<br>87.1(3 yr)<br>*P*<0.01 | 69.1(3 yr)<br>70.4(3 yr)<br>*P*=0.86 |
| Kim et al. | 2020 | Retro<br>PSM | SABR<br>RFA | 313<br>313 | 1.6%<br>2.6% | 83.6(2 yr)<br>68.9(2 yr)<br>*P*<0.001 | 77.6(2 yr)<br>71.1(2 yr)<br>*P*=0.308 |
| Jeong et al. | 2021 | Retro<br>IPTW | SABR<br>RFA | 87<br>179 | 1.1%<br>0.6% | 96.3(4 yr)<br>90.6(4 yr)<br>*P*=0.167 | 70.2(4 yr)<br>71.8(4 yr)<br>*P*=0.786 |
| Kim et al. | 2021 | RCT | Proton<br>RFA | 72<br>72 | 5% | 92.8(2 yr)<br>83.2(2 yr)<br>*P*=0.419 | 91.7(2 yr)<br>90.3(2 yr)<br>*P*=0.821 |
| Fujita et al. | 2022 | Retro<br>PSM | Carbon ion<br>RFA | 54<br>95 | 0.0%<br>1.2% | 90.5% (5 yr)<br>81.1% (5 yr)<br>*P*=0.239 | 57.1(5 yr)<br>69.2(5 yr)<br>*P*=0.101 |
| Bush et al. | 2023 | RCT | Proton<br>TACE | 35<br>39 | similar | PBT superior<br>HR 5.64<br>*P*=0.003 | 68(2 yr)<br>65(2 yr)<br>*P*=0.80 |

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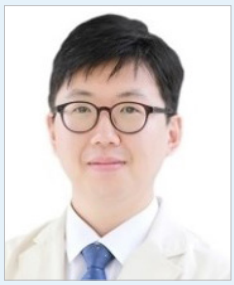

**Ji Won Han**

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## Self Introduction

Prof. Ji Won Han is a Clinical Assistant Professor of the Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Catholic University of Korea.

Prof. Han graduated from The Catholic University of Korea with his medical degree in 2011 and completed his internship and residency at the Department of Internal Medicine at Seoul St. Mary's Hospital. He also achieved his Master's degree from The Catholic University of Korea in 2016. After that, he received his Ph.D. in 2020 at KAIST.

Since 2022, Prof. Han has been taking on a number of roles, including being a member of the Primary Liver Cancer Registry Committee at KLCA, the Publishing/Research/NIT Guideline Committees at KASL, and the Publishing/International Affairs Committee at KSG.

## Research Interests

- Integrative predictive models in patients with chronic liver disease including HCC
- T cell immunology in human liver disease

## Representative Publications

1. "A Machine Learning Algorithm Facilitates Prognosis Prediction and Treatment Selection for Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma" Clin Cancer Res. 2024. Accepted.
2. "IFNL3-adjuvanted HCV DNA vaccine reduces regulatory T-cell frequency and increases virus-specific T-cell responses" Journal of Hepatology. 2020; 73(1):72-83
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5. "Dynamic Changes in Ex Vivo T-Cell Function after Viral Clearance in Chronic HCV Infection" Journal of Infectious Diseases. 2019; 220(8): 1290-1301.

# Evolving Strategies: Treatment Patterns of HCC from Korean Claims Data

**Ji Won Han** *The Catholic University of Korea*

With recent advancements in hepatocellular carcinoma (HCC) treatment, various therapeutic methods are being applied in clinical practice. However, comprehensive and systematic statistical data on these changing treatment trends is lacking. This presentation aims to examine the changes in treatment patterns for Korean HCC patients from 2008 to 2022 using data from the Health Insurance Review and Assessment Service (HIRA).

The study analyzed initial treatment claims and overall treatment claims for patients diagnosed with C22.0 and V193 from 2008 to 2022. Results showed that the incidence and prevalence of HCC have been slightly decreasing since 2008. The primary causes of HCC were identified as chronic hepatitis B, chronic hepatitis C, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) and notably, the proportion of NAFLD has been increasing in recent years. We also observed the trends of increasing age of patients who were diagnosed with HCC.

Initial treatment methods included transarterial treatments, surgical resection, local ablation, systemic treatment, radiation therapy, and liver transplantation. The proportion of systemic treatment has been gradually increasing. However, the proportion of best supportive care has been gradually decreasing. The use of microwave ablation in local ablation has risen, and the application of transarterial radioembolization in transarterial treatments has also increased. In terms of surgical resection, laparoscopic resection compared to the open resection has been significantly increased. Primary systemic treatments included sorafenib, lenvatinib, and atezolizumab-bevacizumab, and their total uses have grown. Particularly, the prescription of atezolizumab-bevacizumab has surged following its inclusion in the national insurance coverage. The analysis of overall treatment claims from 2008 to 2022 highlighted similar trends in HCC treatment to the initial treatments and primary systemic treatments. Of note, the number of prescriptions of RTx and systemic treatments has been gradually increasing.

This presentation aims to clearly outline the changing treatment patterns for Korean HCC patients, thereby enhancing applicability in clinical practice and suggesting future research directions. The findings will provide valuable statistics for clinicians, researchers, and the public.


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THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# HCC in Korea: The Past, Present and the Future

**Chairs:**

**Hyunchul Rhim** (Sungkyunkwan Univ.)

**Jong Young Choi** (The Catholic Univ. of Korea)

**Hae Lim Lee**

*The Catholic University of Korea*

## Self Introduction

Hae Lim Lee is a Clinical Assistant Professor in the Department of Internal medicine, Hepatology, at The Catholic University College of Medicine.

Hae Lim Lee graduated from Ewha Womans University College of Medicine with a medical degree in 2008 and completed internship and residency at the Department of Internal medicine at The Catholic University Hospital, receiving a diploma in Internal Medicine in 2013.

Hae Lim Lee has been serving as a member of the Korean Liver Cancer Association since 2018.
- 대한간암학회 기획위원 (2021-현재)
- 대한간학회 홍보위원 (2024-현재)
- 대한간암학회 홍보위원 (2018-2021)
- 대한간학회 섭외위원 (2022-2023)

## Research Interests

HBV, Hepatocellular carcinoma, Liver cirrhosis

## Representative Publications

1. Core protein inhibitors: Opportunities and challenges at the forefront of hepatitis B cure. Clin Mol Hepatol. 2024 May 14
2. A refined prediction model for survival in hepatocellular carcinoma patients treated with transarterial chemoembolization. Front Oncol. 2024 Mar
3. The role of transjugular intrahepatic portosystemic shunt in patients with portal hypertension: Advantages and pitfall. Clin Mol Hepatol. 2022 Apr
4. Anticancer Effect of Statins in Patients Undergoing Liver Transplantation for Hepatocellular Carcinoma. Liver Transpl. 2022 Mar
5. Anti-fibrotic effects of branched-chain amino acids on hepatic stellate cells. Korean J Intern Med. 2022 Jan

# Hepatocellular Carcinoma in Korea: The Past, Present and the Future

**Hae Lim Lee** *The Catholic University of Korea*

Hepatocellular carcinoma (HCC) ranked as the 7th most common cancer in South Korea in 2021 and the second leading cause of cancer-related deaths, with the highest mortality rate among the working-age population. Although the incidence of HCC is relatively decreasing compared to other cancers, the decline in mortality is gradual. This is attributed to the aging of chronic liver disease patients who, thanks to significant advancements in medical management, including antiviral therapies for hepatitis B and C, avoid severe decompensated outcomes but now fall into high-risk groups for HCC. Data from 2016 indicate that in South Korea, approximately 94% of HCC patients died from their primary cancer, compared to 77.4% of patients with other cancers. Additionally, more than 70% of HCC patients still succumbed to the disease even 10 years after diagnosis. These statistics underscore the substantial disease burden of HCC in our society.

The field of medicine has rapidly advanced over a short period, and HCC treatment is no exception. South Korea boasts world-class standards in both basic research and clinical practice of HCC, with the Korean Liver Cancer Association (KLCA) playing a pivotal role in these advancements. Unlike other cancers, HCC often arises from chronic liver diseases, and its treatment includes a wide array of options beyond surgery, chemotherapy, and radiation therapy, such as transarterial chemoembolization, radiofrequency ablation, and liver transplantation. Although guidelines for HCC treatment by the KLCA, the Barcelona Clinic Liver Cancer strategy, and other international protocols provide a roadmap, the actual clinical application is tailored to each patient. Therefore, multidisciplinary care is crucial in HCC treatment, involving continuous collaboration and research across various fields.

The new HCC white paper by the KLCA, titled "Hepatocellular carcinoma in Korea: The past, Present, and the Future", aims to consolidate these processes. The book is divided into five chapters, each containing three to six sections. Chapter 2, "Epidemiology of HCC in Korea", covers the changing causes and prevalence of HCC, its national disease burden, socioeconomic impact, and forecasts the epidemiological trends of HCC in an aging and globalizing Korea. Chapter 3, "Diagnosis of HCC in Koreans", reviews the yearly and stage-specific diagnosis of HCC, the evolution of radiological and pathological diagnostics, and discusses future directions for diagnostic advancements. Chapter 4, "Advancements and Blueprints for HCC Treatment in Korea", provides a historical overview of HCC treatments in Korea and envisions

future treatment landscapes. Chapter 5, "Policy Recommendations for Future Diagnosis and Treatment of HCC", predicts changes in HCC treatment in the era of artificial intelligence and emphasizes the importance of policy support and resource allocation strategies.

The publication of the HCC white paper holds significant meaning in the history of HCC in Korea. As the title suggests, this book will serve as a mirror reflecting the past, a discussion of the present, and a record predicting the future of HCC in Koreans.

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THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# Special Symposium 1

## Evolving Standards in Liver Disease Management: Guidelines from Theory to Practice

**Chairs:**

**Masatoshi Kudo** (Kindai Univ., Japan)
**Woo Jin Chung** (Keimyung Univ.)

**Joong-Won Park**

*Myongji Hospital, Hanyang University*

## Self Introduction

Joong-Won Park is a Director of the Liver/Liver Cancer Center, a Director of the Cancer Integrative Healing Center, and an Invited Professor of the Department of Gastroenterology and Hepatology at Myongji Hospital, Hanyang University Medical Center. He was a Principal Scientist at the National Cancer Center (NCC), Korea, a Professor at the Graduate School of Cancer Science and Policy, NCC Korea, and a director of the Onco-Innovation Unit NCC Korea, the Head of the Center for Liver Cancer, NCC, Korea, and the Head of Translational and Clinical Research at the NCC Research Institute. Dr. Park completed his Medical degree at Seoul National University, followed by a residency in Internal Medicine and a Clinical Fellowship in Hepatology at Seoul National University Hospital. He achieved a Ph.D. in Medicine at Seoul National University. He was an Assistant and Associate Professor in the Department of Gastroenterology and Hepatology at Chung-Ang University Medical College. He was a Visiting Scientist at the Center for Basic Research in Digestive Diseases, Mayo Clinic, Rochester, USA.

His research interests include the diagnosis and management of primary liver cancer, hepatocarcinogenesis, and viral hepatitis. He has led and participated in many clinical trials and published more than 200 research papers on liver cancer, cirrhosis, and hepatitis, which have been cited more than 30,000 times.

He was a Chair of the Scientific Committee of Asian-Pacific Primary Liver Cancer Experts (APPLE) 2016-2022, and was a Governing Board member of the International Liver Cancer Association (ILCA) 2016-2020. He has been the Chair of the Guideline Committee for the Hepatocellular Carcinoma Management of the Korea Liver Cancer Association-NCC Korea since 2003. He was the President of the Korea Liver Cancer Association (KLCA) 2017-2018. He received the Medical Research Award from the National Academy of Medicine of Korea and the Medical Achievement Award from the Prime Minister of the Republic of Korea in 2021.

# Attributes and Principles for Better Practice Guidelines: An Experience on the Korea Liver Cancer Association (KLCA)-National Cancer Center (NCC) Korea Hepatocellular Carcinoma (HCC) Guidelines

**Joong-Won Park** *Myongji Hospital, Hanyang University*

Clinical practice guidelines (CPGs) are systematically developed statements and recommendations based on the latest research and evidence, and are intended to help healthcare decision-making and improve patient outcomes for specific clinical circumstances. CPGs are not fixed protocols that must be followed but are intended for healthcare professionals and providers to consider. The attributes of CPGs include transparency, clarity, target audience, user-friendliness, and versatility. The overarching principles of CPGs include using evidence-based, multidisciplinary approaches and considering socio-economic, cultural, and contextual factors. The 2022 KLCA-NCC Korea HCC CPG adheres to these attributes and principles, providing recommendations relevant to the Korean healthcare system and designed for reference by various global healthcare professionals.

The KLCA (formerly KLCSG)-NCC Korea practice guidelines for managing HCC were first announced in 2003 and revised four times. As many new studies have been conducted, the KLCA-NCC Korea Practice Guideline Revision Committee (KPGRC) initiated the revision of the guidelines to develop a new recommendation plan that integrates the most up-to-date research findings and expert opinions after the release of the 2018 guidelines. The primary targets of these new guidelines are patients with suspicious or newly diagnosed HCC. The key to treatment according to these guidelines is the initial treatment of patients with newly diagnosed HCC; however, for the first time, we extensively reviewed and discussed residual, progressive, or recurrent cancer after initial treatment. All required funding was provided by the NCC.

Forty-nine experts of KPGRC from the departments of hepatology, oncology, surgery, radiology, interventional radiology, and radiation oncology participated over ten months. According to the PICO process, 1028 of the latest references were reviewed, and 78 recommendations (73 of which were evidence-based and five of which were expert opinion-based) for 16 items were presented. Number of recommendations according to level of evidence and recommendation grade is A1 24; A2 7; B1 27; B2 7; C1 21; C2 7; D1 5. New, more advanced criteria for imaging diagnosis and diagnosis algorithms were recommended. New first-line treatments for the first diagnosed patient and a second-line treatment

for recurrence-remaining-progression are also presented. In addition to the best treatment option, the alternative treatments are also suggested to supplement the gray-zone and blind points of the evidence-based guidelines. 2022 KLCA-NCC CPG included recommendations for HCC patients in the COVID-19 pandemic status.

The complete draft was then reviewed by the advisory board and through a public meeting. It was modified further at the KPGRC department head meeting. The guidelines made through this process were endorsed by the open meeting, the board of directors of the KLCA, and the NCC. The KLCA-NCC Korea will update part or all of these guidelines when new test methods, drugs, or treatments regarding HCC are developed, and significant new research findings are made.


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**Rohit Loomba**

*University of California San Diego, USA*

## Self Introduction

Dr. Rohit Loomba is a Professor of Medicine (with tenure), Chief, Division of Gastroenterology and Hepatology, at the University of California at San Diego. He is an internationally recognized thought leader in translational research and innovative clinical trial design in nonalcoholic steatohepatitis (NASH), and non-invasive assessment of liver disease using advanced imaging modalities.

Dr. Loomba is the founding director of the UCSD MASLD Research Center, which fosters collaborative team science where a multi-disciplinary team of researchers are conducting cutting edge research in all aspects of NAFLD including non-invasive biomarkers, genetics, epidemiology, clinical trial design, imaging end-points, and integrated OMICs using microbiome, metabolome and lipidome. This integrated approach has led to several innovative applications such as establishment of MRI-PDFF as a non-invasive biomarker of treatment response in early phase trials in NASH, which has now been adopted in more than 100 clinical trials conducted worldwide. He holds several patents on non-invasive biomarkers of NASH and fibrosis.

His research is funded by the National Institutes of Health as a Principal Investigator including two R01s, three U01 (two NIDDK and one from NIAAA), clinical core director of P30 (NIDDK) and project director P01 (NHLBI) grant mechanisms, Foundation of NIH, as well as several large multicenter, multi-million dollar investigator initiated research projects funded by the industry. He is the Principal Investigator, UCSD, for the NIDDK-sponsored NASH Clinical Research Network and the Liver Cirrhosis Network. He also serves as on the Scientific Advisory Board of numerous biotechnology and large pharmaceutical companies and guides clinical drug development and biomarker discovery programs globally.

He serves on the Editorial Board of Gastroenterology, Journal of Hepatology, GUT and Nature Reviews in Gastroenterology and Hepatology. He recently completed a 5-year term as the Deputy Editor of HEPATOLOGY, the official journal of the AASLD. Currently, he serves as the co-Editor of Alimentary Pharmacology and Therapeutics, an international journal in the field of gastroenterology and Hepatology. Dr. Loomba has published more than 500 manuscripts and has an H-index of 131. He has been consistently listed among the top 1% of the globally highly cited scientists across all fields since 2019 by Web of Science. He is an elected member of the American Society of Clinical Investigation (ASCI), and the Association of American Physicians (AAP).

### *Education*

| | |
|---|---|
| 08/05-05/07 | Masters of Health Science in Clinical Research (NIH-Duke University Combined Program)<br>Duke University School of Medicine, Durham, NC |
| 08/93 – 03/99 | M.B.B.S. (equivalent of MD) The Armed Forces Medical College, Pune University India |

## Representative Publications

1. Loomba R. Autoimmune hepatitis: a clinical challenge. Nov 2002, Resident Rept J, published by AGA.
2. Loomba R and Liang TJ. Novel approaches to new therapies for hepatitis B virus infection. Antivir ther 2006; 1: 1-16.
3. Lutchman G, Modi A, Pomrat K, Kleiner D, Ghany MG, Heller T, Loomba R, Park Y, Liang TJ, Hoofnagle JH. The effects of discontinuing pioglitazone in patients with nonalcoholic steatohepatitis. Hepatology 2007;46(2): 424-9.
4. Loomba R and Ghany MG. Diagnosis and treatment of chronic HBeAg-negative hepatiis B. Curr Hepatitis Rept 2007; 6:146-153.
5. Loomba R and Liang TJ. Treatment of chronic hepatitis B. Antivir Ther 2007; 12 Suppl 3:H33-41.

# AASLD Guidelines on Clinical Assessment and Management of MASLD

**Rohit Loomba** *University of California San Diego, USA*

**Pierre-Emmanuel Rautou**

*Université Paris-Cité, France*

## Self Introduction

### *Titles and Diplomas*

| | |
|---|---|
| 2015 | Research direction accreditation ("Habilitation de direction de recherches") |
| 2011.06 | PhD. in vascular biology, summa cum laude, University of Paris 7, Paris, France. Supervisor: Dr. Chantal M. Boulanger |
| 2009 | Completion of clinical training in Hepatology, Paris Hospitals, France |
| 2008.06 | Doctor of Medicine (MD), summa cum laude, University of Paris 7. Hepatology. Supervisor: Prof. Dominique Valla |
| 2007 | Master Degree. University of Paris 7, Paris, France |

### *Current Positions*

| | |
|---|---|
| 2019-present | Inserm team leader, Inserm UMR-1149, Research Center on Inflammation, Paris https://www.rautoulab.com/ |
| 2016-present | Full Professor, Hepatology Department, Beaujon Hospital, Clichy, and Université Paris-Cité |
| 2012-present | Head of the Liver Hemodynamic Laboratory, Beaujon Hospital, Clichy, France http://hupnvs.aphp.fr/hemodynamique-hepatique/ |

## Representative Publications

1. Vion AC*, Kheloufi M*, Hammoutene A, Poisson J, Lasselin J, Devue C, Pic I, Dupont N, Busse J, Starke K, Lafaurie-Janvore J, Barakatf AI, Loyer X, Souyri M, Viollet B, Julia P, Tedgui A, Codogno P, Boulanger CM*, Rautou PE*. Autophagy is required for endothelial cell alignment and atheroprotection under physiological blood flow. Proc Natl Acad Sci U S A. 2017 Oct 10;114(41):E8675-E8684 (OA; impact factor 2022: 11.1)
2. Payancé A, Silva-Junior G, Bissonnette J, Tanguy M, Pasquet B, Levi C, Roux O, Nekachtali O, Baiges A, Hernández-Gea V, Laouénan C, Lebrec D, Albuquerque M, Paradis V, Moreau R, Valla D, Durand F, Boulanger CM, Garcia-Pagan JC, Rautou PE. Hepatocyte microvesicle levels improve prediction of mortality in patients with cirrhosis. Hepatology. 2018 Oct;68(4):1508-1518 (OA; impact factor factor 2022: 13.5)
3. Hammoutene A, Biquard L, Lasselin J, Kheloufi M, Tanguy M, Vion AC, Mérian J, Colnot N, Loyer X, Tedgui A, Codogno P, Lotersztajn S, Paradis V, Boulanger CM, Rautou PE. A defect in endothelial autophagy occurs in patients with nonalcoholic steatohepatitis and promotes inflammation and fibrosis. J Hepatol 2020 Mar;72(3):528-538. (OA; impact factor 2022: 25.7)
4. Poisson J, Tanguy M, Davy H, Camara F, El Mdawar MB, Kheloufi M, Dagher T, Devue C, Lasselin J, Plessier A, Merchant S, Blanc-Brude O, Souyri M, Mougenot N, Dingli F, Loew D, Hatem SN, James C, Villeval JL, Boulanger CM, Rautou PE. Erythrocyte-derived microvesicles induce arterial spasms in JAK2V617F myeloproliferative neoplasm. J Clin Invest. 2020 May 1;130(5):2630-2643. (OA; impact factor 2022: 15.9)
5. Elkrief L, Ganne-Carrié N, Manceau H, Tanguy M, Valainathan SR, Riescher-Tuczkiewicz A, Biquard L, Barget N Chaffaut C, Louvet A, Paradis V, Ziol M, Bæk R, Møller Jørgensen M, Van Niel G, Coly PM, Hammoutène A, Dujardin F, Peoc'h K, Poynard T, Chevret S, Rautou PE. Hepatocyte-derived biomarkers predict liver-related events at 2 years in Child-Pugh class A alcohol-related cirrhosis. J Hepatol. 2023. Oct;79(4):910-923 (OA; impact factor 2022: 25.7)

# EASL Guidelines on Vascular Liver Disease

**Pierre-Emmanuel Rautou** *Université Paris-Cité, France*


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DAY 2: June 28 (Fri)

# KASL Symposium 3

## Emerging Therapies and Diagnostics in Steatotic Liver Disease

**Chairs:**

**Sang Hoon Park** (Hallym Univ.)
**Won Kim** (Seoul National Univ.)


## Mark Muthiah

*National University Hospital, Singapore*


## Self Introduction

He graduated from the Yong Loo Lin School of Medicine, National University of Singapore. He subsequently undertook specialist training in Internal Medicine, Gastroenterology, and Hepatology, graduating as the valedictorian of his cohort. He undertook further research training in Hepatology in Virginia Commonwealth University, USA.

Dr Muthiah has a keen interest in Hepatology and liver transplantation and is currently the Medical Director of the Liver Transplantation Programme in the National University Hospital (NUH), Singapore. His research interest is in the interplay of cardiometabolic diseases and the liver, and has published extensively on the topic

## Research Interests

MASLD, liver transplantation

## Representative Publications


1. Lim WH, Ng CH, Tan D, Tseng M, Xiao J, Yong JN, Zeng RW, Cho E, Tay P, Ang CZ, Koh JH, Teng M, Syn N, Kow A, Huang DQ, Tan EX, Rinella ME, Sanyal A, Muthiah M*, Siddiqui MS. Natural history of NASH cirrhosis in liver transplant waitlist registrants. Journal of Hepatology. Epub June 2023.
2. Chew NWS, Ng CH, Tan DJH, Kong G, Lin C, Chin YH, Lim WH, Huang DQ, Quek J, Fu CE, Xiao J, Syn N, Foo R, Khoo CM, Wang JW, Dimitriadis GK, Young DY, Siddiqui MS, Lam CSP, Wang Y, Figtree GA, Chan MY, Cummings DE, Noureddin M, Wong VW, Ma RCW, Mantzoros CS, Sanyal A, Muthiah MD*. The global burden of metabolic disease: Data from 2000 to 2019. Cell Metabolism. March 2023.
3. Smirnova, E., Muthiah, M. D.*, Narayan, N., Siddiqui, M. S., Puri, P., Luketic, V. A., Contos, M. J., Idowu, M., Chuang, J. C., Billin, A. N., Huss, R. S., Myers, R. P., Boyett, S., Seneshaw, M., Min, H. K., Mirshahi, F., & Sanyal, A. J. Metabolic reprogramming of the intestinal microbiome with functional bile acid changes underlie the development of NAFLD. Hepatology. May 2022.
4. Ng, C. Y., Lee, K. L., Muthiah, M. D., Wu, K. X., Chioh, F. W. J., Tan, K., Soon, G. S. T., Shabbir, A., Loo, W. M., Low, Z. S., Chen, Q., Tan, N. S., Ng, H. H., Dan, Y. Y., & Cheung, C. Endothelial-immune crosstalk contributes to vasculopathy in nonalcoholic fatty liver disease. EMBO Reports. Nov 2022.
5. Tan, D. J. H., Ng, C. H., Lin, S. Y., Pan, X. H., Tay, P., Lim, W. H., Teng, M., Syn, N., Lim, G., Yong, J. N., Quek, J., Xiao, J., Dan, Y. Y., Siddiqui, M. S., Sanyal, A. J., Muthiah, M. D., Loomba, R., & Huang, D. Q. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. Lancet Oncology, March 2022.

# Clinical Data Based on Old NAFLD and New MASLD: Shared vs. Separated

**Mark Muthiah** *National University Hospital, Singapore*

This talk will explore the evolving landscape of fatty liver disease, comparing clinical data based on the established diagnosis of Non-alcoholic Fatty Liver Disease (NAFLD) with the recently proposed Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) definition. The speaker will cover the differences in epidemiology, diagnosis, as well as clinical outcomes. He will also discuss implications on clinical trials.

**Byoung Kuk Jang**

*Keimyung University*

## Self Introduction

Prof. Byoung Kuk Jang is a Professor of the Department of Internal medicine, Keimyung University College of Medicine.

Prof. Jang graduated from Keimyung University College of Medicine with his medical degree in 1995 and completed his internship and residency at the Department of Internal medicine at Keimyung University Dongsan Hospital, receiving his diploma in Internal medicine in 2000.

Prof. Jang has been taking a number of roles, including Chairman of the Korean NAFLD study group (2024- ).

## Research Interests

NAFLD, Liver fibrosis, HCC, Autophagy

## Representative Publications

1. JCAD, a new potential therapeutic target in cholestatic liver disease. Jang BK. Clin Mol Hepatol. 2024 Mar 8. doi: 10.3350/cmh.2024.0128.
2. Lobeglitazone inhibits LPS-induced NLRP3 inflammasome activation and inflammation in the liver. PLoS One. 2023 Aug 24;18(8):e0290532.
3. High Sodium Intake, as Assessed by Urinary Sodium Excretion, Is Associated with Nonalcoholic Fatty Liver Disease or Sarcopenia. Gut Liver. 2023 May 15;17(3):456-465.
4. Evogliptin Directly Inhibits Inflammatory and Fibrotic Signaling in Isolated Liver Cells. Int J Mol Sci. 2022 Oct 1;23(19):11636.
5. Increased Levels of Phosphorylated ERK Induce CTGF Expression in Autophagy-Deficient Mouse Hepatocytes. Cells. 2022 Aug 30;11(17):2704.
6. Fibrotic burden during antiviral therapy for chronic hepatitis B, not ALT level, independently predicts liver cancer risk. Liver Int. 2022 Aug;42(8):1902-1906.
7. Kahweol Induces Apoptosis in Hepatocellular Carcinoma Cells by Inhibiting the Src/mTOR/STAT3 Signaling Pathway. J Mol Sci. 2021 Sep 29;22(19): 10509.

# Diagnostic Criteria and Clinical Impact of Steatotic Liver Disease Sub-Classification

**Byoung Kuk Jang** *Keimyung University*

The term "non-alcoholic fatty liver disease" (NAFLD) was initially introduced in 1986 to encompass a spectrum of liver conditions characterized by hepatic steatosis in the absence of significant alcohol consumption. Over time, there was a recognition that the term "non-alcoholic" did not accurately reflect the underlying metabolic factors contributing to hepatic steatosis. In 2020, a group of experts proposed metabolic dysfunction associated fatty liver disease (MAFLD) as a new nomenclature and definition for liver disease associated with hepatic steatosis to better align terminology with metabolic disorders. The newly proposed MAFLD was a new concept that complemented several problems with NAFLD, especially since it is an exclusionary nature of the diagnosis and the lack of recognition of the underlying disease pathophysiology. However, there was controversy over the detailed diagnostic criteria and whether other liver diseases of various causes, such as viral hepatitis and alcoholic liver disease, were also included.

Meanwhile, in 2023, a global Delphi consensus process jointly led by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) was conducted to objectively review the need for a change in the NAFLD nomenclature. As a result of the consensus-building process, the term "metabolic dysfunction associated steatotic liver disease" (MASLD) was proposed to replace NAFLD, reflecting the association of hepatic steatosis with metabolic dysfunction. MASLD was defined as the presence of hepatic steatosis and at least one cardiometabolic risk factor, with specific criteria for alcohol intake and exclusion of other causes of steatosis. Additionally, fatty liver disease (SLD) has been introduced as an umbrella term encompassing a variety of liver diseases characterized by the accumulation of fat in liver cells. These diseases can be broadly categorized into NAFLD, alcoholic liver disease (ALD), and other miscellaneous causes of hepatic steatosis. The diagnosis of SLD is based on identifying hepatic steatosis through imaging techniques (ultrasound, MRI, CT) or liver biopsy, with at least 5% steatosis considered significant. The main categories under the new nomenclature for SLD are that MASLD replaces NAFLD and describes patients with hepatic steatosis and metabolic risk factors. Metabolic dysfunction associated steatohepatitis (MASH) replaces non-alcoholic steatohepatitis (NASH) and is used to describe patients with MASLD and active necroinflammation characterized by lobular inflammation and hepatocyte swelling. Metabolic dysfunction and alcohol-re-

lated liver disease (MetALD) are among MASLD patients with increased alcohol consumption, especially at moderate levels of alcohol consumption. Other conditions included in SLD include alcohol-related liver disease, fatty liver disease due to other causes, and fatty liver disease of unknown etiology.

SLD, especially MASLD, is closely associated with metabolic dysfunction, including obesity, insulin resistance, dyslipidemia, and hypertension, making it an important component of the metabolic syndrome. Classification and diagnosis of SLD subtypes are expected to help healthcare professionals tailor interventions based on underlying etiology and associated risk factors, influencing risk assessment, treatment strategies, and patient outcomes. Understanding the different subtypes of SLD is important for accurate diagnosis, prognosis, and management of patients with liver disease as it allows targeted approaches to address specific metabolic or alcohol-related factors contributing to hepatic steatosis.

In summary, SLD encompasses a variety of conditions characterized by liver fat accumulation, with NAFLD, ALD, and other causes representing the major subtypes. The diagnostic criteria and clinical significance of SLD highlight the importance of considering metabolic dysfunction, alcohol consumption, and other etiologic factors in the evaluation and management of patients with liver disease.


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**Mi Na Kim**

*Yonsei University*

## Self Introduction

### *Education*

M.D., Yonsei University College of Medicine, Seoul, Republic of Korea
Master Degree, Medicine, Graduate School, Yonsei University, Seoul, Republic of Korea
Ph.D., Medicine, Graduate School, Yonsei University, Seoul, Republic of Korea

### *Professional Training & Appointments*

- Internship, Residency, Fellowship & Clinical research assistant professor, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
- Assistant professor & Associate professor, Department of Internal Medicine, CHA University School of Medicine, Seongnam-si, Korea
- Postdoc Research Fellow, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, U.S.A.

### *Current position*

Associate professor, Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

## Research Interests

MASLD and chronic viral hepatitis: Treatment strategies and factors influencing long-term prognosis

## Representative Publications

1. Kim MN, Lee JS, Lee HW, et al. ALT Is Not Associated With Achieving Subcirrhotic Liver Stiffness and HCC During Entecavir Therapy in HBV-Related Cirrhosis. Clin Gastroenterol Hepatol 2023;21(9):2278-2287.e5.
2. Kim MN, Han K, Yoo J, Hwang SG, Zhang X, Ahn SH. Diabetic MAFLD is associated with increased risk of hepatocellular carcinoma and mortality in chronic viral hepatitis patients. Int J Cancer 2023;153(8):1448-1458.
3. Kim MN, Kim BK, Roh YH, Choi NR, Yu SJ, Kim SU. Comparable Efficacy Between Ongoing Versus Initiation of Antiviral Therapy at Treatment for HBV-related Hepatocellular Carcinoma. Clin Gastroenterol Hepatol 2022;20(8):1877-1880.e3.
4. Kim MN, Han K, Yoo J, Hwang SG, Ahn SH. Increased risk of hepatocellular carcinoma and mortality in chronic viral hepatitis with concurrent fatty liver. Aliment Pharmacol Ther 2022;55(1):97-107.
5. Kim MN, Lo CH, Corey KE, et al. Red meat consumption, obesity, and the risk of nonalcoholic fatty liver disease among women: Evidence from mediation analysis. Clin Nutr 2022;41(2):356-364.
6. Kim MN, Lo CH, Corey KE, et al. Weight gain during early adulthood, trajectory of body shape and the risk of nonalcoholic fatty liver disease: A prospective cohort study among women. Metabolism 2020;113:154398.
7. Kim MN, Kim SU, Kim BK, et al. Increased risk of hepatocellular carcinoma in chronic hepatitis B patients with transient elastography-defined subclinical cirrhosis. Hepatology 2015;61(6):1851-9.

# Pathophysiology-Based Treatment Targets and Successful Trials in MASH

**Mi Na Kim** *Yonsei University*

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), is the most common chronic liver disease, affecting approximately one-third of the world's population. Metabolic Associated Steatohepatitis (MASH), formerly known as nonalcoholic steatohepatitis (NASH), is a progressive form of MASLD characterized by hepatic inflammation and damage due to fat accumulation in the liver. MASH and significant fibrosis are associated with a poor prognosis. Understanding the pathophysiological mechanisms underlying MASH is crucial for identifying effective treatment targets and developing successful therapeutic interventions.

MASH is influenced by a complex pathophysiology involving lipotoxicity, insulin resistance and activation of inflammatory and immune pathways, which are closely linked to metabolic disorders. Given the multifactorial nature of MASH, multiple pathophysiological targets are being explored for drug treatment. With several promising drug candidates in phase 3 trials and others in the pipeline, each targeting difference mechanisms of action, the future of MASH therapy appears highly promising. Currently, the significant clinical demand of MASH-specific pharmacotherapies is being addressed by the landmark FDA conditional approval of resmetirom, which is based on a surrogate or intermediate clinical endpoint expected to predict clinical benefit.

In this lecture, we will review the various drugs being developed for MASH, their mechanisms of action, and the findings of their clinical trials.

## References

1. Tilg H, Byrne CD, Targher G. NASH drug treatment development: challenges and lessons. Lancet Gastroenterol Hepatol 2023;8(10):943-954. (In eng). DOI: 10.1016/s2468-1253(23)00159-0.
2. Harrison SA, Loomba R, Dubourg J, Ratziu V, Noureddin M. Clinical Trial Landscape in NASH. Clin Gastroenterol Hepatol 2023;21(8):2001-2014. (In eng). DOI: 10.1016/j.cgh.2023.03.041.
3. Dufour JF, Anstee QM, Bugianesi E, et al. Current therapies and new developments in NASH. Gut 2022;71(10):2123-34. (In eng). DOI: 10.1136/gutjnl-2021-326874.
4. Kokkorakis M, Boutari C, Hill MA, et al. Resmetirom, the first approved drug for the management of metabolic dysfunction-associated steatohepatitis: Trials, opportunities, and challenges. Metabolism 2024;154:155835. (In eng). DOI: 10.1016/j.metabol.2024.155835.
5. Armandi A, Bugianesi E. Dietary and pharmacological treatment in patients with metabolic-dysfunction associated steatotic liver disease. Eur J Intern Med 2024;122:20-27. (In eng). DOI: 10.1016/j.ejim.2024.01.005.

**Tetsuo Takehara**

*Osaka University, Japan*

## Self Introduction

Dr. Tetsuo Takehara is a Professor of Medicine in the Department of Gastroenterology and Hepatology at Osaka University Graduate School of Medicine Japan. He graduated from Osaka University Medical School and received clinical training in internal medicine and gastroenterology at Osaka University Hospital and its affiliated hospitals. He obtained his Ph.D. in Medicine at Osaka University, and studied as a postdoctoral fellow at the Massachusetts General Hospital, Division of Gastroenterology, Boston, MA. He assumed his current position in 2011. Dr. Takehara is a physician scientist in hepatology and gastroenterology and his major research interests include, basic research on cell death and innate immunity and, clinically, viral and non-viral hepatitis, liver fibrosis and HCC. He directs and oversees the Osaka Liver Forum (OLF) study, a large and comprehensive cohort study of hepatitis and HCC patients in the Kansai area. Currently, Dr. Takehara is the director General of the Japan Society of Hepatology (JSH). He received the 2017 JSH Award for his significant contributions to hepatology.

## Research Interests

Steatohepatitis, Viral Hepatitis, Cirrhosis, HCC

## Representative Publications

1. Tahata Y, et al. Posttreatment liver function, but not baseline liver function stratifies patient survival after direct-acting antiviral treatment in decompensated cirrhosis with hepatitis C virus. J Gastroenterol 2023 Dec;58(12):1211-1221
2. Murai H, et al. Multiomics identifies the link between intratumor steatosis and the exhausted tumor immune microenvironment in hepatocellular carcinoma. Hepatology. 2023 Jan 1;77(1):77-91.
3. Maesaka K, et al. Hyperprogressive disease in patients with unresectable hepatocellular carcinoma receiving atezolizumab plus bevacizumab therapy. Hepatol Res. 2022 Mar;52(3):298-307.
4. Myojin Y, et al. Serum growth differentiation factor 15 predicts hepatocellular carcinoma occurrence after hepatitis C virus elimination. Aliment Pharmacol Ther. 2022 Feb;55(4):422-433.
5. Myojin, Y, et al. Hepatic Stellate Cells in Hepatocellular Carcinoma Promote Tumor Growth Via Growth Differentiation Factor 15 Production. Gastroenterology. 2021 Apr;160(5):1741-1754.

# Tumor Immunity and Immunotherapeutic Susceptibility of Steatotic HCC

**Tetsuo Takehara** *Osaka University, Japan*

Lifestyle changes have led to an increase in fatty liver disease and non-viral liver cancer. I would like to address two clinical questions (#1 How to diagnose MASLD at high risk of liver cancer from a very large number of patients? #2 Can molecular classification of non-viral liver cancer be applied to clinical practice?) and to share our recent research findings.

We previously demonstrated that hepatic stellate cells produce GDF15 during liver inflammation and carcinogenesis (Gastroenterology 2021). To examine the significance of serum GDF15 in the risk assessment of MASLD, we used three different cohorts of MASLD (biopsy-proven cohort, biopsy-naïve hospital cohort and health check cohort). Serum GDF15 was an independent risk factor for liver carcinogenesis and useful for identifying patients at high risk of liver cancer from those at risk of fibrosis, as indicated by a FIB-4 index of 1.3 or higher (Aliment Pharmacol Ther, 2024).

Several molecular classifications have been reported. While previous studies have focused on all liver cancers, we focused on non-viral liver cancers and examined molecular classification and genome alterations in 113 tumors. Non-viral liver cancer was classified into three subclasses, well stratified for prognosis after liver resection. Class I was associated with p53 mutations and high proliferative phenotype, while Class III was associated with CTNNB1 mutations and immune cold phenotype. Class II was as a class not characterized as a genetic mutation, but had more immune cell infiltration and more tumors classified in the "immune class". Tumors in the "immune class" were associated with steatotic liver cancers (which contains high level of lipid droplets in tumor cells), Steatotic liver cancers had higher PD-L1 expression and more exhausted T-cell infiltration. Statotic liver cancer may be more sensitive to immunotherapy and if so, MRI could be used for identifying these tumors (Hepatology, 2023).


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# Special Interest Group 1

## Critical Care Strategies for Acute-on-Chronic Liver Failure

**Chairs:**

**Barjesh Chander Sharma** (Govind Ballabh Pant Hospital, India)
**Hong Soo Kim** (Soonchunhyang Univ.)

**Rakhi Maiwall**

*Institute of Liver and Biliary Sciences, India*

## Self Introduction

Dr Rakhi Maiwall is currently working as a Professor of Hepatology at Institute of Liver and Biliary Sciences and is also Incharge of the Liver Intensive Care at ILBS. She is the Vice-secretary of the International club of ascites and has published original articles in indexed journals and has more than 160 publications and contributed 10 book chapters

## Research Interests

- AKI
- Acute and acute on chronic liver failure
- Critical care hepatology
- Extracorporeal Liver support

## Representative Publications

1. Maiwall R, Rao Pasupuleti SS, Hidam AK, Kumar A, Tevethia HV, Vijayaraghavan R, Majumdar A, Prasher A, Thomas S, Mathur RP, Kumar G, Sarin SK. A randomised-controlled trial (TARGET-C) of high vs. low target mean arterial pressure in patients with cirrhosis and septic shock. J Hepatol. 2023 Aug;79(2):349-361.
2. Maiwall R, Kumar A, Pasupuleti SSR, Hidam AK, Tevethia H, Kumar G, Sahney A, Mitra LG, Sarin SK. A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. J Hepatol. 2022 Sep;77(3):670-682.
3. Maiwall R, Rastogi A, Pasupuleti SSR, Hidam AK, Singh M, Kadyan S, Jain P, Kumar G, Sarin SK. Natural history, spectrum and outcome of stage 3 AKI in patients with acute-on-chronic liver failure. Liver Int. 2022 Dec;42(12):2800-2814
4. Maiwall R, Singh SP, Angeli P, Moreau R, Krag A, Singh V, APASL clinical practice guidelines on the management of acute kidney injury in acute-on-chronic liver failure. Hepatol Int. 2024 Jun;18(3):833-869
5. Maiwall R, Pasupuleti SSR, Hidam AK, Rastogi A, Thomas S, Kumar G, Kumar A, Sarin SK. Non-resolution of acute kidney injury in the first week portends the development of chronic kidney disease in critically ill patients with cirrhosis. Aliment Pharmacol Ther. 2023 Sep;58(6):593-610

# Different Definitions and Prognostic Stratification of Acute-on-Chronic Liver Failure

**Rakhi Maiwall** *Institute of Liver and Biliary Sciences, India*

The acute on chronic liver failure is a syndrome which is associated with high short-term mortality and an expedited liver transplant remains the ultimate saviour. The syndrome has been defined by various definitions and still there is no unified definition for describing the syndrome. The Asia Pacific association for the study of liver (APASL) defines ACLF as a syndrome which is characterized by the development of jaundice with a bilirubin more than 5 mg/dl and coagulopathy with an international normalized ratio above 1.5 with ascites and/or hepatic encephalopathy occurring within 4 weeks of the onset of jaundice in a patient with a background presence of diagnosed or undiagnosed chronic liver disease.[1-3] The APASL revised this definition and also included 28-day mortality in the definition. The European association for the study of liver disease defined ACLF based on renal dysfunction with hepatic encephalopathy. Presence of single kidney failure i.e. serum creatinine more than or equal to 2 mg/dl is defined as ACLF grade 2. While 3 or more organ failures is defined as ACLF grade 3. The mortality increases with an increase in the ACLF grade with mortality of almost 77-80% with ACLF grade 3.[4-6] The challenge with the definition is the diagnosis at a very late stage of the disease where the futility can be defined in failure to improve the ACLF grade by day 7. The mortality was 100% with worsening of ACLF grade at day 7 in the prospective study by the EASL-CLIF consortium. The APASL definition compared to the definition by EASL-CLIF identifies patients at the early stage and defines the concept of the "golden window" which can be targeted for spontaneous reversal without liver transplantation. Failure to recover the failing liver in the golden window leads to the development of organ failures which may meet the CLIF criteria for ACLF. The definition of by the North American Association of study of liver disease (NACSELD) defines ACLF with presence of two or more extrahepatic organ failures. This definition identifies patients extremely late in the course of the disease which is associated with extremely high mortality and almost limited chances of reversibility. Late diagnosis of the syndrome may also be a deterrent to a successful outcome with liver transplantation. The American association of study of liver disease (AASLD) has recently put forth a revised definition of ACLF defined as a syndrome characterized by an acute insult in patients with chronic liver disease, compensated or decompensated cirrhosis characterised by jaundice and coagulopathy followed by the development of atleast one extrahepatic organ failure (kidney, brain, circulation or respiration). The Chinese Group on the Study of Severe Hepatitis B-ACLF (COSSH-ACLF) defines, ACLF as an acute decompensation in a patient with HBV-related chronic

liver disease with failure of any of six primary organ systems (liver, coagulation, brain, kidney, circulation, and respiration). The loss is defined as per the definition by CLIF consortium. The different definitions have created a lot of confusion as each definition even though identifies patients with high mortality but recognizes patients heterogeneously in different phases of the disease. There is a need for a global and unified consensus on the diagnosis of ACLF so that a unified prognostication and management protocols could be developed for effective management of patients.

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**Jin Won Huh**

*University of Ulsan*

## Self Introduction

Prof. Jin-Won Huh is a Professor in the Department of Pulmonary and Critical Care Medicine at ASAN Medical Center, University of Ulsan College of Medicine and is currently holding the position of Chief of the Medical Intensive Care Unit at ASAN Medical Center.

Prof. Huh graduated from Kyungpook University College of Medicine with his medical degree in 1998 and received his Ph.D. in 2008 from University of Ulsan College of Medicine. She completed her internship and residency in the Department of Internal Medicine at Asan Medical Center, receiving his diploma in Internal Medicine in 2003.

Since 2010, Prof. Huh has been worked as an intensivist in the Medical ICU, ASAN Medical center

## Research Interests

I am an experienced intensivist with expertise in the management of respiratory failure and a translational scientist with expertise in clinical/translational studies in human sepsis and acute lung injury. As the director of the ASAN Medical Center ICU Biorepository, we have enrolled over 700 critically ill septic subjects, and these biospecimens have permitted many publications presenting new functional biomarkers in sepsis and the acute respiratory distress syndrome (ARDS).

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1. Hyun DG, Lee SY, Ahn JH, Hong SB, Lim CM, Koh Y, Huh JW. Prognosis of mechanically ventilated patients with COVID-19 after failure of high-flow nasal cannula: a retrospective cohort study. Respir Res. 2024 Mar 1;25(1):109.
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# Respiratory Support in Acute-on-Chronic Liver Failure

**Jin Won Huh** *University of Ulsan*

Acute liver failure (ALF) and acute on chronic liver failure (ACLF) are conditions frequently encountered in the ICU and are associated with high mortality.

In these patients, the respiratory support strategy is identical to that of critically ill patients with respiratory failure.

- High-flow nasal cannula (HFNC) is preferred over noninvasive ventilation in hypoxic critically ill patients with ALF or ACLF
- Noninvasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation is preferred over HFNC in hypercapnic respiratory failure in patients with ALF or ACLF considering the impact on intracranial pressure (ICP) and venous return
- A low tidal volume strategy (limiting Vt to 4–8 mL/kg predicted body weight and maintaining plateau airway pressure <30 cmH2O) is favored over a high tidal volume strategy in patients with ALF or ACLF and ARDS
- Cautious use of high PEEP over low PEEP (at 8 cmH2O or 12 cmH2O) is recommended in patients with ALF or ACLF and ARDS after balancing the potential benefit with the risks of increasing ICP and reducing venous return

The recognition of ventilator-induced lung injury (VILI) has led to the concept of low tidal volume ventilation strategies with appropriate levels of PEEP to minimize lung distention and atelectrauma. Low tidal volume ventilation strategies may require increased sedation and/or paralysis. While deep sedation may affect cognition and arousal, patient-ventilator dyssynchrony could potentially worsen VILI and lead to weaning failure.

Specific respiratory complications in patients with liver failure include portopulmonary hypertension (POPH) and hepatopulmonary syndrome.

- Supportive care with supplemental oxygen is used in the treatment of hepatopulmonary syndrome, pending possible liver transplantation
- Agents approved for pulmonary arterial hypertension (PAH) are recommended in patients with a

mean pulmonary artery pressure greater than 35 mm Hg

Due to the high risk of infection and bleeding in critically ill patients with liver failure, a ventilator strategy to decrease the ventilator time is important.

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## Guadalupe Garcia-Tsao

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## Self Introduction

Dr. Garcia-Tsao is Professor of Medicine at Yale University School of Medicine and at the VA-Connecticut Healthcare System. She is Chair of the Baveno (International Portal Hypertension) Cooperation and Director of the Clinical Core of the NIH-funded Yale Liver Center. Dr. Garcia-Tsao was on the Governing Board of the American Association for the Study of Liver Diseases (AASLD) from 2008 to 2013 and was its President in 2012. Dr. Garcia-Tsao was Associate Editor of Journal of Hepatology from 2001 to 2004, Associate Editor of Hepatology from 2011 to 2016 and has been Associate Editor of the New England Journal of Medicine since 2019. Dr. Garcia-Tsao has contributed to the science and practice of cirrhosis, portal hypertension and its complications, having authored over 300 original articles, including 24 practice guidelines (h-index 110). She has received numerous awards including the International Recognition Award (from EASL), the Distinguished Clinician Educator and Mentor Award (from AASLD) and the Distinguished Scientific Achievement Award (from the American Liver Foundation).

## Research Interests

Dr. Garcia-Tsao's investigation focuses on cirrhosis, portal hypertension and related complications, specifically varices and variceal hemorrhage, ascites and acute kidney injury. Interest in cirrhosis includes staging of the disease: compensated, decompensated and further decompensated as well as the new stage of recompensation. She has has authored over 300 original research publications in addition to several society guidelines and position papers in the field.

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# Workup and Management of Acute Kidney Injury in Patients with with Acute-on-Chronic Liver Failure

**Guadalupe Garcia-Tsao** *Yale University, USA*

- Variceal hemorrhage (VH) is an acute complication of cirrhosis associated with significant short-term morbidity and mortality
- Standard initial management is based on a combination of:
  - o splanchnic vasoconstrictors (octreotide, terlipressin) that decrease portal pressure by decreasing portal venous inflow
  - o antibiotics (norfloxacin) that decrease bacterial translocation that increases with hemorrhage, worsening splanchnic vasodilation and can lead to infections;
  - o endoscopic variceal ligation that will directly control bleeding at the variceal rupture site
- In general, Child A (mostly compensated) patients and Child B ("early" decompensated patients with moderately altered liver function) who are not actively bleeding at the time of endoscopy respond favorably to this treatment strategy. However, in patients with Child C cirrhosis (further decompensated and with altered liver function) standard therapy often fails and patients often rebleed despite standard initial therapy. Rebleeding in this setting is associated with a high mortality
- Ultimately, the therapy that will lead to a rapid reduction in portal pressure with cessation of bleeding, is placement of the transjugular intrahepatic porto-systemic shunt (TIPS). However, by shunting blood away from the liver it can be associated with porto-systemic encephalopathy (PSE) and even liver failure, particularly in already decompensated patients.
- TIPS was previously considered as salvage therapy, i.e. its use was reserved to patients in whom standard therapy had failed. However, given that such failure occurs mostly in Child C patients, salvage TIPS was associated with a very high mortality (>80%)
- A landmark multicenter study by Garcia-Pagan et al showed that early (within 72 hours of admission) placement of TIPS (placed in anticipation of rebleed, that is, preemptive placement of TIPS or pTIPS) in patients identified as having a high risk of rebleeding (Child C or B (7-8 score) was associated with decreased rebleeding and mortality without significantly increasing the risk of hepatic encephalopathy. The benefits of p-TIPS were also described in an RCT by Lv et al that included Child C and B patients. In contrast, the survival benefit of p-TIPS was not observed in an RCT by Dunne et al with a higher risk of HE. \

- In a post-hoc analysis by Trebicka et al of 380 patients with acute-on-chronic liver failure included in a larger cohort of patients with VH showed that p-TIPS was associated with a decreased risk of 6-week rebleeding and mortality
- Meta-analyses of studies on pTIPS differ in their conclusions (Nicoara-Farcau et al; Hussain et al)
- Most of these studies have included patients bleeding from esophageal varices. Data regarding the efficacy of pTIPS in the prevention of rebleeding and death in patients with fundal varices is being explored in a multicenter trial (GAVAPROSEC) that uses glue obliteration as a comparator
- A large multicenter randomized trial (REACT-AVB) comparing pTIPS with the standard of care in patients with CPT scores 7–13 is underway in the United Kingdom. The results will hopefully clarify effect on survival and, importantly, the patient population that most benefits from pTIPS
- Also, different prognostic scores are being developed to best select patient who will most benefit from pTIPS
- Nevertheless, and unless these ongoing studies conclude differently,
  - Baveno consensus recommendations state: pre-emptive TIPS with polytetrafluoroethylene (PTFE)-covered stents within 72 h (ideally <24 h) is indicated in patients bleeding from esophageal varices who meet any of the following criteria: Child-Pugh class C <14 points or Child-Pugh class B >7 with active bleeding at initial endoscopy or HVPG >20 mmHg at the time of hemorrhage. In patients fulfilling the criteria for pre-emptive TIPS, ACLF, hepatic encephalopathy at admission and hyperbilirubinemia at admission should not be considered contraindications.
  - AASLD guidance recommends: In patients with CTP class B score >7 and active bleeding on endoscopy or CTP class C score 10–13, preemptive TIPS creation (within 72 hours and ideally within 24 hours of initial upper endoscopy) should be recommended in absence of absolute contraindications to TIPS. If TIPS is not locally available, transfer to a center with the capacity to intervene should be considered.

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*The Catholic University of Korea*

## Self Introduction

Prof. Myeong Ju Song is a Professor of the Division of Hepatology, Department of Internal medicine, College of Medicine, The Catholic University of Korea.

Prof. Song graduated from College of Medicine, The Catholic University of Korea with his medical degree in 2001 and completed his internship and residency at the Department of Hepatology at Seoul St. Mary's University Hospital, receiving his diploma in Hepatology in 2014.

Since 2013, Prof. Song has been taking a number of roles, including Director, External Affairs Committee of the Korean Association of the Study of the Liver (2022-2023), and currently as Deputy Director of Editorial Board of the Korean association of Gastroenterology (2024- ).

## Research Interests

Dr. Song has a special interest in the treatment and prediction of chronic liver disease including Viral hepatitis, fatty liver, liver cirrhosis and liver cancer. With his expertise in cirrhosis and HCC, he is focusing on prognosis in patients with kidney injury and novel biomarkers or scoring system. Innovative, translational, and longstanding clinical research has ever been a pursuit in his academic career.

## Representative Publications

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# Approach to Abnormal Liver Blood Tests in Inpatients and Outpatients

**Myeong Jun Song** *The Catholic University of Korea*

Abnormal liver blood tests are common clinical findings, often indicating underlying liver disease. This presentation provides a comprehensive approach to evaluating abnormal liver blood tests in both inpatient and outpatient settings. The approach involves a detailed history and physical examination, followed by laboratory investigations and specialized tests when necessary. Common causes of abnormal liver blood tests include viral hepatitis, drug-induced liver injury, alcoholic liver disease, fatty liver, and systemic disease (non-hepatic origin). Management strategies focus on identifying the underlying etiology, risk stratification, and multidisciplinary collaboration for optimal patient care. A systematic approach to abnormal liver blood tests is essential in clinical practice, facilitating timely intervention and improved patient outcomes in both inpatient and outpatient settings.

## Introduction

Abnormal liver blood tests are frequently encountered in clinical practice and serve as important indicators of underlying liver disease. Prompt and accurate evaluation of abnormal liver blood tests is essential for timely diagnosis and appropriate management. This aims to provide a comprehensive approach to the assessment and management of abnormal liver blood tests in both inpatient and outpatient settings.

## Evaluation

The evaluation of abnormal liver blood tests begins with a comprehensive assessment of the patient's medical history and a thorough physical examination. 1) Key elements of the history include exploration of alcohol consumption, medication history, potential exposure to viral hepatitis, and any family history of liver disease. 2) Clinical examination may reveal telltale signs such as jaundice, hepatomegaly, or ascites. 3) Laboratory investigations play a pivotal role in the evaluation, encompassing liver function tests (PLT, PT INR, bilirubin, albumin, AST, ALT, ALP, rGTP), viral serologies (HBsAg, anti-HCV, anti-HAV), and 4) imaging studies (abdominal ultrasound, CT/MRI, Fibroscan). These diagnostic tests aid in distinguishing between different types of liver injury: hepatocellular injury, characterized by elevated AST and ALT levels; cholestatic injury, identified by elevated ALP and bilirubin levels; and mixed-type injury, which pres-

ents with a combination of hepatocellular and cholestatic features.

**Hepatocellular Injury:** characterized by damage to the liver parenchyma,

***1. Diagnostic Markers:***

- Aspartate transaminase (AST): Elevated levels suggest hepatocellular damage but are not liver-specific as AST is also present in muscles, kidneys, and heart.
- Alanine transaminase (ALT): Elevated ALT levels are more specific to liver injury than AST and are often used in conjunction with AST to assess hepatocellular damage.

***2. AST/ALT Ratio:***

- An **AST/ALT ratio of >1** may suggest alcoholic liver disease or cirrhosis, whereas a ratio of <1 is commonly seen in non-alcoholic fatty liver disease (NAFLD) and acute viral hepatitis.

***3. Additional Tests:***

- Viral serologies: To rule out viral etiologies.
- Autoimmune markers: Such as antinuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) for autoimmune hepatitis.
- Imaging: Ultrasound or elastography to assess liver parenchyma and fibrosis.

**Cholestatic Injury:** marked by impaired bile formation or flow, leading to accumulation of bile constituents in the blood.

***1. Diagnostic Markers:***

- Alkaline phosphatase (ALP): An enzyme associated with the biliary epithelium. Elevated ALP levels suggest cholestasis or biliary obstruction.
- Bilirubin: A breakdown product of heme. Elevated levels of direct (conjugated) bilirubin indicate impaired excretion into the bile, seen in cholestasis.

***2. Gamma-glutamyl transferase (GGT):***

- GGT is often used in conjunction with ALP to confirm that the source of elevated ALP is the liver, as ALP is also present in bone, intestine, and placenta.

***3. Imaging:***

- Ultrasound, CT, or MRI: To evaluate for biliary obstruction or structural abnormalities.

**Mixed-Type Injury:** characterized by elements of both hepatocellular and cholestatic injury, often suggesting more complex liver pathology.

***1. Diagnostic Profile:***

- A combination of elevated AST/ALT and ALP/bilirubin levels.
- The pattern may be variable, and the specific ratios of these enzymes can point toward different etiologies.

### *2. Further Evaluation:*

- Comprehensive history and examination: To identify potential causes such as drugs, toxins, or systemic diseases.
- Liver biopsy: May be considered to clarify the diagnosis when noninvasive tests are inconclusive.

## Conclusion:

A systematic approach to abnormal liver blood tests is essential for accurate diagnosis and effective management. Distinguishing between hepatocellular, cholestatic, and mixed-type liver injuries is critical for the diagnosis and management of liver diseases. A thorough understanding of the diagnostic tests and their interpretation, combined with clinical assessment, is essential for hepatologists. Further investigation, including imaging and possibly liver biopsy, may be necessary to confirm the diagnosis and guide treatment strategies. By integrating detailed history-taking, appropriate laboratory investigations, and multidisciplinary collaboration, we can provide timely interventions and improve patient outcomes in both inpatient and outpatient settings.

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**Eun Ju Cho**

*Seoul National University*

## Self Introduction

Dr. Cho graduated from Seoul National University College of Medicine (Seoul, Korea) in 2005. She got a Master's and a Doctor's degree of Medicine from the same college in 2011 and 2013, respectively. After she accomplished residency (from 2006 to 2010) and fellowship (from 2010 to 2012) at Seoul National University Hospital (Seoul, Korea), she joined the faculty at the Seoul National University Hospital since 2014.

## Research Interests

HCC biomarker, NAFLD/MAFLD

## Representative Publications

1. USP44 promoter can detect early-stage hepatocellular carcinoma in blood samples. BMB Rep. 2022 Aug 26:5673. (coauthor)
2. Comprehensive Metabolomic Search for Biomarkers to Differentiate Early Stage Hepatocellular Carcinoma from Cirrhosis. Cancers 2019, 11, 1497. (co-first author)
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# Adverse Events of Systemic Therapy in HCC Patients: Assessment and Education

**Eun Ju Cho** *Seoul National University*

**Hyun Suk Park**

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## Self Introduction

Hyun Suk Park is currently the manager of oncology clinical trial unit at ASAN Medical Center.

She graduated from Hallym University College of Nursing in Science in 2000 and she gained experience of Medical intensive care & cardiovascular unit experience in Kangdong Sacred heart hospital and Asan medical Center. She is currently enrolled in the graduate program in Genetic Counseling At Ulsan University.

Currently he has been taking a role as Deputy Director of Education Department of the KACRC (Korean Association for Clinical Research Coordinator)(2022- ).

# Role of Artificial Intelligence to Assist Clinical Research Coordinators

**Hyun Suk Park** *Asan Medical Center*

Artificial Intelligence (AI) has fundamentally transformed the landscape of clinical trials, bringing unprecedented efficiency, accuracy, and innovation to the field. This transformation is evident in various aspects of clinical trial management, from patient recruitment and data analysis to predictive modeling and personalized medicine. This introduction will explore how AI is revolutionizing clinical trials, with specific references to its implementation in hospitals and its impact on Clinical Research Coordinators (CRCs). We will also highlight significant milestones in AI development, such as AlphaFold and Digital Twin technology, that underscore the potential of AI in this domain.

## 1. Enhancing Patient Recruitment and Retention

AI-driven tools have streamlined the patient recruitment process, identifying suitable candidates more efficiently by analyzing large datasets of patient records and clinical histories. This not only reduces the time and cost associated with recruitment but also ensures a more diverse and representative patient population. For instance, machine learning algorithms can sift through electronic health records (EHRs) to match patients with relevant trials, improving enrollment rates significantly (Borah et al., 2020; Weng et al., 2019).

## 2. Optimizing Data Management and Analysis

The complexity of data management in clinical trials has been vastly simplified by AI. AI algorithms can handle vast amounts of data, ensuring more accurate and comprehensive analysis. This has led to improved data integrity and faster decision-making processes. AI-powered platforms can identify patterns and anomalies in data that might be missed by human analysts, thus enhancing the overall quality of clinical trials (Geng et al., 2022; Andaur Navarro et al., 2020).

## 3. Predictive Modeling and Personalized Medicine

One of the most promising applications of AI in clinical trials is predictive modeling. AI can predict patient outcomes based on historical data, which helps in designing more effective and safer trials. Per-

sonalized medicine, which tailors treatment plans to individual patients based on genetic, environmental, and lifestyle factors, is also being advanced by AI. Techniques such as machine learning and deep learning are pivotal in analyzing genomic data, thus paving the way for more precise and personalized treatment plans (Esteva et al., 2019; Beam et al., 2020).

## 4. Impact on Clinical Research Coordinators (CRCs)

The introduction of AI in hospitals has significant implications for CRCs. AI tools can automate routine tasks such as data entry and monitoring, allowing CRCs to focus on more complex activities like patient interaction and protocol management. This not only increases efficiency but also enhances job satisfaction among CRCs by reducing the burden of administrative tasks (Verma & Madan, 2021; Miotto et al., 2018).

## 5. Historical Milestones: AlphaFold and Digital Twin

The development of AlphaFold by DeepMind represents a major breakthrough in protein folding, solving a problem that has perplexed scientists for decades. AlphaFold's ability to predict protein structures with remarkable accuracy has profound implications for drug discovery and development, accelerating the timeline of clinical trials (Jumper et al., 2021; Senior et al., 2020).

Digital Twin technology, which creates a virtual model of a physical entity, is another transformative AI application. In the context of clinical trials, Digital Twins can simulate patient responses to treatments, allowing for more precise and personalized trial designs. This technology not only enhances the predictive accuracy of trials but also reduces the need for extensive and time-consuming physical trials (Bruynseels et al., 2018; Tao et al., 2019).

## Conclusion

The integration of AI in clinical trials is revolutionizing the field, offering enhanced efficiency, accuracy, and personalization. From improving patient recruitment and data analysis to advancing predictive modeling and personalized medicine, AI is reshaping every aspect of clinical trial management. The impact on CRCs is significant, allowing them to focus on more meaningful tasks, and historical milestones like AlphaFold and Digital Twin technology highlight the vast potential of AI in clinical trials. As AI continues to evolve, its role in clinical trials is expected to expand, further transforming the landscape of medical research.

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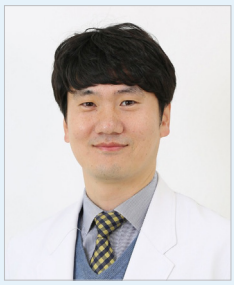

**Seong Jae Kim**

*Gyeongsang National University*

## Self Introduction

Prof. Seong Jae Kim is a associate professor of the Department of Ophthalmology, Gyeongsang National University College of Medicine and is currently holding a position of Director of the External Cooperation in Gyeongsang National University Hospital.

Prof. Hong graduated from Gyeongsang National University College of Medicine with his medical degree in 2002 and completed his internship and residency at the Department of Ophthalmolgy at Gyeongsang National University Hospital, receiving his diploma in Ophthalmology in 2010.

Since 2017, Prof. Kim has been taking a number of roles, including Section Editor of Journal of Korean Ophthalmology Societry, a Committee member of Korean Cataract and Refractive Surgery, Korean Corneal Society, Korean Contact Lens Association, and currently as Vice President of the Hannam Corneal Society (2023- ).

In 2023, he established SMO (Site Management Organization) GNUN Co., Ltd. and currently serves as CEO.

## Research Interests

Cytomegalovirus Endotheliitis, corneal wound healing, dry eye syndrome, Deep learing based ophthalmic disease and severity evaluation, diabetic retinopathy

## Representative Publications

1. Cytomegalovirus Corneal Endotheliitis: A Comprehensive Review, Ocul Immunol Inflamm. 2024 Feb 28:1-10.
2. SARS-CoV-2 infection exacerbates the cellular pathology of Parkinson's disease in human dopaminergic neurons and a mouse model. Cell Rep Med. 2024 May 10:101570.
3. Role of Chondroitin Sulfate Proteoglycan 5 in Steroid-Induced Cataract. Cells. 2023 Jun 23;12(13):1705.
4. New Surgical Approach for Secondary Intraocular Lens Implantation Using an Artificial Bag with Optic Capture in Patients with Intraocular Lens Dislocation. Retina. 2023 Aug 1;43(8):1403-1407.
5. Development of the Integrated Glaucoma Risk Index. Diagnostics (Basel). 2022 Mar 17;12(3):734.

# Current Status and Prospects of Site Management Organization (SMO) in Clinical Trials

**Seong Jae Kim** *Gyeongsang National University*

Site Management Organizations (SMOs) play a pivotal role in the successful conduct of clinical trials by providing comprehensive support and services to clinical research sites. With the increasing complexity of clinical research, the demand for specialized expertise in study management, regulatory compliance, and patient recruitment has led to the emergence of SMOs as indispensable partners in the clinical trial ecosystem.

This presentation introduces the concept of SMOs, highlighting their key functions, benefits, and contributions to clinical research. We discuss the role of SMOs in streamlining study startup activities, optimizing site performance, and ensuring adherence to protocol requirements and regulatory standards. Additionally, we explore the advantages of partnering with SMOs, including access to a network of experienced investigators, enhanced patient recruitment capabilities, and centralized study oversight and coordination.

By leveraging their expertise and resources, SMOs facilitate efficient and high-quality execution of clinical trials, ultimately accelerating the development of new therapies and improving patient outcomes. This presentation provides a foundational understanding of SMOs and their value proposition in the dynamic landscape of clinical research.

Focusing on the importance of Site Management Organizations (SMOs) in clinical trials involves highlighting their critical role in optimizing study execution, ensuring regulatory compliance, and enhancing overall trial efficiency. Here are several key points to emphasize:

SMOs specialize in study management, regulatory affairs, and operational logistics, providing invaluable expertise to clinical research sites. By leveraging their experience and resources, SMOs streamline study startup activities, expedite regulatory approvals, and facilitate efficient site operations, allowing trials to proceed smoothly and on schedule.

SMOs play a crucial role in maintaining high-quality standards throughout the clinical trial process. They implement robust quality assurance and quality control measures to ensure adherence to protocol requirements, regulatory guidelines, and Good Clinical Practice (GCP) standards. By conducting site assessments, monitoring visits, and data audits, SMOs help identify and address potential issues proac-

tively, mitigating risks and safeguarding data integrity.

SMOs possess extensive networks of clinical research sites and investigators, enabling them to identify suitable study sites and recruit eligible participants efficiently. Through targeted recruitment strategies, patient engagement initiatives, and retention efforts, SMOs help maximize patient enrollment and minimize dropout rates, thereby accelerating study timelines and enhancing statistical power.

SMOs provide centralized support and resources to clinical research sites, alleviating administrative burdens and allowing investigators to focus on patient care and study conduct. From protocol development and study budgeting to site training and ongoing support, SMOs offer comprehensive assistance tailored to the specific needs of each trial, optimizing resource allocation and maximizing operational efficiency.

SMOs help mitigate operational and regulatory risks associated with clinical trials by implementing robust risk management strategies and compliance frameworks. Through proactive risk assessment, monitoring, and issue resolution, SMOs minimize the likelihood of protocol deviations, data discrepancies, and regulatory non-compliance, ensuring the integrity and credibility of trial results

SMOs foster collaborative partnerships between sponsors, clinical research sites, and other stakeholders, promoting synergy, communication, and mutual accountability throughout the trial lifecycle. By serving as a liaison between sponsors and sites, SMOs facilitate effective communication, problem-solving, and decision-making, fostering a cohesive and productive research environment.

THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# KLTS Symposium 1

## Beyond Boundaries: The Promise of Liver Transplants in Unusual Situations

**Chairs:**

**Gi-Won Song** (Univ. of Ulsan)
**Wipusit Taesombat** (Chulalongkorn Univ., Thailand)

**Jongman Kim**

*Sungkyunkwan University*

## Self Introduction

Jongman Kim received his MD from Korea University in 2000 and trained in the Department of Surgery, Korea University Medical Center until 2005. From 2008 to 2011, he worked as a fellow in the Transplantation Division, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine in Seoul, Korea. He studied solid organ transplantation and HCC in those periods.

He completed his Ph.D. (Korea University, 2009), which subject was immunotherapy using a 4-1BB antibody against cancer. As a professor, his career has continued in the Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine until now (2024).

He operated on laparoscopic liver resection in liver malignancy and living liver donors and has studied HCC hepatectomy patients. He has performed many prospective clinical trials, and international multicenter registration studies and thus published many papers. In addition, he has operated on living or deceased donor liver transplantation. His focus projects were minimal invasive surgical techniques, surgical techniques of liver transplantation, ABO-incompatibility, HCC, and immunosuppression in liver transplantation. He performed several clinical trials as principal investigator at this time. He published approximately 400 articles related to liver transplantation and/or HCC in the Journal of Hepatology, Hepatology, Annals of Surgery, British Journal of Surgery, Liver Transplantation, and Transplantation.

## Research Interests

- Living donor liver transplantation
- Post-transplant management
- Immunosuppression
- Surgical techniques
- Living liver donors
- Hepatocellular carcinoma

## Representative Publications

1. Jong Man Kim, Choon Hyuck David Kwon, Jae-Won Joh, Eun-Suk-Kang, Jae Berm Park, Joon Hyeok Lee, Sung Joo Kim, Seung Woon Paik, Suk-Koo Lee, Dae-Won Kim. ABO-incompatible Living Donor Liver Transplantation is Suitable in Patients without ABO-matched Donor. J Hepatol 2013 Dec;59(6):1215-1222
2. Jong Man Kim, Choon Hyuck David Kwon, Jae-Won Joh, Sangbin Han, Dong Hyun Sinn, Gyu-Seong Choi, Eun-Suk Kang, Joon Hyeok Lee, Gaabsoo Kim, Suk-Koo Lee. Case-matched comparison of ABO-incompatible and ABO-compatible living donor liver transplantation. Br J Surg 2016 Feb;103:276-283
3. Jong Man Kim, Choon Hyuck David Kwon, Jae-Won Joh, Dong Hyun Sinn, Sanghoon Lee, Gyu-Seong Choi, Suk-Koo Lee. The Conversion of Once-daily Extended-release Tacrolimus is Safe in Stable Liver Transplant Recipients: A Randomized Prospective Study. Liver Transplant 2016;22:209-216
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5. Rhu J. Kim JM, Choi GS, Kwon CHD, Joh JW. Validation of the alpha-fetoprotein model for hepatocellular carcinoma recurrence after transplantation in an Asian population. Transplantation 2018;102(8):1316-1322 (Corresponding author)

# Patient Selection and Result for Unresectable Hepatic Metastasis from Colorectal Cancer

**Jongman Kim** *Sungkyunkwan University*

During the last decade, liver transplantation has emerged as a possible treatment option for highly selected patients with nonresectable colorectal liver metastasis (CRLM). It is, however, still a controversial topic with several unclarified issues in terms of optimal selection criteria, scarcity of donor grafts, as well as clinical work-up, and optimal timing for the removal of the primary colorectal tumor.

In a comparative study between the Nordic VII chemotherapy trial and the SECA-1 trial on liver transplantation for CRLM, 64 out of 571 (11%) were found to have liver-only disease among the nonresectable patients, indicating that a high degree of careful selection is required to identify patients that can be possible transplant candidates [5]. Given an adequate preselection process that indicates liver-only metastasis, it is still necessary to eliminate other negative predictive factors, such as a right-sided primary tumor, BRAF mutation, N2 status, and poor differentiation of the primary since they are all associated with inferior outcomes [6].This approach to management has reached a consensus in the guidelines on liver transplantation for CRLM from the International Hepato-Pancreato-Biliary Association (IHPBA) [7].

Nonresectable colorectal liver metastasis is emerging as an indication for liver transplantation in selected patients. Survival compatible with conventional indications for liver transplantation can be obtained by adhering to stringent selection criteria. The role of technical resectability as an exclusion criterion for patients with a high number of lesions and favorable transplant criteria remains unclarified and merits further investigation.

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**Julie K. Heimbach**

*Mayo Clinic, USA*

## Self Introduction

Dr. Julie Heimbach is a Professor of Surgery and the Director of the William von Liebig Center for Transplantation at Mayo Clinic in Rochester, Minnesota. She is an abdominal transplant surgeon who has focused on living donor liver transplantation and liver transplantation for hilar cholangiocarcinoma. Dr. Heimbach has also been very active in organ allocation policy development at the national level, having served as the chair of the OPTN/UNOS Liver Committee. She has also served on the board of the American Society of Transplant Surgeons and the governing board of the AASLD. In addition, Dr. Heimbach serves as an Associate Editor of the Journal of Hepatology.

## Research Interests

- Liver transplant for malignancy
- Obesity and liver transplant
- Living donor liver transplantation

## Representative Publications

1. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, Jou JH, Kulik LM, Agopian VG, Marrero JA, Mendiratta-Lala M, Brown DB, Rilling WS, Goyal L, Wei AC, Taddei TH.Hepatology. 2023 Dec 1;78(6):1922-1965. doi: 10.1097/HEP.0000000000000466. Epub 2023 May 22.PMID: 37199193
2. Liver Transplantation as a New Standard of Care in Patients With Perihilar Cholangiocarcinoma? Results From an International Benchmark Study. Breuer E, Mueller M, Doyle MB, Yang L, Darwish Murad S, Anwar IJ, Merani S, Limkemann A, Jeddou H, Kim SC, López-López V, Nassar A, Hoogwater FJH, Vibert E, De Oliveira ML, Cherqui D, Porte RJ, Magliocca JF, Fischer L, Fondevila C, Zieniewicz K, Ramírez P, Foley DP, Boudjema K, Schenk AD, Langnas AN, Knechtle S, Polak WG, Taner CB, Chapman WC, Rosen CB, Gores GJ, Dutkowski P, Heimbach JK, Clavien PA
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5. Long-term outcomes of patients undergoing simultaneous liver transplantation and sleeve gastrectomy. Zamora-Valdes D, Watt KD, Kellogg TA, Poterucha JJ, Di Cecco SR, Francisco-Ziller NM, Taner T, Rosen CB, Heimbach JK.Hepatology. 2018 Aug;68(2):485-495. doi: 10.1002/hep.29848. Epub 2018 May 14.PMID: 29457842

# Perihilar Cholangiocarcinoma: Current Strategy and Future Directions

**Julie K. Heimbach** *Mayo Clinic, USA*

Hilar Cholangiocarcinoma is a malignancy of the bile duct epithelium which affects approximately 1.2/100,000 in the United States annually and has a grim prognosis.[1] The most common risk factor in the western world is Primary Sclerosing Cholangitis (PSC), with the risk of developing CCA for patients with PSC at about 10-15%. The standard therapy is surgical resection, though due to involvement of bilateral biliary or vascular structures or the presence of underlying liver disease due to PSC, many patients present with disease which is not amenable to complete resection. Of those who are thought to be resectable on presentation, only about 70-80% of attempted resections are successful in achieving negative margins.[2] Overall survival for patients who undergo resection is approximately 25-30% 5 year survival, but for patients with a margin-negative, lymph-node negative resection, 5 year survival improves to 35-45%. [2-4]

Due to the large number of patients who are not eligible for resection, liver transplantation was initially proposed as an ideal solution given it would not be limited by margins, and would provide treatment for underlying liver disease in cases of CCA associated with PSC. However, early data from Penn et al demonstrated rapid recurrence and very poor outcomes and for many years, hilar cholangiocarcinoma was considered to be a contra-indication for liver transplantation.[5] However, a protocol which utilized aggressive neoadjuvant chemoradiotherapy followed liver transplantation was developed both at the University of Nebraska as well as at the Mayo Clinic. Utilizing this strategy, which at the Mayo Clinic, involves administration of external beam radiotherapy given with continuous 5-fluorouracil for 3 weeks to a total does of 4500 cGy followed by an additional brachytherapy boost of approximately 1500 cGy, followed by oral Capecitabine given 2 out of every 3 weeks until transplant. Due to the high predilection for lymph node metastases, patients undergo formal staging laparoscopy near the time of LT.

Utilizing this combined protocol, the intention to treat survival is approximately 50% at 5 years.[6] For patients who are able to be successfully transplanted, the 5 year survival is approximately 70%. Though questions have been raised about whether these results could be duplicated outside of Mayo Clinic, a multi-center analysis reporting the experience of 279 patients across 12 large US transplant centers was reported by Darwish-Murad et al in 2012 and demonstrated a similar 65% disease-free 5 year survival which improved to 72% 5 year disease free survival when standardized inclusion criteria were adhered

to.[7] Because of the successful adoption of neoadjuvant treatment followed by LT at multiple centers, patients with early stage hilar CCA are eligible to receive a standard MELD exception when they undergo treatment at a center which has an approved protocol

Careful analysis of outcomes following the treatment protocol has identified which patients are more likely to experience waitlist drop out, as well as which patients are at an increased risk of recurrence. These data have been useful in counseling patients as well as in developing adjuvant therapy strategies for higher-risk post-transplant patients. However, the difficulty in establishing an early diagnosis of hilar CCA (prior to the development of disease metastasis) as well as prolonged wait time to transplant in the setting of the morbidity of the neoadjuvant therapy remain major challenges. Increasing the utilization of living donor LT to reduce waiting time as well as exploring other forms of neoadjuvant therapy such as stereotactic body radiation or proton beam radiotherapy may lead to improved outcomes, though methods of establishing an earlier diagnosis as well as the development of an effective systemic therapy for patients with advanced disease are greatly needed.

The main controversies for this protocol have been at both ends of the spectrum. Questions have been raised regarding the utility of the neoadjuvant therapy, with the argument being that the superior outcomes observed with neoadjuvant therapy followed by liver transplantation compared to prior results with transplantation are related to optimal patient selection, in choosing only patients with very early stage disease. While a randomized trial comparing patients with and without neoadjuvant therapy has not been performed, the indirect evidence is evidence in support of neoadjuvant therapy is compelling. A series Canada report on patients transplanted with incidental CCA (thus no neoadjuvant therapy and presumably early disease since it was not recognized prior to transplantation) found high recurrence rate. Similarly a series from Spain on outcomes for perihilar CCA demonstrated only a 30% survival at 3 years with the vast majority of deaths being due to recurrence. In addition, patients with the same stage of disease prior to enrollment (T2, N0) with microscopic or no residual cholangiocarcinoma in the explanted liver are at a lower risk of recurrence of disease than those with bulky residual disease, supporting the role of obliteration of the tumor by the neoadjuvant therapy in improving survival. Surprisingly, even patients with no residual disease in the explant have developed disease recurrence so this effect is not universally protective. The second area of controversy is given that outcomes for the combined protocol in unresectable hilar CCA (presumably more advanced than resectable) are generally superior to that which can be achieved with resection, should this also be offered to patients with resectable hilar cholangiocarcinoma? The primary future directions are what strategies can be employed to allow earlier identification of perihilar CCA in patients with known risk, such as PSC, what can be done to increase the efficacy of neodajuvant therapy, and whether there is an effective adjuvant therapy regimine that may have an acceptable qrisk/benefit ratio.

In summary, the standard therapy for hilar cholangiocarcinoma is resection, with 5 year survival of 35-50% possible in the setting of R0 resection though many patients present with unresectable disease.

For selected patients who are not eligible for resection, neoadjuvant chemoradiation followed by liver transplantation has demonstrated excellent 5-year recurrence-free survival.

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**Ho Joong Choi**

*The Catholic University of Korea*

## Self Introduction

### *Education*

| | |
|---|---|
| 1997-2003 | College of Medicine, The Catholic University, Seoul, Korea |
| 2011-2017 | Ph.D., College of Medicine, The Catholic University, Seoul, Korea |

### *Professional Experience*

| | |
|---|---|
| 2003-2004 | Internship, Catholic Medical Center |
| 2004-2008 | Surgical Residency, Catholic Medical Center |
| 2011-2013 | Fellowship, HBP Division, Department of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |
| 2013-2016 | Clinical Assistant professor of Surgery, Bucheon St. Mary's hospital, The Catholic University of Korea |
| 2016-2017 | Clinical Assistant professor of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |
| 2018-2019 | Clinical Associate professor of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |
| 2019-2023 | Assistant professor of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |
| 2023- | Associate professor of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |

## Research Interests

- HCC
- LT
- Liver resection
- Minimal invasive liver surgery

## Representative Publications

1. The Clinical Outcomes of Patients with Portal Vein Tumor Thrombi After Living Donor Liver Transplantation. Liver Transplantation 2017.
2. Clinical Course of Hepatic Artery Thrombosis After Living Donor Liver Transplantation Using the Right Lobe. Liver Transplantation 2018.
3. Comparison of the long-term efficacy and safety of generic tacrolimus, Tacrobell, with Prograf in liver transplant recipients. Drug Design, Development and Therapy 2018.
4. Combining Everolimus and Ku0063794 Promotes Apoptosis of Hepatocellular Carcinoma Cells via Reduced Autophagy Resulting from Diminished Expression of miR-4790-3p. International Journal of Molecular Science 2021.
5. Intrahepatic IgA complex induces polarization of cancer-associated fibroblasts to matrix phenotypes in the tumor microenvironment of HCC. Hepatology 2024.

# The Role of Liver Transplantation for Intrahepatic Cholangiocarcinoma

**Ho Joong Choi** *The Catholic University of Korea*

Primary liver cancer is the fourth leading cause of cancer-related death worldwide. Among these primary liver cancers, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) are the most common. The role and indication of liver transplantation (LT) in HCC are relatively well established. However, LT in ICC has been avoided due to poor prognosis.

In general, ICC represents a challenging malignancy with limited treatment options and poor prognosis, particularly in advanced stages. Liver resection (LR) is the only recommended effective curative treatment for patients with ICC, but even after curative resection, the prognosis of ICC patients remains poor. Even after curative resection, the prognosis of ICC remains very poor, with a 5-year overall survival (OS) rate of only 20–35%.

Early experiences with LT for ICC were fraught with concerns about tumor recurrence and overall survival, and accordingly, LR is currently the only widely accepted treatment for ICC. However, recent studies have shown encouraging results, particularly in carefully selected patients meeting strict criteria. Advancements in immunosuppressive regimens, perioperative management, and surveillance protocols have contributed to improved outcomes and reduced rates of tumor recurrence post-transplant.

Key considerations in patient selection for LT in ICC include tumor size, number, and extent, as well as absence of extrahepatic disease and vascular invasion. Rigorous pre-transplant evaluation, incorporating advanced imaging techniques, tumor markers, and histopathological assessment, is essential to accurately assess tumor burden and predict post-transplant outcomes.

Furthermore, the integration of novel strategies such as neoadjuvant therapy, locoregional treatments, and molecular profiling holds promise for optimizing patient selection and enhancing the efficacy of LT in ICC. Multidisciplinary collaboration among hepatobiliary surgeons, oncologists, radiologists, and transplant specialists is paramount for the comprehensive management of patients undergoing LT for ICC.

In conclusion, liver transplantation represents a viable therapeutic option for select patients with intrahepatic cholangiocarcinoma, offering the potential for long-term disease control and survival benefit than LR. Continued research efforts aimed at refining patient selection criteria, optimizing perioperative management strategies, and exploring adjunctive therapies are essential for further advancing the role of LT in the management of ICC.

**Kwangho Yang**

*Pusan National University*

## Self Introduction

### *Education*

| | |
|---|---|
| 1996-2002 | Pusan National University, School of Medicine |

### *Professional Experience*

| | |
|---|---|
| 2003-2007 | Resident, Department of Surgery, Pusan National University Hospital |
| 2010-2012 | Fellow, Division of HBP and transplantation surgery, Department of Surgery, Pusan National University Yangsan Hospital |
| 2012-2017 | Assistant Professor, Division of HBP and transplantation surgery, Department of Surgery, Pusan National University Yangsan Hospital |
| 2017- | Associate Professor, Division of HBP and transplantation surgery, Department of Surgery, Pusan National University Yangsan Hospital |

## Research Interests

Liver transplantation and outcomes

## Representative Publications

1. Yang K, Park Y, Moon K, Ryu J, Chu C. Caudal middle hepatic vein trunk preserved right lobe graft in living donor liver transplantation. Ann Surg Treat Res. 2014 Oct;87(4):185-91.
2. Lee TB, Ko HJ, Shim JR, Choi BH, Ryu JH, Yang K. ABO-Incompatible Living Donor Liver Transplantation With a Simplified Desensitization and Immunosuppression Protocol: A Single-Center Retrospective Study. Exp Clin Transplant. 2021 Jul;19(7):676-685.
3. Yang K, Lee TB, Choi BH, Park YM, Ryu JH, Joo DJ, Chu CW. Development and Applicability of the A-P 200 Criteria for Liver Transplantation for Hepatocellular Carcinoma. Transplant Proc. 2016 Dec;48(10):3317-3322.

# HCC with Portal Vein Tumor Thrombosis

**Kwangho Yang** *Pusan National University*

Portal vein tumor thrombosis (PVTT) is detected in 10-40% of patients with hepatocellular carcinoma (HCC) at the time of diagnosis, and is associated with a dismal prognosis. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, HCC with PVTT is considered an advanced stage and systemic treatment is recommended as the first treatment option. And also, most published society guidelines, such as those from the American Association of Study of Liver Disease (AASLD), the Asian Pacific Association for the Study of Liver (APASL), and the European Association for the Study of Liver (EASL), recommend systemic therapy in patients with HCC and PVTT. Thus, liver transplantation (LT) for HCC with PVTT is not traditionally recommended due to high recurrence rate.

However, recent studies have shown promising outcomes after LT in selected cases of HCC with PVTT. Japanese liver cancer study group reported favorable outcomes after living donor LT (LDLT) in patients with HCC and PVTT, with better 3- and 5-year survival rates than in patients receiving systemic therapy, especially in patients with segmental PVTT.1 In Korean studies, relatively good 5-year survival rates were reported after LDLT in patients with HCC and PVTT, especially in those with low alpha-fetoprotein (AFP), low fluorodeoxygluscose-18 (FDG-18) uptake on positron emission tomography (PET), and small tumor size.2,3

Some studies have focused on LT after downstaging for HCC with PVTT. Soin et al. reported 5-year survival rate over 50% in patients with HCC and PVTT who underwent LDLT after successful downstaging using stereotactic body radiation therapy (SBRT) with or without transarterial chemoembolization (TACE) or transarterial radioembolization (TARE).4 Jeong et al. analyzed the oncologic outcomes of LDLT after downstaging using TACE and radiotherapy for HCC with major vascular invasion. 1- and 3-year disease free survival rates were 70.6 and 57.8%, respectively, and 1- and 3-year overall survival rates were 87.4 and 60.5%, respectively in this study.5 In a recent meta-analysis on HCC and PVTT after LT, the 5–year survival rate of patients with HCC and PVTT who were successfully downstaged before was 63%.6

To date, there are some limitations to make clear indication of LT for HCC with PVTT patients. Most studies on LT for HCC and PVTT were retrospective and included small cases. Moreover, downstaging protocols, timing of LT, and postoperative adjuvant therapy are heterogeneous.

In conclusion, LT for patients with HCC and PVTT, especially segmental PVTT, may be justified if down-staging is successful or tumor biology is favorable. More prospective, well-designed, large- scale studies are needed to make optimal criteria for indications of LT for patients with HCC and PVTT.

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6. Liu J, Qian J, Yang Z, et al. Patients with Hepatocellular carcinoma and portal vein tumour thrombosis after successful downstaging may be candidates for liver transplantation: A meta-analysis. J Hepatol. 2024;80(5):e219-e221.

THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# KLTS Coordinator Session

## Concerns for Living Liver Donors

**Chairs:**

**Kyoung Ock Jeon** (Severance Hospital)
**Seungheui Hong** (Samsung Medical Center)

**YoungRok Choi**

*Seoul National University*

## Self Introduction

### *Education*

| | |
|---|---|
| 1999-2003 | Busan National University College of Medicine, |
| 2007-2012 | M.S., College of Medicine, Seoul National University |
| 2014- | Ph.D. candidate, College of Medicine, Seoul National University |

### *Training*

| | |
|---|---|
| 2003.3-2004.2 | Intern-ship, Busan National University Hospital, Busan, Korea |
| 2004.3-2008.2 | Resident-ship in Department of Surgery, Seoul National University Hospital, Seoul, Korea |

## Research Interests

- Graft DSA in liver transplantation
- Bile exome excretion after liver transplantation
- Bile duct ischemia

## Representative Publications

1. Long-term outcomes of liver transplantation using grafts from donors with active hepatitis B virus replication: a multicenter cohort study, Annals of Surgical Treatment and Research 104 (4), 183
2. Total robot-assisted recipient's surgery in living donor liver transplantation: First step towards the future, J hepatobiliary pancreas science, https://doi.org/10.1002/jhbp.1327
3. Changes in Awareness Toward Minor's Organ Donation Through Structured Information; Survey, Transplant Int https://doi.org/10.3389/ti.2023.10795
4. Long - term outcomes of laparoscopic versus open liver resection for intrahepatic combined hepatocellular - cholangiocarcinoma with propensity score matching, Annals of Gastroenterological Surgery 6 (4), 562-568
5. Changes in Indices of Steatosis and Fibrosis in Liver Grafts of Living Donors After Weight Reduction, Front. Surg. 2022;9: 827526

# Long-Term Follow-up and Support Programs for Living Liver Donors in Korea

**YoungRok Choi** *Seoul National University*

Living organ donation, especially liver donation, is an incredible act of altruism that provides a critical lifeline for patients with end-stage liver disease. Despite its life-saving potential, it's crucial to recognize the physical and psychological impacts on the donor, making comprehensive short-term and long-term follow-up care essential.

Living liver donation involves a complex surgical procedure, and while many donors recover without major issues, the surgery is not without risks. Immediately following surgery, donors face potential complications such as infections, bleeding, and deep vein thrombosis. They also experience significant pain and discomfort, which requires effective pain management. Additionally, gastrointestinal issues like stress-related peptic ulcers can arise due to the physical and emotional stress of the surgery.

Long-term physical health monitoring is equally important. It's vital to maintain normal liver function and watch for potential liver failure. Some donors might experience chronic liver issues that require ongoing medical attention. Persistent pain at the surgical site can affect a donor's quality of life, lasting for months or even years after surgery. Moreover, abdominal hernias can develop, sometimes needing further surgical intervention. Recently, studies using the Korean national database have shown that the risk of metabolic diseases, high blood pressure, and diabetes may be higher than that of very healthy adults.

The psychological impact of living liver donation is substantial. In the short term, donors may suffer from anxiety and depression due to the stress of surgery and recovery, coupled with concerns about the recipient's health. They might also struggle with adjustment disorders as they adapt to temporary reductions in physical capacity and lifestyle changes. Long-term psychological issues include the risk of post-donation regret, particularly if complications arise or the recipient's health does not improve as expected. Chronic stress and post-traumatic stress disorder (PTSD) can also occur given the traumatic nature of the donation process.

Surveillance protocols for living donors differ across institutions and countries. In South Korea, organ transplantation centers have established their own detailed follow-up schedules involving frequent visits and comprehensive tests. These protocols include regular blood tests and imaging studies such as

CT scans to monitor the donor's recovery and detect any complications early. Internationally, the United States follows the OPTN policy, requiring a minimum of two years of follow-up with specific intervals at discharge, six months, one year, and two years, focusing on physical and socio-economic impacts. The United Kingdom recommends lifelong annual check-ups, with more frequent visits in the initial post-operative period, while Switzerland mandates follow-up at one, three, five, seven, and ten years post-donation, then biennially, including socio-economic surveys.

Enhancing these protocols with additional tests and support systems is crucial for ensuring donor well-being. Regular psychological evaluations using tools like PHQ-9 and GAD-7 at three months and one-year post-donation, and as needed for long-term monitoring, can help address mental health issues early. Surveillance for hypertension, diabetes, hyperlipidemia are recommended to monitor the long-term complications. For liver donors, assessing liver stiffness and detecting fibrosis might be particularly beneficial, especially in those with pre-existing conditions like fatty liver.

Support systems are vital for the donor's recovery. Financial assistance for medical follow-ups and any arising complications is essential, potentially including living donors in health insurance plans or providing stipends to cover medical costs. Access to professional mental health support to address anxiety, depression, and PTSD, with specialized programs for donors facing significant stress or trauma, can significantly improve the donor's psychological health. Peer support networks, where donors can share experiences and support each other, have shown to be beneficial in mitigating psychological distress. Additionally, educational programs informing donors about potential risks and post-donation care can help manage expectations and improve compliance with follow-up care.

In conclusion, living organ donors exhibit extraordinary generosity, and it is imperative that healthcare systems provide robust support to ensure their long-term well-being. Comprehensive medical and psychological follow-up, tailored to the specific needs of each donor, is essential. By implementing standardized surveillance protocols and enhancing support systems, we can honor the selflessness of living donors and safeguard their health and quality of life. Ensuring donor safety and health not only respects their altruistic act but also encourages future donations, thereby helping to address the critical shortage of organs available for transplantation.


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**Minkyung Nam**

*Hanyang University Hospital*

## Self Introduction

1999 Graduated from the Department of Nursing at Hanyang University
2008 Master's degree at Yonsei University College of Nursing
2012 Working as an organ transplant coordinator at Hanyang University Hospital Transplant Center

# Current Status of Living Liver Donor Management at Low Volume Center

**Minkyung Nam** *Hanyang University Hospital*

The most important concern in selecting a living liver donor is donor safety. Potential liver donors undergo a step-by-step medical treatment, consultation, and examination process over several weeks by various transplant team members.

Management of liver donors is divided into pre-operative care, surgery, and post-operative care. Preoperative management requires donor counseling, explanation of risks, assessment of donation motivation, confirmation of voluntary donation, and clinical examination. Donors need explanation and consent for the first and second consultations, examinations, and treatment procedures. Tests are conducted at each stage, and if abnormal findings are found in the test results, the donor is excluded. It must be explained that donation can be withdrawn if the donor is not willing to donate voluntarily or is unwilling to donate due to fear.

Liver donors should be assisted in making decisions about voluntary donation. Donors require treatment by a psychiatric specialist. Organ donation is possible based on expert opinion of a psychiatrist, and it is necessary to confirm whether donation is voluntary. Additionally, for KONOS organ transplant approval, it is necessary to conduct a purity evaluation to check whether there is motivation for organ donation and whether there is family pressure.

To help donors make prudent decisions, sufficient explanation of the postoperative pain, procedure, morbidity, complications, and death associated with liver donation is necessary during consultation and treatment.

Even after surgery, continuous management is necessary to ensure the health of the donor.

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2. Experiencesofphysicalcomplicationsandsequelaeamonglivingliverdonors. Jeong SJ, Kim HN.Korean J Transplant. 2019 Jun 30;33(2):36-45. doi: 10.4285/jkstn.2019.33.2.36.
3. Selectionandoutcomeof thepotentialliveliverdonor.Pamecha V, Mahansaria SS, Bharathy KG, Kumar S, Sasturkar SV, Sinha PK, Sarin SK.Hepatol Int. 2016 Jul;10(4):657-64. doi: 10.1007/s12072-016-9715-8. Epub 2016 Mar 17.
4. Evaluationof thedonorliverforlivingdonorlivertransplantation.Brandhagen D, Fidler J, Rosen C.Liver Transpl. 2003 Oct;9(10 Suppl 2):S16-28. doi: 10.1053/jlts.2003.50222.

**Ji Eun Lee**

*Severance Hospital*

## Self Introduction

| | |
|---|---|
| 1998 | Graduated from Yonsei University, Wonju College of Nursing. |
| 2021 | Master's degree from Yonsei University Graduate School of Public Health |
| 2000-2009 | Worked as a nurse in the organ transplant ward of Yonsei Medical Center Severance Hospital |
| 2009- | Working as an organ transplant coordinator at Yonsei Medical Center Severance Hospital |

## Representative Publications

1. 알코올성 간질환으로 간이식을 시행한 환자의 알코올 의존도와 가족의 공동 의존 정도 분석
2. Effect of symptom distress, social support and work change after liver transplantation on the recipients` quality of life
3. Pre-and postoperative care for Living liver donors

# Considerations for Liver Donor Management

**Ji Eun Lee** *Severance Hospital*

말기 간질환 및 간세포암 환자의 생존율이나 삶의 질에 긍정적인 결과를 보이면서 표준 치료법으로 자리를 잡은지 오래이나 우리나라는 뇌사 장기기증자의 절대적인 부족으로 가족간 생체 간이식이 활발하게 시행되고 있다. 국립장기조직혈액관리원 통계연보에 따르면 2022년 국립장기조직혈액관리원 통계 연보 기준 간이식 대기자는 6,351명으로, 한해 동안 시행된 간이식 1,453건 중 뇌사 간이식은 342건으로 전체 간이식의 23.5%, 생체 간이식은 1,111건으로 전체 간이식의 76.5%를 차지하고 있다. 현재 간이식 수술은 술기의 발전과 면역억제제 등 다양한 약물의 발전 등에 힘입어 혈액형 부적합 간이식이나 듀얼 생체 간이식 등 기증자의 영역이 점차 확대되고 있다.

이렇게 생체 간이식이 증가함에 따라 간기증자의 안전과 신체적 회복, 합병증 예방 등에 많은 노력을 기울이고 있지만 아직까지도 많은 관심과 연구는 간이식 수혜자 중심의 치료 과정과 수술 성공율, 삶의 질 등에 맞춰져 있는 것이 사실이다. 생체 간기증자는 본인의 질병이 아닌 수혜자의 건강 회복을 위하여 장기를 기증하는 자로, 기증을 결정하는 순간부터 수술 전 검사 및 상담 과정, 수술 직후 관리, 퇴원 후 일상으로의 복귀, 장기적 삶의 질, 신체적 및 정서적 후유증 등 다양한 정보의 제공과 지속적인 관리가 필요하다.

본 발표에서는 간 기증자가 간기증 관련 상담을 시작하면서부터 퇴원 후 일상생활로 복귀할 때까지의 과정을 살펴보고, 신체 및 정신건강의 회복, 사회로의 복귀를 하는데 어떠한 어려움과 요구도가 있는지 연구된 사례를 고찰하여, 기증자가 장기적으로 신체적, 정신적으로 건강을 영위하기위해 기증 후 F/U loss 되지 않고 건강관리를 받을 수 있게 하기위해 어떠한 제도적인 도움이 필요할지에 대한 대안을 제시하고자 한다.


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DAY 2: June 28 (Fri)

# KLTS Symposium 2

## A Little Less Seriously: Can Long-Term Complications be Prevented in Liver Transplantation?

**Chairs:**

**Dong-Sik Kim** (Korea Univ.)
**Dong Jin Joo** (Yonsei Univ.)

**Woo-Hyoung Kang**

*University of Ulsan*

## Self Introduction

Prof. Woo-Hyoung Kang is a Clinical associate professor of the Department of Surgery, Asan Medical Center and Ulsan University College of Medicine.

Prof. Kang graduated from Chungnam National University College of Medicine with his medical degree in 2006 and completed his internship, residency and fellowship at the Department of Surgery at Asan Medical Center, receiving his PhD in General Surgery in 2018.

## Research Interests

Liver transplantation, Hepatocellular carcinoma, Posttransplant management

## Representative Publications

1. Asian Pacific Association for the Study of the Liver clinical practice guidelines on liver transplantation.
2. Validation of quantitative prognostic prediction using ADV score for resection of hepatocellular carcinoma: A Korea-Japan collaborative study with 9200 patients.
3. Application of Proximal Splenic Vein Embolization to Interrupt Complicated Large Splenorenal Shunts in Adult Living Donor Liver Transplantation.
4. Diagnostic Role of Tumor Markers for Hepatocellular Carcinoma in Liver Transplantation Candidates: An Analysis Using the Korean Organ Transplantation Registry Database.
5. Efficacy and Safety Evaluation After Conversion From Twice-Daily to Once-Daily Tacrolimus in Stable Liver Transplant Recipients: A Phase 4, Open-Label, Single-Center Study.

# De Novo Malignancies: Long-Term Experience and Surveillance Strategy

**Woo-Hyoung Kang** *University of Ulsan*

Liver transplantation (LT) has significantly improved long-term survival rates, but recipients face increased risks of De novo malignancy (DNM) due to immunosuppression. DNM patterns differ worldwide, with post-transplant lymphoproliferative disorder (PTLD) common in Western countries, while South Korea sees more gastric and colorectal cancers. Risk factors include immunosuppressive drugs, underlying conditions, and lifestyle factors. Screening strategies should be tailored to regional DNM patterns, with regular surveillance crucial for early detection and management. Minimizing immunosuppressant usage and prompt local treatment upon DNM detection offer favorable outcomes for LT recipients.

**Jae Geun Lee**

*Yonsei University*

## Self Introduction

I am Liver transplantation Surgeon in Yonsei University College of Medicine, Severance hospital. I underwent resident program for Surgery and fellowship program for Transplant Surgery in Severance hospital. I graduated Yonsei University College of Medicine in 2009 and acquired Master of Science in Nano Science and Technology in 2015. I have worked as Assistant Prof. in Yonsei University College of Medicine since 2015.3.

Member of Academic committee in Korean Liver Cancer Association
Member of Academic committee in Korean Association of HBP surgery
Member of Academic committee in Korean Transplantation Society
Member of International collaboration committee in Korean Liver Transplantation Society
Member of Academic committee in International Living Donor Liver Transplantation Society
Member of Academic committee in International Society of Liver Surgeons

## Research Interests

- Liver transplantation
- HCC
- Immuosuppresant
- Infection

## Representative Publications

1. Entecavir versus tenofovir on the recurrence of hepatitis B–related HCC after liver transplantation: A multicenter observational study. Liver Transpl. 2023 Dec 1;29(12):1272-1281.
2. Risk factors for late-onset Pneumocystis jirovecii pneumonia in liver transplant recipients. Int J Infect Dis. 2023 Jun:131:166-172. Epub 2023 Apr 11.
3. Effect of statins on the recurrence of hepatocellular carcinoma after liver transplantation: An illusion revealed by exposure density sampling. Liver Int. 2023 Sep;43(9):2017-2025.
4. Tacrolimus Monotherapy within 12 Months after Liver Transplantation in the Era of Reduced Tacrolimus and Mycophenolate Mofetil: National Registry Study. J Clin Med . 2022 May 17;11(10):2806.
5. Renal safety of tenofovir disoproxil fumarate and entecavir with hepatitis B immunoglobulin in liver transplant patients. J Viral Hepat. 2020 Aug;27(8):818-825
6. Functions of human liver CD69(+)CD103(-)CD8(+) T cells depend on HIF-2alpha activity in healthy and pathologic livers. J Hepatol. 2020 Jun;72(6):1170-1181
7. Outcomes of Robotic Living Donor Right Hepatectomy From 52 Consecutive Cases: Comparison With Open and Laparoscopy-assisted Donor Hepatectomy. Ann Surg. 2022 Feb 1;275(2):e433-e442

# How to Prevent Chronic Kidney Disease after Liver Transplantation?

**Jae Geun Lee** *Yonsei University*

## Abstract

Risk factors contributing to chronic kidney disease (CKD) after liver transplantation (LT) are multifaceted, involving episodes of acute kidney injury (AKI), donor-related factors, and immunosuppressive medication, notably calcineurin inhibitors (CNIs). AKI is a common complication post-LT, affecting nearly half of all patients, with approximately 15% requiring kidney replacement therapy. Recipient factors such as metabolic syndrome, diabetes, obesity, age, ethnicity, hepatitis C infection, and prior malignancy contribute to post-transplant CKD. Maintenance immunosuppressive regimens, particularly early CNI administration, may exacerbate CKD progression by inducing chronic vasoconstriction of kidney arterioles. Early detection of risk factors, addressing modifiable ones, and minimizing perioperative AKI are essential focuses for high-risk individuals. Prioritizing strategies targeting CKD management, diabetes, and hypertension, along with the utilization of Kidney Disease Improving Global Outcomes (KDIGO) recommendations, is crucial for effective management. Blood pressure targets, pharmacological interventions, and timely referral to nephrologists for access creation are integral components of CKD management. Additionally, optimization of immunosuppressive protocols, primarily through CNI minimization or withdrawal, and considering alternative agents like mammalian target of rapamycin (mTOR) inhibitors or antimetabolites, play pivotal roles in preserving renal function. Adjusting the immunosuppressive regimen, particularly by minimizing CNIs in the first post-transplant year, can slow kidney dysfunction progression. Identifying and addressing risk factors for renal dysfunction, optimizing perioperative care, and tailoring immunosuppressive regimens are essential steps to enhance long-term outcomes following LT.

## Introduction

Liver transplant (LT) recipients frequently experience chronic kidney disease (CKD), which significantly heightens the risk of mortality.[1,2] Among nonsolid organ transplant recipients, those who undergo liver transplants have the second-highest prevalence of chronic kidney disease,[2] and after LT, the cumulative occurrence of chronic kidney failure within a 5-year span amounted to 18%.[1] In this research, individuals with a measured glomerular filtration rate (GFR) below 30 mL/min exhibited a risk of death more than 2.6 times higher compared to those without CKD.[3] The aim of this study is to investigate the impact of periop-

erative risk factors and immunosuppressive regimens on the development of CKD following LT, with a focus on identifying strategies for early detection, modification of modifiable risk factors, and optimization of immunosuppression to preserve renal function and improve long-term outcomes.

## Risk factors of CKD

The initial decline in kidney function following transplantation is typically viewed as multifaceted. Factors contributing to this decline include unresolved episodes of AKI post LT surgery, donor-related factors, and the administration of immunosuppressive medications, particularly calcineurin inhibitors (CNIs). AKI stands out as one of the most prevalent complications following LT, affecting nearly 50% of patients, with approximately 15% necessitating kidney replacement therapy. Additionally, the utilization of extended criteria liver grafts poses a potential risk factor for post-transplant CKD, correlating with elevated rates of CKD among recipients of such grafts.[4] In another study, recurrence of hepatocellular carcinoma and infections emerged as risk factors for CKD.[5]

The gradual deterioration in kidney function following transplantation can be linked to various recipient factors, such as metabolic syndrome, diabetes, obesity, age, ethnicity, hepatitis C infection, and a previous history of malignancy. Since the inception of the model for end-stage liver disease (MELD) score in Jun 2016, Korea, individuals with elevated serum creatinine levels have been given priority for listing and subsequent LT and it's quite common to observe the persistence and progression of CKD following LT. [6]

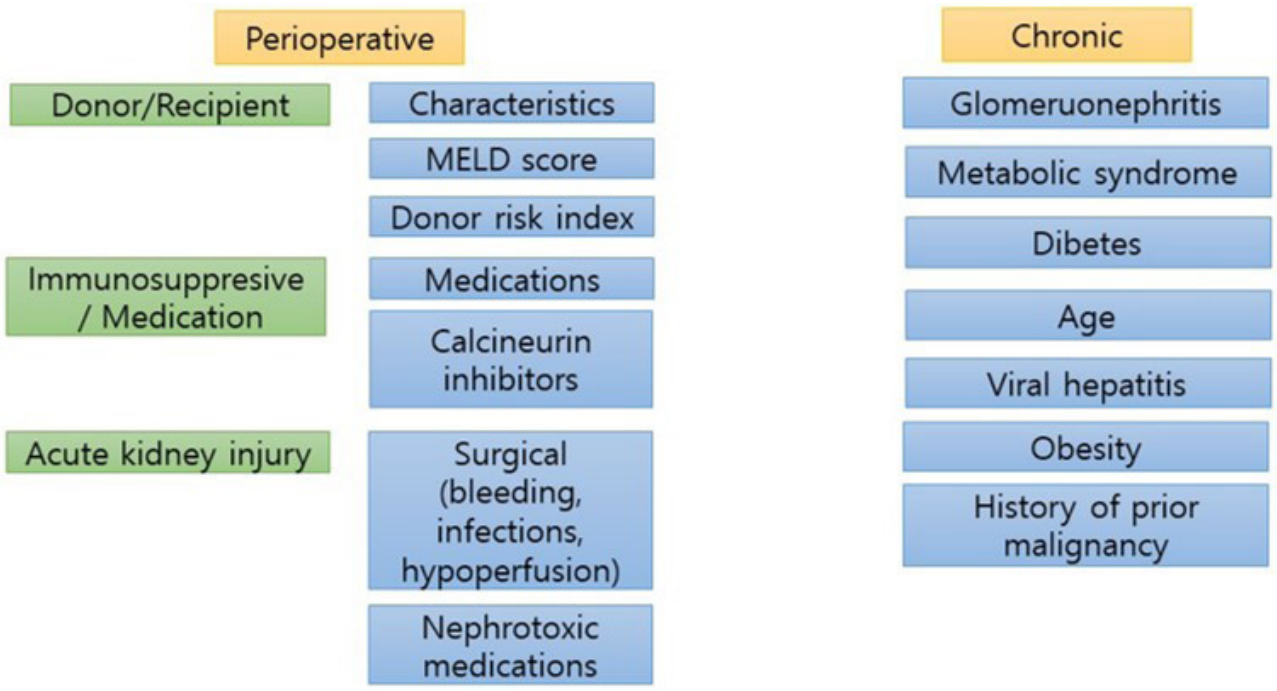


**Figure 1.** Risk Factors for Chronic Kidney Disease Following Liver Transplantation.

There have been indications pointing towards maintenance immunosuppressive regimens as possible factors linked to the advancement of CKD within this population. The hypothesis suggests that the early administration of CNIs and their vasoconstrictive impact on the afferent arteriole could detrimentally affect kidneys experiencing AKI from various causes. It is presumed that the chronic vasoconstriction of kidney arterioles and associated endothelial damage contribute to the progression of kidney disease in transplant recipients.[7]

Various predictive scoring systems have been developed in attempts to identify risk factors.[8-10] The primary focus should be directed towards early detection of risk factors, addressing modifiable ones, and minimizing perioperative AKI for individuals at high risk patients (Figure 1).

## General management of CKD

Due to the scarcity of data concerning CKD management in liver transplant recipients, it is imperative to prioritize strategies targeting CKD management, diabetes, and hypertension. Liver transplant recipients ought to undergo an annual evaluation of renal function alongside assessment for albuminuria. The CKD Epidemiology Collaboration and Modified Diet in Renal Disease equations have proven to be accurate in non-kidney solid organ transplant recipients and should thus be employed in liver transplant recipients for kidney function assessment.[11] However, for individuals with lower muscle mass or body mass index, the CKD Epidemiology Collaboration cystatin C equation should be utilized as a confirmatory test.[12-14] Guidance from the Kidney Disease Improving Global Outcomes (KDIGO) clinical recommendations, pertinent to this demographic, can be applied and consolidated for reference, as outlined in Table 2.[15,16]

For patients with CKD, blood pressure targets should aim for less than or equal to 140/90 mmHg if there's no proteinuria, and <130/80 mmHg if proteinuria or diabetes is present. Calcium channel blockers are suggested as the primary treatment for hypertension in liver transplant recipients, as they may counteract CNI-induced vasoconstriction.[17] Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are also considered safe and effective post-transplant, especially for patients with proteinuria. Sodium/glucose cotransporter 2 inhibitors are recommended as the initial therapy for diabetes in CKD patients, as they can slow CKD progression in both diabetic and nondiabetic individuals.[18,19] However, their usage in non-kidney solid organ transplant recipients requires further investigation due to potential infection and metabolic risks, necessitating careful monitoring.

The current KDIGO guideline emphasizes timely referral to a nephrologist for access creation, considering the anticipated time to dialysis.[20] This decision is informed by kidney risk failure equations and the clinical judgment of nephrologists. For kidney transplant recipients with declining allograft function, referral for access evaluation is recommended when GFR falls between 20 and 30 mL/min per 1.73 $m^2$, a guideline that can also apply to liver transplant recipients. Early referral offers opportunities for patients

to explore dialysis access options, such as hemodialysis versus peritoneal dialysis, as well as kidney transplant evaluation. Mortality rates among LT recipients on chronic dialysis exceed those of matched non-transplant dialysis cohorts.[21] Several studies have shown a survival advantage of kidney transplantation over remaining on dialysis for non-kidney solid organ transplant recipients.[22,23] However, due to organ shortages and potential comorbidities, many liver transplant recipients with CKD will require initiation of dialysis for kidney failure treatment. Hemodialysis is the predominant modality among liver transplant recipients with kidney failure, possibly due to factors such as delayed nephrology referral, limited dialysis modality education, infection risk, and feasibility following prior abdominal surgery.[21] Nonetheless, studies have shown that peritoneal dialysis can be a viable option for liver transplant recipients, highlighting the importance of patient education on available modalities.[24]

**Table 2.** Recommendations from KDIGO Clinical Practice Guidelines for CKD and Hypertension That Are Relevant to Liver Transplant Recipients.

| | Recommendations |
|---|---|
| HTN | • Systolic blood pressure exceeding 140 mmHg: manage aiming for a target below 140 mmHg (Grade 1B).<br>• Urinary albumin excretion (UAE) ranging from 30 to 300 mg/d: consider Renin-Angiotensin System inhibitors (RASi) (Grade 2C).<br>• UAE equal to or greater than 300 mg/d: initiate treatment with RASi (Grade 1B).<br>• In cases of diabetes mellitus (DM) and UAE between 30 to 300 mg/d: commence therapy with RASi (Grade 1B) |
| Diabetes | • Tailored HbA1c targets, varying from less than 6.5% to less than 8.0%, are recommended for patients with diabetes and chronic kidney disease (CKD) who are not undergoing dialysis (Grade 1C)<br>• For individuals with Type 2 Diabetes (T2D), CKD, and an estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 $m^2$ or higher, treatment with metformin is advised (Grade 1B) |
| Diet | • Limit sodium intake to less than 2 g per day or less than 90 mmol per day (Grade 2C).<br>• Refrain from consuming excessive protein (>1.3 g/kg/day).<br>• For individuals with a glomerular filtration rate (GFR) below 30 mL/min/1.73 $m^2$, maintain protein intake at 0.8 g/kg/day (Grade 2B) |
| Metabolic acidosis | • Bicarbonate supplementation should be administered to ensure serum bicarbonate levels remain within the normal range for individuals with serum bicarbonate below 22 mmol/L (Grade 2B). |
| Lifestyle | • Engage in physical activity that promotes cardiovascular health and is well-tolerated (striving for a minimum of 30 minutes, five times per week), maintain a healthy weight (with a BMI between 20 and 25, adjusted according to country-specific demographics), and discontinue smoking (Grade 1D) |

| | Recommendations |
|---|---|
| Nephrology referral | • Acute kidney injury (AKI) or a sudden sustained decline in glomerular filtration rate (GFR).<br>• GFR below 30 mL/min/1.73 $m^2$.<br>• Consistent and significant albuminuria (urinary albumin-to-creatinine ratio ≥ 300 mg/g or albumin excretion rate ≥ 300 mg/d, equivalent to urinary protein-to-creatinine ratio ≥ 500 mg/g or protein excretion ≥ 500 mg/d).<br>• Progression of chronic kidney disease (CKD).<br>• Presence of urinary red cell casts or more than 20 red blood cells per high-power field, which is sustained and not easily explained.<br>• CKD combined with hypertension resistant to treatment with four or more antihypertensive agents.<br>• Persistent abnormalities in serum potassium levels.<br>• Recurrent or extensive nephrolithiasis.<br>• Hereditary kidney disease |

## General Principle of Management of Immunosuppression

The primary focus in preventing post-LT renal dysfunction involves optimizing immunosuppressive protocols, primarily by minimizing the utilization of CNIs. Additionally, it is crucial to address and manage metabolic disorders, which are known risk factors for CKD, as they can exacerbate the nephrotoxic effects induced by CNIs.

A significant contributor to AKI during the immediate post- LT phase is the dose-dependent renal arteriolar vasoconstriction induced by CNIs.[25] This vasoconstrictive effect can be mitigated or reversed by minimizing CNI exposure immediately following LT.[26] To achieve this, induction immunosuppression with T-cell depleting agents like anti-thymocyte globulin (ATG) or interleukin-2 receptor antagonist such as Basiliximab allows for delayed CNI introduction and the use of lower CNI doses.[25,26] Studies have indicated that maintaining lower tacrolimus levels (6–10 ng/mL) shortly after LT is associated with reduced renal dysfunction at 1-year post-LT compared to standard tacrolimus levels (>10 ng/mL).[27] Early initiation of mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) or antimetabolites like mycophenolate mofetil (MMF) or mycophenolic acid (MPA) also facilitates lower CNI doses during the immediate post-LT period.[25,26] Besides the acute vasoconstrictive effects of CNIs, many patients develop CNI-induced ischemic glomerular and tubular toxicity, which can progress to CKD.[25,27] Although rare, CNI use can lead to thrombotic microangiopathy, which carries a poor prognosis.[25-27]

Various strategies aimed at protecting renal function have been explored and documented, as summarized in Table 3 and Table 4. These encompass: (1) postponing the initiation of CNIs following induction therapy with ATG or interleukin-2 receptor antagonist (2) lowering CNIs levels through the addition of

MMF or mTOR inhibitors, (3) complete withdrawal from CNI through early conversion to mTOR inhibitors, optionally with MMF/ MPA, (4) utilization of sustained-release formulations of tacrolimus to mitigate peak concentrations and potential CNI-associated toxicity.

**Table3.** Maximizing the Utilization of Immunosuppressive Treatment to Mitigate Renal Dysfunction Following Liver Transplantation

| | Recommendations |
|---|---|
| Induction therapy (Basiliximab) | • Consideration should be given to basiliximab induction in patients exhibiting baseline renal impairment or those at a high anticipated risk of renal dysfunction immediately after transplantation.<br>• Basiliximab induction may also be contemplated for all liver transplant recipients, regardless of their renal function status.<br>• Basiliximab induction facilitates the postponement of tacrolimus initiation.<br>• Basiliximab induction facilitates the maintenance of lower tacrolimus levels during the immediate post-transplant period. |
| Calcineurin inhibitor (Tacrolimus) | • Avoiding excessive tacrolimus exposure (>10 ng/mL) during the initial post-liver transplant phase.<br>• Delaying the initiation of tacrolimus until day 4 following transplantation.<br>• Maintaining tacrolimus trough levels at a lower range (5–7 ng/mL) during the first three months.<br>• Adjusting tacrolimus trough levels to an even lower range (3–5 ng/mL) after the initial three months.<br>• Considering tacrolimus discontinuation after the first year in patients experiencing ongoing renal dysfunction.<br>• For patients continuing tacrolimus therapy, minimizing levels after the initial 3–6 months while closely monitoring liver allograft function.<br>• Exploring the use of once-daily delayed-release tacrolimus formulations in all patients. |
| Mycophenolate | • Initiating mycophenolate within the first two weeks enables the lowering of tacrolimus doses.<br>• There's an elevated risk of rejection when mycophenolate is employed as the sole immunosuppressive agent.<br>• In cases where mTOR inhibitors are inaccessible or not well-tolerated, the utilization of mycophenolate may serve as an alternative for minimizing tacrolimus exposure. |
| mTOR inhibitor (Everolimus) | • Incorporating everolimus into a tacrolimus-based immunosuppressive regimen facilitates the reduction of tacrolimus dosage.<br>• Contemplate initiating everolimus early (<4 weeks) in patients experiencing ongoing renal dysfunction post-transplant.<br>• Aim for everolimus levels between 5–8 ng/mL when planning to reduce tacrolimus trough levels to 3–5 ng/mL..<br>• Consider early initiation of everolimus (<3 months) in all patients with identified risk factors for renal dysfunction.<br>• Early initiation of everolimus may be warranted in all patients if there are no contraindications and the patient demonstrates good tolerability. |

## Role of immunosuppression induction agents

Administering high-dose corticosteroids, typically methylprednisolone, during the anhepatic phase is standard procedure.[28] However, even with high-dose steroids, it's crucial to initiate calcineurin inhibitors (CNI) on the first or second postoperative day to prevent early rejection.[28] The high dose and early use of CNIs are nephrotoxic, prompting the development of regimens aimed at delaying their introduction. One proposed method involves initiating induction immunosuppression therapy with ATG or interleukin-2 receptor antagonist and introducing CNIs after the first 3–5 days.[13,29,30] This approach circumvents the synergistic vasoconstrictive effects of CNIs when combined with known perioperative risk factors for AKI. Multiple clinical trials have demonstrated that induction therapy with ATG or interleukin-2 receptor antagonist followed by delayed CNI introduction at a lower dose yields superior renal outcomes in individuals with preoperative renal dysfunction.[31-34] While ATG is less frequently used in LT due to its adverse effects such as prolonged lymphopenia and infection risk,[35] studies have shown that interleukin-2 receptor antagonist induction, particularly with basiliximab, offers similar efficacy with fewer side effects compared to ATG.[35-37] Basiliximab induction followed by delayed CNI introduction has been found beneficial for renal function without increasing short-term rejection rates (<12 months) or other complications.[33,36,38,39] interleukin-2 receptor antagonist induction also eliminates the need for corticosteroids, enabling steroid-free immunosuppression and consequently reducing the risk of opportunistic infections and metabolic complications. In practice, basiliximab 20 mg is intravenously administered on postoperative days 0 and 4, with tacrolimus withheld until postoperative day 5. Another induction regimen involving the co-stimulation blockade agent belatacept was discontinued due to higher rates of acute rejection and unexplained mortality in the belatacept group.[40]

## Role of mTOR inhibitors and antimetabolites (MMF/MPA)

Given the inherent nephrotoxicity of calcineurin inhibitors (CNI), it's logical to pursue strategies aimed at reducing CNI levels or completely discontinuing them to preserve or enhance renal function in post-liver transplant (LT) patients.[41] At present, alternative immunosuppressive agents include mTOR inhibitors and MMF and MPA. However, relying solely on monotherapy with either mTOR inhibitors or antimetabolites, while beneficial for renal function, poses a high risk of rejection and thus isn't recommended.[41]

In a multicenter prospective study that randomized de novo LT patients to standard tacrolimus or reduced tacrolimus with MMF, the reduced tacrolimus group exhibited higher one-year estimated glomerular filtration rate (eGFR) along with a reduced risk of acute rejection.[42] Concerning mTOR inhibitors, the use of sirolimus isn't advised in the immediate postoperative period (<1 month) due to its association with increased risks such as hepatic artery thrombosis, impaired wound healing, graft loss, sepsis, and excess mortality.[43] However, studies evaluating sirolimus beyond the initial month post-LT have shown renal protective benefits.[44]

In the multicenter Spare the Nephron Liver trial, the sirolimus with MMF group demonstrated superior renal function improvement compared to the CNI with MMF group, although rates of acute rejection and discontinuation due to adverse events were higher in the sirolimus arm.[44] Conversely, early initiation of everolimus with tacrolimus has been proven safe and offers renal protective advantages. In studies where everolimus was introduced 4 weeks after LT, adverse events such as hepatic artery thrombosis and impaired wound healing were notably absent.[44-49] Additionally, everolimus boasts a considerably shorter half-life than sirolimus, facilitating easier dose adjustments and drug level monitoring.[41] Consequently, many transplant centers now favor everolimus over sirolimus in renal protective protocols.

Although mTOR inhibitors offer nephroprotection, both sirolimus and everolimus can induce proteinuria and exacerbate pre-existing renal dysfunction. The precise mechanism by which mTOR inhibitors impact glomerular permeability and provoke proteinuria remains unclear, but the reduction in vascular endothelial growth factor synthesis and expression is thought to be a contributing factor, leading to compromised podocyte structural integrity.[50,51]

Transitioning from CNI to mTOR inhibitor therapy should be approached cautiously in patients presenting with existing proteinuria (>800 mg/day) or an eGFR <40 mL/min.[41,52] Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers may be beneficial in managing mild proteinuria. However, if proteinuria worsens, discontinuation of the mTOR inhibitor may be necessary to mitigate the risk of renal failure. Typically, proteinuria resolves within several months following mTOR inhibitor discontinuation, with most patients exhibiting no long-term residual kidney damage.[53]

Early initiation of mTOR inhibitor therapy is crucial for improving renal function in patients with CNI-induced nephropathy.[45-49] Studies have demonstrated that patients receiving everolimus within 30 ± 5 days or even earlier (≤10 days) post-liver transplant show significant improvement in eGFR of 8–12 mL/min/1.73 m2 at 12 months after transplantation.[47-49] Notably, the pivotal phase-3 H2304 trial revealed that renal function was significantly enhanced up to 36 months in patients receiving everolimus alongside reduced tacrolimus compared to those on standard tacrolimus, with comparable rejection rates.[46] The HEPHAISTOS trial further supported this, showing a numerically higher eGFR in patients receiving early everolimus introduction along with reduced-dose tacrolimus.[54] Similarly, the EPOCAL study demonstrated significantly higher eGFR in patients receiving very early everolimus introduction, as early as 2 weeks after randomization.[55] Additionally, the PROTECT study explored the feasibility of de novo everolimus use without CNI therapy post-transplantation, revealing notable improvements in eGFR over time.[49] The adjusted mean eGFR benefit at 3 years favored an everolimus-based tacrolimus-free regimen, with similar rates of acute rejection, graft loss, and mortality between the two groups.[47]

Once renal function declines significantly (GFR <60 mL/min/1.73 $m^2$), attempts to lower tacrolimus levels and introduce everolimus or MMF/MPA may be less effective in improving GFR, possibly due to irreversible renal structural damage. In fact, initiating mTOR inhibitors after renal dysfunction sets in

may exacerbate existing renal disease and induce proteinuria. Late conversion to MMF monotherapy or combined with low-dose CNI has shown limited efficacy in increasing GFR. A recent systematic review examining complete CNI withdrawal in favor of MMF for renal dysfunction found that GFR improved by an average of 8.3 mL/min when MMF was used alongside CNI reduction or elimination, even in cases with GFR <30 mL/min.

The Everolimus Liver Registry (EVEROLIVER) is an observational database spanning nine centers in France, documenting all liver transplant recipients prescribed everolimus.[56] Over a five-year period, REAL-LIFE data from this registry revealed that CNI withdrawal was achievable in 57.7% of patients by month 60. Remarkably, even individuals with pre-existing CKD at baseline demonstrated enhanced eGFR at both 36 and 60 months.

Notably, early conversion to everolimus (<3 months) was linked to a higher likelihood of eGFR improvement compared to late conversion (55% vs 39.4%) in CKD patients. However, the utilization of everolimus is hindered by side effects, limiting its use in approximately 20% of cases, including cytopenia, aphthous ulcers, edema, proteinuria, and dyslipidemia. Similarly, complete cessation of CNI in favor of everolimus alone poses an elevated risk of early rejection unless supplemented with MMF/MPA.[56]

Once renal function declines significantly (GFR <60 mL/min/1.73 $m^2$), attempts to lower tacrolimus levels and introduce everolimus or MMF/MPA may be less effective in improving GFR, possibly due to irreversible renal structural damage.[41,57] In fact, initiating mTOR inhibitors after renal dysfunction sets in may exacerbate existing renal disease and induce proteinuria.[57] Late conversion to MMF monotherapy or combined with low-dose CNI has shown limited efficacy in increasing GFR.[58] A recent systematic review examining complete CNI withdrawal in favor of MMF for renal dysfunction found that GFR improved by an average of 8.3 mL/min when MMF was used alongside CNI reduction or elimination, even in cases with GFR <30 mL/min.[59]

## Conclusions

CKD post-LT is common with associated adverse outcomes, stemming from various risk factors. Early identification and modification are crucial. Utilizing KDIGO recommendations for CKD and hypertension management is reasonable. Adjusting the immunosuppressive regimen, particularly by minimizing CNIs in the first post-transplant year, can slow kidney dysfunction progression. Identifying and addressing risk factors for renal dysfunction, optimizing perioperative care, and tailoring immunosuppressive regimens are essential steps to enhance long-term outcomes following LT.

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**Sang Hoon Lee**

*Sungkyunkwan University*

## Self Introduction

Dr. Sanghoon Lee is a pediatric and transplant surgeon, currently serving as an Associate Professor at Sungkyunkwan University School of Medicine, affiliated with Samsung Medical Center in Seoul, South Korea. He earned his M.D. from Sungkyunkwan University School of Medicine in 2003, followed by extensive clinical training at Samsung Medical Center, including internships, residencies, and clinical fellowships in both transplant and pediatric surgery. Dr. Lee holds a Korean Medical License and is certified by the Korean Board of Surgery. He is an active member of several professional organizations, including the Korean Society for Transplantation and the Korean Association of Pediatric Surgeons.

## Research Interests

Dr. Lee's research interests focus on various aspects of pediatric and transplant surgery, including liver transplantation, intestinal rehabilitation, and minimally invasive surgical techniques. He has published extensively on topics such as the management of intestinal failure-associated liver disease, risk factors for post-transplant complications, and innovative surgical approaches for congenital conditions.

## Representative Publications

1. Rhu J, Ha SY, Lee S, Kim JM, Choi GS, Joh JW, et al. Risk factors of silent allograft fibrosis 10 years post-pediatric liver transplantation. Sci Rep. 2020;10(1):1833.
2. Cho CW, Lee S, Kim JM, Choi GS, Kwon CHD, Joh JW, et al. Independent Factors Predicting Postoperative 30-Day Mortality in 101 Infants Following Liver Transplantation. Ann Transplant. 2017;22:631-7.
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4. Lee S, Kim JM, Choi GS, Park JB, Kwon CH, Choe YH, et al. De novo hepatitis b prophylaxis with hepatitis B virus vaccine and hepatitis B immunoglobulin in pediatric recipients of core antibody-positive livers. Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2016;22(2):247-51.

# Treading a Tightrope: A Strategy That Provides Minimal Immune Suppression while Reducing Rejection and Graft Fibrosis

**Sang Hoon Lee** *Sungkyunkwan University*

Anti-rejection therapy through chronic immunosuppression is crucial for maintaining graft functionality in patients after liver transplantation. However, immunosuppression is associated with significant morbidities, including cancers, infections, and chronic kidney disease. This has led to interest in minimizing or withdrawing immunosuppression to achieve operational tolerance, where long-term survival of the transplanted organ is possible without immunosuppression and without chronic allograft disease.

Recent advancements in immune tolerance and immunosuppression minimization for liver transplant recipients have shown promising potential to improve patient outcomes by reducing the need for lifelong immunosuppressive therapy. Key mechanisms underlying immune tolerance include the roles of regulatory T cells, alongside specific genetic and molecular factors. Advances in biomarker identification, such as cytokine profiles and gene expression signatures, have enabled better prediction and monitoring of tolerance, facilitating more personalized and targeted approaches to immunosuppressive therapy.

Innovative immunosuppressive agents are being explored as alternatives to traditional therapies, offering potential benefits in reducing nephrotoxicity and other long-term side effects. Additionally, combination therapies that integrate tolerogenic approaches with conventional immunosuppression are under active investigation, showing promise in enhancing graft survival while minimizing overall immunosuppressive burden.

Future directions in this field focus on further refining and validating predictive biomarkers, optimizing personalized immunosuppressive regimens, and exploring novel therapeutic agents and combination strategies. Ongoing research and clinical trials will be essential in overcoming current challenges and implementing these advances into routine clinical practice, ultimately aiming to improve long-term outcomes for liver transplant recipients.

**Won Kim**

*University of Ulsan*

## Self Introduction

Prof. Won Kim is an Associate Professor of the Department of Rehabilitation Medicine, University of Ulsan College of Medicine, Asan Medical Center.

Prof. Kim graduated from Seoul National University College of Medicine with his medical degree in 2004 and earned his Doctoral degree in 2019. He completed his residency and fellowship at the Department of Rehabilitation at Seoul National University Hospital.

He has been working at Asan Medical Center since 2013 and is currently responsible for the rehabilitation of intensive care and transplant patients.

## Research Interests

- Sarcopenia
- Digital Therapeutics
- Musculoskeletal Medicine
- Organ Transplantation Rehabilitation

## Representative Publications

1. Early Gait Function After Lung Transplantation in Patients With and Without Pretransplant Extracorporeal Membrane Oxygenation Support. Transplant Proc. 2023 Apr;55(3):616-622
2. Simplified Diagnosis of Critical Illness Polyneuropathy in Patients with Prolonged Mechanical Ventilation: A Prospective Observational Cohort Study. Journal of Clinical Medicine 2020, . 2020, 9, 4029.
3. Effect of sarcopenic obesity on deterioration of physical function in the elderly. Archives of gerontology and geriatrics 2020, 89, 104065.
4. Association between metabolic syndrome and knee osteoarthritis: A cross-sectional nationwide survey study. Journal of rehabilitation medicine 2019, 51, (6), 464-470.
5. Pioglitazone-Primed Mesenchymal Stem Cells Stimulate Cell Proliferation, Collagen Synthesis and Matrix Gene Expression in Tenocytes. Int. J. Mol. Sci. 2019, 20, (3).

# Physical Therapy and Exercise to Improve Quality of Life after Liver Transplantation

**Won Kim** *University of Ulsan*

Patients who need organ transplantation often suffer from chronic illnesses that impair physical functions and lead to muscle loss, a condition known as sarcopenia. In liver transplant patients, factors such as alcohol-induced liver cirrhosis can compound issues of nutrition, physical inactivity, and mental health problems, contributing to sarcopenia. Recent research has increasingly highlighted how sarcopenia adversely affects patient outcomes after surgery, including mortality rates, graft survival, and length of hospital stay. Consequently, the European Society of Organ Transplantation (ESOT) issued a Consensus statement in 2023 advocating for prehabilitation before surgery. This statement recommended incorporating aerobic and respiratory muscle exercises into prehabilitation, maintaining optimal weight according to the patient's condition, managing anxiety, and providing comprehensive care. However, challenges such as insurance coverage and personnel and geographical barriers between patients' residences and medical facilities hinder the widespread implementation of these recommendations.

Just as preoperative management is crucial, postoperative care, including ongoing physical therapy, especially for severely impaired patients, is also essential. Collaboration with rehabilitation medicine specialists for specialized evaluation and treatment is recommended. Following surgery, rehabilitation therapy begins in the hospital, preferably starting in the intensive care unit and continuing after transfer to general wards. This includes respiratory exercises to prevent pulmonary complications and functional training, including walking, to facilitate successful discharge. Moreover, in cases where neuromuscular complications are suspected, collaboration with rehabilitation medicine specialists is necessary to identify and provide tailored treatment.

After discharge, liver transplant recipients also require ongoing rehabilitation due to pre-existing liver diseases and surgical-related functional impairments. Prolonged use of immunosuppressive drugs can exacerbate muscle weakness, necessitating a combination of aerobic and strength exercises. While there's no direct evidence that rehabilitation during this period improves survival rates, considering the positive effects of exercise, it's presumed to benefit patient outcomes.


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# KLTS Symposium 3

## Minimally Invasive Surgery for Recipients of Living Donor Liver Transplantation

**Chairs:**

**Jae-Won Joh** (Sungkyunkwan Univ.)
**Young Kyoung You** (The Catholic Univ. of Korea)

**Kwang-Woong Lee**

*Seoul National University*

## Self Introduction

Professor Lee graduated from Seoul National University. He has been with Samsung Medical Center and National Cancer Center, Korea as a hepatic and transplant surgeon. He has also been in Johns Hopkins University Hospital as a LDLT consultant. He is a professor of department of surgery, Seoul National University, Korea. He performed the first successful hepatocyte transplantation in Korea when he was in Samsung Medical Center. He developed several innovative techniques to reduce biliary complications after liver transplantation such as high hilar dissection (HHD) and Tailored Telescopic Reconstruction (TTR) of bile duct. He also played an important role to change deceased donor allocation system in Korea (split liver transplantation regulation and Deceased donor allocation system based on MELD) by publishing several important papers analyzing Korean database. H has performed more than 150 cases of LDLT in Kazakhstan, Georgia and Myanmar since 2013. He performed most of living donors by laparoscopically since Dec. 2015 and performed the world first minimal invasive recipient surgery using Robot and/or laparoscopic approach. He is currently the president of Korean Liver Transplantation Society and a secretary general of iLDLTG (international living donor liver transplantation group).

## Research Interests

His research topics are related to the unmet needs in liver transplantation such as diagnostic or aggressive marker of HCC in liquid biopsy, hepatocyte or liver tumor organoids, microbiome research in liver transplantation, gene delivery into the graft, cancer stem cell, best immunosuppressant for HCC, GWAS so on.

## Representative Publications

1. Total robot-assisted recipient's surgery in living donor liver transplantation: First step towards the future. Lee KW, Choi Y, Lee S, Hong SY, Suh S, Han ES, Hong SK, Yang SM, Yi NJ, Suh KS J Hepatobiliary Pancreat Sci. 2023 Mar 3. doi: 10.1002/jhbp.1327.
2. Laparoscopic donor and recipient hepatectomy followed by robot-assisted liver graft implantation in living donor liver transplantation. Lee KW, Choi Y, Hong SK, Lee S, Hong SY, Suh S, Han ES, Yi NJ, Suh KS. Am J Transplant. 2022 Apr;22(4):1230-1235. doi: 10.1111/ajt.16943. Epub 2022 Jan 11. PMID: 34971490
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# Seoul National University Hospital Experience

**Kwang-Woong Lee** *Seoul National University*

Minimally invasive surgery has been introduced for liver transplantations. Although laparoscopic or robot-assisted living donor hepatectomy is being used, minimally invasive surgery is rarely performed in recipients during liver transplantation.

Our center has developed and successfully performed PLDRH (pure laparoscopic donor right hepatectomy) for more than 750 patients until 2023. We extended the laparoscopic surgery to recipients based on these accumulated experiences in performing PLDRH. Beginning with laparoscopic liver mobilization only for the recipients, we performed the laparoscopic explant hepatectomy followed by graft implantation using the upper midline. We then expanded our trial to graft implantation by robotic/laparoscopic hybrid method (anastomosis of the hepatic and portal veins by laparoscopic surgery, and anastomosis of the hepatic artery and bile duct by robot-assisted surgery). Then, we performed robot-assisted liver graft implantation after a total laparoscopic explant hepatectomy in living donor LT (LDLT). After these experiences, we performed robot-assisted recipient surgery.

Due to several limitations of minimally invasive surgery, adequate indication is important. Also, surgical tips to overcome the limitation of these innovative techniques need to know.

In this presentation, I will introduce the surgical tips and adequate indications of these minimally invasive recipient surgery.

# Samsung Medical Center Experience

**Gyu-seong Choi**

*Sungkyunkwan University*


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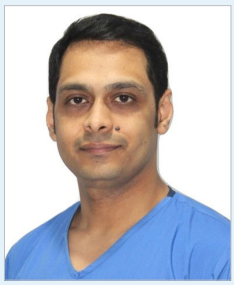


## Ashwin Rammohan

*Rela Hospital, India*


## Self Introduction

Dr.Rammohan is a Consultant Hepatobiliary & Liver Transplant Surgeon at the Dr.Rela Institute & Medical Centre, Chennai, India. He is also the Director of Academics & Research and oversees the fellowship curricula, animal lab & research facilities at the Institute.

A graduate of Madras Medical College, Dr.Rammohan did his Basic & Higher Surgical Training in Surgical Gastroenterology & HPB Surgery from Stanley Medical College, India, and was awarded the National Gold Medal in General Surgery, The National Board of Examinations, India. He went on to complete his Higher Surgical Training in Gastrointestinal Surgery and FRCS from Cambridge University Associated Hospitals, UK. He was awarded the University Diploma in Advanced Upper GI Minimal Access Surgery from L'Université de Strasbourg, France.

He has over 200 peer reviewed publications,15 book chapters and 2 research theses to his credit. He works with several engineering colleges and enterprises to develop novel technologies in liver disease and transplantation, and has two patents to his name. He is an invited peer reviewer and associate editor of various international journals including Transplantation. Dr.Rammohan's name features in the Guinness Book of Records as a part of the GlobalSurg initiative. He has also won several awards at National & International levels including the best paper & young investigator awards by the ILTS, ASI, IASG and IHPBA. Apart from being an International Surgical Advisor, Dr.Rammohan is also a College Clinical Educator at the Royal College of Surgeons & Physicians of Glasgow, UK

## Research Interests

- Portal Hemodynamics in Living Donor Liver Transplantation
- Transplant Immunobiology & Translational Research into Liver Tolerogenicity
- The application of AI and Robotics in Liver Transplantation

## Representative Publications


1. Rammohan A, Rela M. Future Perspectives of Robotics in Liver Transplantation. Updates Surg. 2024 Epub Ahead of Print
2. Rammohan A, Rajalingam R, Cherukuru R, Rela M. Global Dissemination of Robotics in Liver Transplantation – The Way Forward. Transplantation 2024 Epub Ahead of Print
3. Rela M, Rajalingam R, Cherukuru R, Palaniappan K, Kumar AS, Kanagavelu R, Narasimhan G, Rajakumar A, Kaliamoorthy I, Rammohan A. Experience with Establishing a Robotic Donor Hepatectomy Program for Paediatric Liver Transplantation. Transplantation 2023;107(12):2554-2560
4. Rela M, Rajalingam R, Shetty G, Cherukuru R, Rammohan A. Robotic monosegment donor hepatectomy for pediatric liver transplantation: First report. Pediatr Transplant. 2022;26(1):e14110.
5. Rammohan A, Rela M. Robotic donor hepatectomy: Are we there yet? World J Gastrointest Surg. 2021;13(7):668-677.

# Dr. Rela Institute Experience

**Ashwin Rammohan** *Rela Hospital, India*


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DAY 2: June 28 (Fri)

# KASL Branch EMW 1 [Gwangju-Chonnam]

## Strategies to Reach HCV Elimination in Prevalent Lesion of Korea

**Chairs:**

**Gun Young Hong** (Kwangju Christian Hospital)
**Sung Bum Cho** (Chonnam National Univ.)

**Ga Ram You**

*Chonnam National University*

## Self Introduction

Prof. Ga Ram You is an assistant professor of the department of gastroenterology and hepatology in Chonnam National University Hwasun Hospital.

Prof. You graduated from Chonnam National University College of Medicine in 2018 and earned master's degree in 2022 from the Chonnam National University Graduate school. And she completed her internship and residency at the Department of Internal medicine at Chonnam National University Hospital, receiving her diploma in Internal medicine in 2022.

Prof. You is a currently a member of the Korean Liver Association and the Korean Liver Cancer Association.

## Research Interests

Hepatocellular carcinoma, Viral hepatitis, Alcoholic liver disease

## Representative Publications

1. "Acute respiratory distress syndrome and severe pneumonitis after atezolizumab plus bevacizumab for hepatocellular carcinoma treatment: A case report." World journal of gastrointestinal oncology vol. 15,5 (2023): 892-901.
2. "Successful Transcatheter Arterial Embolization of Abdominal Wall Hematoma from the Left Deep Circumflex Iliac Artery after Abdominal Paracentesis in a Patient with Liver Cirrhosis: Case Report and Literature Review." The Korean journal of gastroenterology = Taehan Sohwagi Hakhoe chi vol. 83,4 (2024): 167-171.
3. "Impact of Prospero Homeobox-1 (PROX-1) on the Oncogenic Phenotypes of Hepatocellular Carcinoma Cells." Cancer genomics & proteomics vol. 21,3 (2024): 295-304.

# Overview of HCV in Gwangju and Cheolla Province

**Ga Ram You** *Chonnam National University*

Hepatitis C is the second most common cause of chronic viral hepatitis in South Korea, following the hepatitis B virus. According to data from the Korean National Health Insurance Service (KNHIS) from 2008-2018, it accounts for about 10% of liver cancer causes.[1-2] The chronicity rate of hepatitis C is approximately 54-86%, higher than that of hepatitis B, and the annual risk of developing liver cancer if cirrhosis occurs is 1-5%.[3-6]

According to a 2021 WHO report, approximately 58 million people worldwide are chronically infected with the hepatitis C virus, with about 1.5 million new infections occurring annually and about 290,000 deaths from hepatitis C-related liver diseases and liver cancer each year.[7]

Currently, the most widely used screening test for hepatitis C virus (HCV) in South Korea is the HCV antibody test. A 2015 study of over 270,000 individuals aged 20 and older showed an age, sex, and region-adjusted HCV antibody prevalence rate of 0.6%.[8] However, the prevalence of HCV antibodies varies by region within South Korea. A 2009 domestic study found the highest HCV antibody prevalence rates in Cheonnam (2.07%) and Busan (1.53%), while the prevalence was relatively low in Seoul and Gyeonggi regions.[9]

Since June 2017, South Korea has classified asymptomatic hepatitis C patients as a third-class infectious disease to detect and treat them early, implementing a comprehensive surveillance system. According to infection data reported by the Korea Disease Control and Prevention Agency, Cheonnam had the second-highest incidence rate of hepatitis C in the country, with 29.48 cases per 100,000 people, following Busan (34.16 per 100,000), particularly in coastal areas.[10] There is a report suggesting the association with intravenous drug abuse according to the characteristics of the port areas,[11] and the hypothesis that there is a cause such as unhygienic acupuncture was suggested, considering that it mainly appears in the elderly population, but epidemiological investigations did not find the source of infection.

In response, the Cheollanam-do Provincial Government initiated the first-ever hepatitis C eradication project in South Korea in 2023, encompassing antibody testing, genetic analysis, and free treatment. This initiative brings South Korea closer to achieving the WHO's 2030 hepatitis C elimination goals of diagnosing over 90% and treating over 80% of cases.

Based on the pilot project in Cheollanam-do, we can anticipate the establishment of national strategies for identifying and treating asymptomatic patients, paving the way for the active eradication of hepatitis C in South Korea.

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5. 보건복지부 질병관리본부. 2023년도 바이러스 간염 관리지침.
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9. Kim DY, Kim IH, Jeong SH, et al. A nationwide seroepidemiology of hepatitis C virus infection in South Korea. Liver Int 2013;33:586-94.
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11. Seong MH, Kil H, Kim YS, et al. Clinical and epidemiological features of hepatitis C virus infection in South Korea: a pro spective, multicenter cohort study. J Med Virol 2013;85:17


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**Jae Hyun Yoon**

*Chonnam National University*

## Self Introduction

Prof. Jae Hyun Yoon is a Professor of the Department of Gastroenterology and Hepatology, Chonnam National University Hospital, College of Medicine and is currently holding a position as assistant professor since 2020.

Prof. Yoon graduated from Chonnam National University College of Medicine with his medical degree in 2011 and completed his Doctor's degree in same institute at 2023.

Prof. Yoon has been taking a number of roles, including member of committee of publication, committee of education in Korean Association for the Study of the liver (KASL), and member of committee of academy in Korean Liver Cancer Association (KLCA).

## Research Interests

Viral hepatitis, Hepatocellular carcinoma, Alcoholic hepatitis, Microbiome

## Representative Publications

1. Management of early-stage hepatocellular carcinoma: challenges and strategies for optimal outcomes (Journal of liver cancer, 2023. 09.)
2. Prognosis of Patients with Chronic Hepatitis C Genotype 1b Infection Treated Using Daclatasvir/Asunaprevir after Sustained Virologic Response: A 6-Year Multicenter Prospective Observational Study (Meidicina(Kaunas, 2023.08.)
3. Altered Frequency, Activation, and Clinical Relevance of Circulating Innate and Innate-Like Lymphocytes in Patients With Alcoholic Liver Cirrhosis (Immune network, 2023.04.)
4. Early extrahepatic recurrence as a pivotal factor for survival after hepatocellular carcinoma resection: A 15-year observational study (World J of gastroenterology, 2022.09.)
5. Etiology and clinical characteristics of acute viral hepatitis in South Korea during 2020-2021: a prospective multicenter study (Sci Rep, 2023.08.)

# Strategies to HCV Elimination

**Jae Hyun Yoon** *Chonnam National University*

Hepatitis C Virus (HCV) infection poses a significant global health burden, with an estimated 71 million people chronically infected worldwide.[1] While direct-acting antiviral (DAA) therapies have revolutionized HCV treatment, achieving elimination goals necessitates addressing gaps in the cascade of care, particularly in the linkage of care phase.[2] This abstract examines the importance of enhancing linkage of care strategies in the context of HCV elimination efforts.

Linkage of care refers to the process of connecting individuals diagnosed with HCV to appropriate medical services for evaluation and treatment. Despite advances in treatment, significant challenges persist in ensuring that individuals diagnosed with HCV successfully navigate through the healthcare system to receive care. These challenges include lack of awareness, stigma associated with HCV, socioeconomic barriers, and fragmented healthcare systems.

Effective linkage of care strategies are crucial in overcoming these barriers and facilitating access to treatment for all individuals diagnosed with HCV.[3] Such strategies encompass multifaceted approaches, including targeted outreach and education programs, integration of HCV screening into existing healthcare services, peer support initiatives, and strengthening collaboration between healthcare providers and community organizations.

Enhanced linkage of care not only increases treatment uptake but also contributes to the broader goal of HCV elimination by reducing transmission and preventing progression to advanced liver disease.[4, 5] Moreover, addressing barriers to linkage of care promotes health equity by ensuring equitable access to HCV care for marginalized populations.

In conclusion, prioritizing enhanced linkage of care strategies is essential for advancing towards the goal of HCV elimination. Multidisciplinary collaboration, innovative interventions, and sustained efforts are imperative to overcome existing challenges and achieve meaningful progress in the global fight against HCV.

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3. Mendizabal M, Alonso C, Silva MO. Overcoming barriers to hepatitis C elimination. Frontline Gastroenterol 2019;10:207-209.
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THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# Radiology Seminar

## LI-RADS in Focus: Past, Present, and Future Challenges in HCC Imaging

**Chairs:**

**So Yeon Kim** (Univ. of Ulsan)
**Sung Won Lee** (The Catholic Univ. of Korea)

**Sunyoung Lee**

*Yonsei University*

## Self Introduction

| | |
|---|---|
| 2007.2 | Korean Board Certificate of Medical Doctor |
| 2012.2 | Korean Board of Internal Medicine |
| 2016.2 | Korean Board of Radiology |
| 2016.3-2017.2 | Clinical Fellow: Department of Radiology, Samsung Medical Center |
| 2017.3-2018.2 | Clinical Fellow: Department of Radiology, Asan Medical Center |
| 2018.3-2024.2 | Assistant Clinical Professor: Department of Radiology, Severance Hospital, Yonsei University College of Medicine |
| 2024.3-present | Associate Clinical Professor: Department of Radiology, Severance Hospital, Yonsei University College of Medicine |

## Research Interests

Liver Imaging

## Representative Publications

1. Percentages of Hepatocellular Carcinoma in LI-RADS Categories with CT and MRI: A Systematic Review and Meta-Analysis. Radiology. 2023 Apr;307(1):e220646.
2. Effect of Microvascular Invasion Risk on Early Recurrence of Hepatocellular Carcinoma after Surgery and Radiofrequency Ablation. Ann Surg. 2021 Mar;273(3):564-571.
3. Intraductal Papillary Neoplasm of the Bile Duct: Assessment of Invasive Carcinoma and Long-Term Outcomes using MRI. J Hepatol. 2019 Apr;70(4):692-699.
4. Radiofrequency ablation vs. surgery for perivascular hepatocellular carcinoma: Propensity score analyses of long-term outcomes. J Hepatol. 2018 Jul;69(1):70-78.
5. Preoperative gadoxetic acid–enhanced MRI for predicting microvascular invasion in patients with single hepatocellular carcinoma. J Hepatol. 2017 Sep;67(3):526-534.

# Past and Present of LI-RADS in HCC Diagnosis

**Sunyoung Lee** *Yonsei University*

The Liver Imaging Reporting and Data System (LI-RADS), endorsed by the American College of Radiology (ACR), is a comprehensive system for standardizing the terminology, technique, interpretation, reporting, and data collection of liver imaging.[1] LI-RADS was released in 2011,[2] and then updated in 2013,[3] 2014,[4] 2017,[5] and 2018.[1] From LI-RADS 2014,[4] the option to use MRI with hepatobiliary agent was incorporated into the diagnostic algorithm.

Compared with LI-RADS version 2014,[4] CT/MRI LI-RADS version 2017 includes revised categories, modified definitions of major features, clarified instructions on the use of ancillary features, and explicit criteria for LR-M.[5] In CT/MRI LI-RADS v2017, the new diagnostic category, LR-NC, has been added, and substantive change has been made to LR-TIV (previously LR-5V).[5] The definition of major features has been revised–that is, arterial phase hyperenhancement (APHE) to exclude rim arterial phase hyperenhancement, washout to exclude peripheral washout, and capsule to exclude nonenhancing capsule.[5] Furthermore, ancillary imaging features have been designated as optional and their use has been clarified.[5] Ultrasound visibility as a discrete nodule has been designated an ancillary feature favoring malignancy in general, not hepatocellular carcinoma (HCC) in particular and nonenhancing capsule, an ancillary feature favoring HCC in particular.[5] In addition, the imaging criteria for inclusion in category LR-M have been redefined in CT/MRI LI-RADS version 2017.[5]

CT/MRI LI-RADS version 2018 revised the definition of threshold growth to ≥ 50% size increase of a mass in ≤ 6 months, eliminated the -g (threshold growth) and -u (visibility at screening ultrasound) designations, and incorporated a 10–19 mm hepatic observation with nonrim APHE and nonperipheral washout appearance into LR-5 criteria.[1] These modifications were made to achieve concordance with the American Association for the Study of Liver Diseases (AASLD); subsequently, LI-RADS was fully integrated into the AASLD 2018 HCC clinical practice guidance.[1]

The contrast-enhanced ultrasound (CEUS) LI-RADS is a comprehensive system for standardizing the terminology, techniques, interpretation, reporting, and data collection of CEUS examinations for the evaluation of focal hepatic lesions detected in patients at high risk for HCC.[6,7] The ACR published CEUS LI-RADS versions in 2016 and 2017.[6,7] Although the fundamental concepts and principles of CEUS LI-RADS are similar to those of CT/MRI LI-RADS, the algorithms are not identical, reflecting intrinsic differences

between the imaging modalities and their corresponding contrast agents.[6,7] Since CEUS uses purely intravascular microbubble contrast agents and permits real-time scanning with high temporal and spatial resolution, the CEUS LI-RADS includes different diagnostic imaging features compared with the CT/MRI LI-RADS.[6,7] The major imaging features or the LR-M criteria for the CEUS LI-RADS include lesion size (< 20 mm or ≥ 20 mm and < 10 mm or ≥ 10 mm), presence and pattern (not rim and not peripheral discontinuous globular and rim) of APHE, and presence, onset (early < 60 seconds and late ≥ 60 seconds), and degree (mild and marked) of washout.[6,7]

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**Subin Heo**

*University of Ulsan*

## Self Introduction

Dr. Subin Heo is a Senior Clinical Fellow at the Department of Radiology, Ulsan University College of Medicine, and is currently working at Asan Medical Center.

Dr. Heo graduated with her medical degree from Ajou University College of Medicine in 2016 and completed her internship and residency at the Department of Radiology at Ajou University Hospital, where she received her diploma in Radiology in 2021.

In 2021-2022, Dr. Heo underwent clinical fellowship in Abdominal Radiology at Asan Medical Center. She worked as a clinical assistant professor at Ajou University Hospital in 2022-2023 and has been serving as a Senior Clinical Fellow at Asan Medical Center since 2023.

## Research Interests

Dr. Heo's research interest lies in liver imaging including diffuse liver disease, hepatocellular carcinoma (diagnosis, prognosis, and treatment response evaluation), and hepatocellular adenomas.

## Representative Publications

1. Heo S, Lee SS, Choi SH, Kim DW, Park HJ, Kim SY, Lee SJ, Kim KM, Shin YM. CT Rule-in and Rule-out Criteria for Clinically Significant Portal Hypertension in Chronic Liver Disease. Radiology. 2023 Oct;309(1):e231208. doi: 10.1148/radiol.231208.
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4. Heo S, Choi SH, Hong S, Kim DW. Visualization Score of Gadoxetic Acid-Enhanced Magnetic Resonance Imaging: The Effect on the Diagnostic Accuracy for Hepatocellular Carcinoma. J Magn Reson Imaging. 2023 Mar;57(3):941-949. doi: 10.1002/jmri.28357.
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# LI-RADS: It Is Time to Focus on Prognosis

**Subin Heo** *University of Ulsan*

Hepatocellular carcinoma (HCC) is a malignancy characterized by intra-tumoral and inter-tumoral heterogeneity, resulting in varied clinical outcomes. With recent advancements in treatment options, there is a growing need for effective prognostic biomarkers to guide personalized therapy. As HCC diagnosis relies primarily on imaging rather than pathologic confirmation, pathologic biomarkers offer limited prognostic value before treatment.

Emerging evidence suggests that several imaging features correlate with key pathologic and molecular drivers of prognosis. Imaging features associated with adverse prognostic subtypes, such as CK19-positive HCC,[1] macrotrabecular massive subtype HCC,[2-4] proliferative HCC[5], and TP53-mutated HCC,[6] have been identified Moreover, imaging features and models have shown promise in predicting microvascular invasion in HCC,[7] Some studies even propose an independent prognostic role of imaging phenotypes, such as the LI-RADS category M, irrespective of pathologic subtype.[8,9] Recent research is increasingly focused on developing noninvasive, imaging-based prognostic models for HCC.[10-12]

Despite these promising developments, several limitations must be addressed before noninvasive imaging biomarkers can be clinically applicable. The most pressing issue is the need for standardized terminology and definitions to improve communication and synthesis of evidence. This lecture aims to summarize key literature on the prognostic imaging features of HCC and the challenges and future directions in developing these features for clinical translation.

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**Hanyu Jiang**

*Sichuan University, China*

## Self Introduction

### *Education/Training*

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| 2021.08-Present | Department of Radiology, West China Hospital, Sichuan University, Post-doc |
| 2017.07-2021.06 | Department of Radiology, West China Hospital, Sichuan University, Resident |
| 2011.09-2020.06 | West China School of Medicine, Sichuan University, MD program |
| 2019.09-2020.04 | Department of Radiology, Duke University Medical Center, Visiting Student |
| 2016.02-2016.06 | Department of Radiology and Pathology, University of Massachusetts Medical Center, Visiting Student |
| 2010.09-2011.06 | Shanghai Medical College of Fudan University, Clinical Medicine |

### *Personal Statement*

Dr. Jiang's primary research interest is in liver MRI. Her main previous research work concluded diagnosis of liver tumors, pathomolecular feature assessment and prognostication in hepatocellular carcinoma, and artificial intelligence. Dr. Jiang has co-authored over 70 peer-reviewed SCI journal papers (including several published in Radiology), and serves as an Associate Editor for Abdominal Radiology (2023 Exemplary Editor Award). Dr. Jiang also serves as an active reviewer for several scientific journals including Radiology (2023 Editor's Recognition Award for Reviewing with Distinction), The Lancet Digital Health, and Liver Cancer.

## Representative Publications

1. Jiang H, Yang C, Chen Y, et al. Development of a model including MRI features for predicting advanced-stage recurrence of hepatocellular carcinoma after liver resection. Radiology. 2023;309(2):e230527.
2. Jiang H, Wei H, Yang T, Qin Y, Wu Y, Chen W, Shi Y, Ronot M, Bashir M, Song B*. VICT2 trait: prognostic alternative to peritumoral HBP hypointensity in hepatocellular carcinoma. Radiology. 2023:221835.
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# Future Perspectives and New Challenges in LI-RADS

**Hanyu Jiang** *Sichuan University, China*

## Lecture Summary

Since its initial release in 2011, the Liver Imaging Reporting and Data System (LI-RADS) has evolved and expanded in scope. This lecture aims to discuss current major gaps in knowledge, which include challenges derived from unmet clinical (i.e., surveillance, limited sensitivity of LR-5 category, and marked complexity) as well as technical (i.e., inadequate reproducibility, lack of explainability, suboptimal integration of multimodal data, and automatic reporting) needs. Looking ahead, this lecture also aims to discuss potential future directions, which will focus on mitigating the current challenges and incorporating advanced imaging and artificial intelligence technologies. Collectively, the speaker envisions that LI-RADS will gradually transform into a probability-based system for individualized diagnosis and prognostication of liver cancers that integrates patient characteristics and quantitative imaging features, while accounting for imaging modality and contrast agent.

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THE LIVER WEEK 2024

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# Radioembolization Symposium

## Experience of TARE for the Treatment of Liver Cancer in Asian-Pacific Region

**Chairs:**

**Yoon Jun Kim** (Seoul National Univ.)

**Pierce Chow** (National Cancer Centre Singapore, Singapore)

**Dongho Hyun**

*Sungkyunkwan University*

## Self Introduction

### *Education*

| | | |
|---|---|---|
| 1997.03-2003.02 | Bachelor's degree | Soonchunhyang University, College of Medicine, College of Medicine, ChungcheongnamDo, South Korea |
| 2008.03-2010.08 | Master's degree | Ulsan University, College of Medicine, Radiology, Ulsan City, South Korea |
| 2014.03-present | Doctor's degree | Soonchunhyang University, College of Medicine, Radiology, ChungcheongnamDo, South Korea |

### *Career*

| | |
|---|---|
| 2003.03-2004.02 | Internship in Asan Medical Center, Seoul, South Korea |
| 2004.04-2007.04 | Military service in 17th infantry Division, Gyeonggi province, South Korea |
| 2007.05-2011.02 | Radiology, Resident training in Asan Medical Center, Seoul, South Korea |
| 2011.03-2012.02 | Radiologist in Osan Hankook Hospital, Gyeonggi province, South Korea |
| 2012.03-2014.02 | Interventional radiology fellowship in Samsung Medical Center, Seoul, South Korea |
| 2014.03-2015.02 | Instructor, Samsung Medical Center, Seoul, South Korea |
| 2015.03-2017.02 | Clinical Assistant professor, Samsung Medical Center, Seoul, South Korea |
| 2017.03-2019.02 | Assistant professor, Samsung Medical Center, Seoul, Korea |
| 2019.03-Present | Associate professor, Samsung Medical Center, Seoul, Korea |

## Research Interests

Transarterial treatment of hepatocellular carcinoma (cTACE, TARE, combination treatment), lymphatic intervention, LT-related intervention, portal hypertension-related intervention, EVAR

## Representative Publications

1. Cha DI, Lee MW, Hyun D, Ahn SH, Jeong WK, Rhim H. Combined Transarterial Chemoembolization and Radiofrequency Ablation for Hepatocellular Carcinoma Infeasible for Ultrasound-Guided Percutaneous Radiofrequency Ablation: A Comparative Study with General Ultrasound-Guided Radiofrequency Ablation Outcomes. Cancers (Basel). 2023 Oct 28;15(21):5193. doi: 10.3390/cancers15215193. PMID: 37958370; PMCID: PMC10650828.
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5. Lee HN, Hyun D. Complications Related to Transarterial Treatment of Hepatocellular Carcinoma: A Comprehensive Review. Korean J Radiol. 2023 Mar;24(3):204-223. doi: 10.3348/kjr.2022.0395. Epub 2023 Jan 19. PMID: 36788765; PMCID: PMC9971838.

# Recent Advances in TARE

**Dongho Hyun** *Sungkyunkwan University*


## Nutcha Pinjaroen

*Chulalongkorn University, Thailand*


## Self Introduction

Dr. Nutcha Pinjaroen graduated radiology residency training from Chulalongkorn University faculty, Bangkok, Thailand and joined the faculty in 2007. She persued Interventional Oncology fellowship training at Oregon Health & Science University (OHSU), USA. After completing her fellowship in 2012, she came back to be an attending IR. Dr. Nutcha's main interests have been transarterial and percutaneous treatments such as RFA, MWA, Cryoablation, TACE, PVE and Y-90 SIRT for hepatic tumors and other malignancies, as well as, HCC surveillance.

## Research Interests

- HCC: TACE, Ablation. Y-90 SIRT, PVE
- Combined treatment for hepatic malignancies

## Representative Publications


1. Chaikajornwat J, Tanasoontrarat W, Phathong C, Pinjaroen N, Chaiteerakij R. Clinical outcome of Yttrium-90 selective internal radiation therapy (Y-90 SIRT) in unresectable hepatocellular carcinoma: Experience from a tertiary care center. Liver Research 2022.
2. Pinjaroen N, Chailapakul P, Sriphoosanaphan S, Chuaypen N, Tangkijvanich P. Predictive Role of Pretreatment Circulating miR-221 in Patients with Hepatocellular Carcinoma Undergoing Transarterial Chemoembolization. Diagnostics (Basel) 2023.

# Role of TARE in the Management of BCLC Stage A HCC

**Nutcha Pinjaroen** *Chulalongkorn University, Thailand*

Y-90 radioembolization has been proven to show better effective tumor control than TACE, as noted in two phase-II RCT trials[1,2]. Furthermore, the concept of radiation segmentectomy, which is the delivery of a high dose of radiation to the tumor in a selective fashion to achieve complete tumor necrosis, showed no significant difference when compared with TACE combined with Microwave ablation in patients with HCC up to 3 cm[3].

Based on the impressive results of the LEGACY study[4], Y-90 radioembolization with selective infusion for solitary HCC less than 8 cm has shown an ORR (best response) of 88.3%, duration of response (DoR) ≥ 6 months of 62.2%, and a 3-year OS of 86.6%. Therefore, Y-90 radioembolization is the recommended treatment choice for early-stage HCC patients (single lesion, less than 8 cm) who are not feasible candidates for ablation or resection, according to the BCLC guideline 2022 update.

Y-90 radioembolization also plays a significant role in downsizing or downstaging tumors for resection or transplantation. Based on a single-center comparative analysis[5], Y-90 appears to outperform TACE for downstaging HCC from UNOS T3 to T2.

Y-90 alone, using the radiation hepatectomy concept, is also safe and effective for larger tumors. A retrospective study[6] on 25 patients with preserved liver function who underwent an ablative dose of radioembolization for large HCC (≥5 cm) when FLR exceeded 30% showed a duration of response (DoR) in the treated area of 22.0 months, time to progression (TTP) of 17.1 months, and a 5-year overall survival (OS) of 83.2%.

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**Pi-Yi Chang**

*Taichung Veterans General Hospital, Taiwan*

## Self Introduction

I am a Consultant Radiologist specializing in Interventional Oncology at Taichung Veterans General Hospital, Taiwan. I have a strong interest in CT and MR imaging diagnosis and interventional radiology, including TACE, HAIC, and TARE. Over the past decade, I've spoken at international conferences about embolic treatments in hepatocellular carcinoma (HCC).

I began working on HCC in Taichung in 2002 and became an assistant professor at the University of Miami in 2010. Since 2011, I've been practicing in Taichung and currently serve as the President of the Taiwan Society of Interventional Radiology. I also lecture on embolic techniques for HCC and have published several essays on imaging and liver tumors.

I hold a PhD in hospital management, focusing my research on transarterial chemoembolization (TACE) for HCC. My goal is to improve imaging interpretation for liver tumor diagnosis and enhance multi-modal intra-arterial therapies for liver tumors.

## Research Interests

1. Interventional Radiology, including TACE, HAIC and TARE
2. CT and MR abdominal imaging diagnosis

## Representative Publications

1. Multidisciplinary Taiwan Consensus Recommendations for the Use of DEBDOX-TACE in Hepatocellular Carcinoma Treatment, Liver Cancer 2018; Published online: March 29, 2018, DOI: 10.1159 /000487608
   Pi-Yi Chang, Chun-Chieh Huang, Chao-Hung Hung, Chih-Yung Yu, Ding-Kwo Wu, Jen-I Hwang, Po-Chin Liang, Reng-Hong Wu, Wei-Lun Tsai, Yih-Jyh Lin, Yi-Sheng Liu, Huei-Lung Liang, Rheun-Chuan Lee, Chien-Hung Chen.
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# Role of TARE in the Management of BCLC Stage B HCC

**Pi-Yi Chang** *Taichung Veterans General Hospital, Taiwan*

Transarterial Radioembolization (TARE) has emerged as a pivotal treatment modality for hepatocellular carcinoma (HCC), particularly for patients classified under the Barcelona Clinic Liver Cancer (BCLC) Stage B. This stage includes patients with multinodular HCC who are not suitable candidates for curative treatments but require effective local-regional therapy to control disease progression and improve survival outcomes. One of the significant advantages of TARE is its potential for downstaging tumors, making previously unresectable tumors resectable. Studies have shown that TARE can lead to a decrease in viable tumor nodules and significant tumor downsizing, with some patients subsequently becoming eligible for surgical resection or liver transplantation. This downstaging ability not only expands treatment options but also improves long-term survival outcomes. Moreover, for patients who are not candidates for curative treatments, TARE serves as an effective local-regional therapy, offering superior overall survival and progression-free survival rates compared to traditional methods like transarterial chemoembolization (TACE). TARE is associated with a favorable safety profile, reduced post-embolization syndrome, and lower hepatic toxicity. This presentation will explore the critical role of TARE in managing BCLC Stage B HCC, emphasizing its benefits in downstaging for surgery and its efficacy as a local-regional therapy to control disease progression and improve patient survival outcomes.

**Keywords:** Transarterial Radioembolization, Hepatocellular Carcinoma, BCLC Stage B, Downstaging, Local-regional Therapy, Interventional Radiology


## Chow Wei Too

*Singapore General Hospital, Singapore*


## Self Introduction

Too Chow Wei is the deputy HOD of the Department of Vascular and Interventional Radiology, Singapore General Hospital. With interests in interventional oncology, MSK and pain interventions, portal hypertension and pulmonary embolism

# Role of TARE in the Management of BCLC Stage C HCC

**Chow Wei Too** *Singapore General Hospital, Singapore*

Recent advances in Y90 has been ablative in nature. Is there still a role for Y90 in advanced HCC?


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# KASL Branch EMW 2 [Daejeon-Sejong-Chungcheong]

**Chair:**

**Tae-Hee Lee** (Konyang Univ.)

**Myeong Jun Song**

*The Catholic University of Korea*

## Self Introduction

Prof. Myeong Ju Song is a Professor of the Division of Hepatology, Department of Internal medicine, College of Medicine, The Catholic University of Korea.

Prof. Song graduated from College of Medicine, The Catholic University of Korea with his medical degree in 2001 and completed his internship and residency at the Department of Hepatology at Seoul St. Mary's University Hospital, receiving his diploma in Hepatology in 2014.

Since 2013, Prof. Song has been taking a number of roles, including Director, External Affairs Committee of the Korean Association of the Study of the Liver (2022-2023), and currently as Deputy Director of Editorial Board of the Korean association of Gastroenterology (2024- ).

## Research Interests

Dr. Song has a special interest in the treatment and prediction of chronic liver disease including Viral hepatitis, fatty liver, liver cirrhosis and liver cancer. With his expertise in cirrhosis and HCC, he is focusing on prognosis in patients with kidney injury and novel biomarkers or scoring system. Innovative, translational, and longstanding clinical research has ever been a pursuit in his academic career.

## Representative Publications

1. Ryu JE, Song MJ, et al. Safety and effectiveness of direct-acting antivirals in patients with chronic hepatitis C and chronic kidney disease Korean J Intern Med. 2022 Sep;37(5):958-968
2. Tan EX, Lee JW, Jumat NH, Chan WK, Treeprasertsuk S, Goh GB, Fan JG, Song MJ, et al. Non-obese non-alcoholic fatty liver disease (NAFLD) in Asia: an international registry study Metabolism. 2022 Jan;126:154911. doi: 10.1016/j.metabol.2021.154911. Epub 2021 Oct 12.
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# Management of High-Risk HCC Patients

**Myeong Jun Song** *The Catholic University of Korea*

High-risk hepatocellular carcinoma (HCC) patients present a significant clinical challenge due to their advanced disease stage and increased recurrence risk. They are defined as those with advanced-stage HCC or a high risk of recurrence after curative treatment. Accurate diagnosis using dynamic contrast-enhanced imaging and serum biomarkers is crucial for guiding treatment decisions. Therapeutic strategies include curative interventions, locoregional therapy, and systemic therapies such as molecularly targeted agents and immunotherapies. Multidisciplinary collaboration is essential for optimizing treatment outcomes in this complex patient population. This early morning workshop emphasizes the importance of tailored approaches to effectively manage high-risk HCC patients and improve long-term survival.

## Introduction

High-risk hepatocellular carcinoma (HCC) patients represent a significant challenge in clinical management due to their advanced disease stage and increased likelihood of recurrence. This workshop aims to define high-risk HCC patients, including those with advanced HCC and a high risk of recurrence, and discuss the appropriate diagnostic and therapeutic strategies for this patient population.

## Definition of High-Risk HCC Patients

High-risk HCC patients encompass individuals with advanced-stage HCC, typically characterized by large tumor size, vascular invasion, extrahepatic spread, and/or inadequate liver function reserve. Additionally, patients who have undergone curative treatment for HCC but are at a high risk of recurrence due to underlying liver disease or other risk factors also fall into this category.

## Diagnostic Strategies

Accurate diagnosis and staging are crucial for guiding appropriate management decisions in high-risk HCC patients. Diagnostic modalities such as dynamic contrast-enhanced imaging (e.g., multiphase CT scan or MRI) and serum biomarkers (e.g., AFP, PIVKA) play pivotal roles in identifying tumor characteristics, vascular invasion, and extrahepatic spread. Furthermore, non-invasive methods such as transient elastography can assess liver function and help stratify patients based on their risk profile.

## Therapeutic Strategies

### *Curative Intent:*

For high-risk patients with resectable tumors and preserved liver function, surgical resection or liver transplantation remains the cornerstone of curative therapy. However, careful patient selection and multidisciplinary evaluation are essential to optimize outcomes and minimize the risk of recurrence.

### *Locoregional Therapies:*

Locoregional therapies, including radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and radioembolization, play a crucial role in managing unresectable HCC or as bridging therapies to transplantation. These modalities offer the advantage of targeting tumor lesions while preserving surrounding liver parenchyma.

### *Systemic Therapy:*

The advent of molecularly targeted agents and immunotherapies has revolutionized the systemic treatment landscape for advanced HCC. Atezolizumab plus bevacizumab combination therapy has shown promising results in both resected/ablated high-risk HCC patients (IMbrave050 trial) and those with advanced HCC (Atezolizumab plus bevacizumab for advanced HCC study). This regimen has demonstrated efficacy in improving overall survival and delaying disease progression in high-risk HCC patients.

### *Surveillance and Follow-up:*

Regular surveillance with imaging studies and serum biomarkers is imperative for detecting early recurrence and initiating timely interventions. Close monitoring allows for prompt adjustment of treatment strategies and enhances long-term outcomes in high-risk HCC patients.

## Conclusion

Management of high-risk HCC patients necessitates a comprehensive approach that integrates diagnostic, therapeutic, and surveillance strategies tailored to individual patient characteristics and disease stage. Multidisciplinary collaboration is essential to optimize treatment outcomes and improve patient survival in this challenging population.

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# Basic Research 1

## From Cells and Systems: Spatial and Organoid Technologies

**Chairs:**

**Sang Geon Kim** (Dongguk Univ.)
**Haeng Ran Seo** (Institut Pasteur Korea)

**Kwon Joong Na**

*Seoul National University*

## Self Introduction

Dr. Kwon Joong Na is a distinguished medical professional specializing in thoracic and cardiovascular surgery. He began his academic journey at Seoul National University, College of Medicine, earning a Bachelor's degree in 2010, a Master of Science in Clinical Medical Sciences in 2013, and is currently pursuing a PhD in the same field. His extensive education has provided a strong foundation for his professional career.

Dr. Na has a rich professional background, including an internship and residency at Seoul National University Hospital, where he specialized in thoracic and cardiovascular surgery. He served as a public health doctor during his military service and completed a fellowship in General Thoracic Surgery. Since 2019, Dr. Na has held academic positions, advancing to Clinical Associate Professor in 2024, demonstrating his expertise in both clinical practice, research, and medical education.

Dr. Na is an active member of several prestigious national and international medical societies. Domestically, he is a member of The Korean Society of Thoracic and Cardiovascular Surgery, The Korean Association of Lung Cancer, and The Korean Bronchoesophagological Society. Internationally, he is affiliated with the International Association for the Study of Lung Cancer, the European Society of Thoracic Surgeons, the European Respiratory Society, and the European Society of Medical Oncology. His involvement in these organizations highlights his dedication to staying at the forefront of medical advancements and contributing to the global medical community.

## Research Interests

- Thoracic oncology (lung cancer, esophageal cancer, thymic epithelial tumor)
- Translational research (genomics, transcriptomics, single cell RNA sequencing, spatial transcriptomics)

## Representative Publications

1. Bae S, Na KJ, Koh J, et al. CellDART: cell type inference by domain adaptation of single-cell and spatial transcriptomic data. Nucleic Acids Res 2022;50(1):e57. (1st author)
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# Understanding Spatial Transcriptomics in Hepatology: From Sample Preparation to Application

**Kwon Joong Na** *Seoul National University*

Spatial transcriptomics in hepatocellular carcinoma (HCC) research holds immense potential for advancing our understanding of the tumor microenvironment (TME). HCC, as the most common type of primary liver cancer, remains a significant cause of cancer-related mortality worldwide. The TME in HCC comprises various cell types, including cancer cells, immune cells, fibroblasts, and endothelial cells, whose interactions significantly influence tumor progression, metastasis, and response to therapies. Traditional transcriptomic approaches often fail to preserve the spatial context of gene expression, which is critical for understanding these cellular interactions. Spatial transcriptomics (ST) has emerged as a revolutionary technique that retains spatial information, offering a more comprehensive analysis of the TME in HCC.

The spatial transcriptomics technique integrates high-throughput sequencing and imaging technologies to map gene expression patterns within tissue sections. The process begins with sample preparation, where tissue samples are fixed, embedded, and sectioned onto specialized slides containing spatially barcoded oligonucleotides. RNA molecules from the tissue sections hybridize to these barcoded oligonucleotides, allowing spatially resolved RNA capture. The captured RNA is then reverse-transcribed, amplified, and sequenced. Sequencing data is subsequently processed to map gene expression back to the spatial coordinates, involving alignment, clustering, and visualization techniques to identify spatial gene expression patterns and cellular interactions. This approach enables researchers to visualize the spatial distribution of transcripts across the tissue, providing a high-resolution map of gene activity within the TME.

Spatial transcriptomics is particularly useful in studying tumor evolution, the tumor microbiome, and biomarker research regarding immunotherapy in HCC. It facilitates the study of tumor heterogeneity and clonal evolution by analyzing the spatial distribution of genetic mutations and gene expression profiles. This capability allows researchers to trace the lineage of cancer cells and understand their evolution in response to selective pressures within the TME, informing strategies to overcome therapeutic resistance and improve patient outcomes. Moreover, spatial transcriptomics can map the spatial organization of microbial communities within the tumor tissue and their interactions with host cells, shedding light on the role of the microbiome in cancer progression and treatment response. Understanding

these interactions may reveal new avenues for microbiome-based therapies in HCC.

The identification of spatially resolved biomarkers is crucial for developing effective immunotherapies. Spatial transcriptomics can uncover the spatial heterogeneity of immune cell infiltration and activation states within the TME. This information is vital for identifying predictive biomarkers for immunotherapy response and designing combination therapies that modulate the immune landscape of HCC. By preserving spatial context, spatial transcriptomics provides unique insights into tumor evolution, the tumor microbiome, and biomarker discovery for immunotherapy. This technique holds great promise for improving the diagnosis, treatment, and prognosis of HCC, ultimately leading to better patient outcomes.

Spatial transcriptomics represents a powerful tool for advancing our understanding of the TME in HCC. By offering a high-resolution map of gene activity within the TME, it provides critical insights into the mechanisms driving tumor evolution, immune evasion, and therapeutic resistance. The application of this technique in HCC research promises to improve patient outcomes by informing the development of personalized therapeutic strategies and enhancing our understanding of the complex interplay between cancer cells and their microenvironment.


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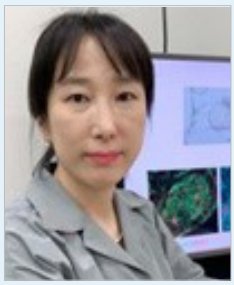


## Myung Jin Son

*Korea Research Institute of Bioscience and Biotechnology*


## Self Introduction

Dr. Myung Jin Son is a Principal Research Scientist at the Stem Cell Convergence Research Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB), and currently serves as a professor of the Department of Functional Genomics, the University of Science & Technology in Korea (UST) simultaneously.

Dr. Myung Jin Son received a Ph.D. degree in Molecular Biology from Pusan National University in 2005 and worked as a postdoctoral research fellow and research professor at Samsung Medical Center/Sungkyunkwan University School of Medicine until 2006. Dr. Son then held the position of Postdoctoral Visiting Fellow at the National Institutes of Health (NIH) and National Cancer Institute (NCI) in the United States until 2009.

Since 2009, Dr. Son has been employed at KRIBB, focusing on the development of a human pluripotent stem cell-based liver organoid platform for disease modeling and safety assessment.

## Research Interests

Development of drug safety/efficacy evaluation platform using human pluripotent stem cell-derived liver organoids

## Representative Publications


1. Lee J, Gil D, Park H, Lee Y, Mun SJ, Shin Y, Jo E, Windisch MP, Kim J*, Son MJ*. A multicellular liver organoid model for investigating hepatitis C virus infection and non-alcoholic fatty liver disease progression. Hepatology, accepted.
2. Mun SJ, Hong Y, Shin Y, Lee J, Cho H, Kim D, Chung K*, Son MJ*. Efficient and reproducible generation of human induced pluripotent stem cell-derived expandable liver organoids for disease modeling. Sci Rep., 13:22935, 2023.
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5. Mun SJ, Ryu J, Lee M, Son YS, Oh SJ, Cho H, Son M, Kim D, Kim SJ, Yoo HJ, Lee H, Kim J, Jung C, Chung K*, Son MJ*. Generation of expandable human pluripotent stem cell-derived hepatocyte-like liver organoids. Journal of Hepatology, 71, 970, 2019.

# Emerging Organoid Technologies to Apply for Precision Medicine in Hepatology

**Myung Jin Son** *Korea Research Institute of Bioscience and Biotechnology*

The liver is the most important metabolic organ in the body, which is responsible for the metabolism of substances, including pharmaceuticals, industrial chemicals, pesticides, and food additives. Some of these substances or their toxic metabolite generated through the detoxification process, can lead to acute liver failure or chronic liver diseases. Drug safety issues continue to occur despite the approval of drugs following comprehensive clinical studies. Model systems that recapitulate the complex organ structure and cell compositions of the human liver are insufficient for studying liver biology and assessing the toxicity of chemicals. Conventional in vitro human liver models, such as two-dimensional hepatic cell lines, lack in vivo physiological relevance, and animal studies have limitations due to species differences and regulatory restrictions. To resolve this issue, an increasing number of three-dimensional human liver systems, including organoids, are being developed. We have successfully established self-renewing and functionally mature human pluripotent stem cell-derived liver organoids as an alternate to primary human hepatocytes. Notably, liver organoids exhibited significant toxic responses to clinically relevant concentrations of drugs that had been withdrawn from the market due to hepatotoxicity. Moreover, the organoids were applied to screening platforms for evaluating drugs that target metabolic dysfunction-associated steatotic liver disease. Disease modeling for infectious liver diseases and genetic liver diseases is also being conducted. Overall, these liver organoids can be a practical and renewable cell source of a versatile and valuable platform for human cell-based and personalized 3D liver model.


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# Translational Research 2

## Metabolic Mechanisms and Therapeutic Innovations in Hepatic Oncology

**Chairs:**

**Seung Kew Yoon** (The Catholic Univ. of Korea)
**Won-Il Jeong** (KAIST)


## Jungwook Hwang

*Hanyang University*


## Self Introduction

### *Education*

| | |
|---|---|
| 2008 | Postdoctoral Fellow, Biophysics and Biochemistry, University of Rochester Medical Center |
| 2008 | Ph.D. Integrative Biosciences, The Pennsylvania State University |
| 1999 | M.E. Biomaterial Science and Engineering, Yonsei University |
| 1997 | B.S. Biotechnology, Yonsei University |

### *Professional Experience*

| | |
|---|---|
| 2020-Present | Professor, Hanyang University, Seoul, Korea |
| 2016-2020 | Associate Professor, Hanyang University, Seoul, Korea |
| 2011-2016 | Assistant Professor, Hanyang University, Seoul, Korea |

## Research Interests

My research in the laboratory delves into the intricate role of RNA within cellular metabolism, with a specific focus on conditions such as hepatocellular carcinoma, nonalcoholic fatty liver disease, melanoma, and stem cell biology. Utilizing CRISPR-based techniques, we investigate the regulation of RNA abundance. Our primary objective is the development of therapeutic strategies and biomarkers leveraging various noncoding RNA including long noncoding RNA, miRNA, and circular RNA. Currently, our emphasis is on circular RNA, which plays a pivotal role in understanding diseases like hepatocellular carcinoma, melanoma, and nonalcoholic fatty liver disease, as well as guiding the complex processes of stem cell differentiation and proliferation. By decoding the language of circRNA, our goal is to reveal intricate connections and explore potential therapeutic avenues within this captivating field.

## Representative Publications


1. Role of UPF1-LIN28A interaction during early differentiation of pluripotent stem cells (2024) Nature Communications, 15(1):158
2. Role of UPF1 in lncRNA-HEIH regulation for hepatocellular carcinoma therapy (2024) Experimental & Molecular Medicine, 56(2):344
3. UPF1 inhibits hepatocellular carcinoma growth through DUSP1/p53 signal pathway (2022) Biomedicines, 10(4):793
4. UPF1/SMG-7-dependent microRNA-mediated gene regulation (2019) Nature Communications, 10(1):4181
5. Lin28B and miR-142-3p regulate neuronal differentiation by modulating Staufen1 expression (2018) Cell Death & Differentiation, 25:432-443

# Hepatocellular Carcinoma in RNA Biology: Long Concoding RNA/miRNA and Circular RNA in Hepatocellular Carcinoma

**Jungwook Hwang** *Hanyang University*

Hepatocellular carcinoma (HCC) has a high mortality rate because of the lack of effective treatments. Multityrosine kinase inhibitors (sorafenib and lenvatinib) and a combination of atezolizumab (anti-PD-L1 antibody) and bevacizumab (anti-VEGF antibody) are currently approved for HCC therapy[1]. However, these drugs may lead to drug resistance and extend life by only a few months. To overcome these hurdles of HCC therapy, extensive studies on HCC therapeutics have been conducted at the molecular and cellular levels. One approach is the study of noncoding RNAs (ncRNAs), including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNA (circRNA). In this presentation, I will introduce two approaches, lncRNA[2] and circRNA (unpublished), to reveal the molecular mechanisms and the potential gene therapy for HCC.

## Chapter 1: Role of UPF1 in lncRNA-HEIH regulation for hepatocellular carcinoma therapy

In terms of molecular functions, lncRNAs act by regulating transcription via interaction with transcription factors, translating functional peptides from small open reading frames, mediating posttranscriptional regulation via interaction with diverse RNA-binding proteins (RBPs), and acting as miRNA sponges or decoys.

UPF1, a well-known posttranscriptional regulator, regulates the abundance of lncRNAs and mRNAs. The functionality of UPF1 in the nonsense-mediated mRNA decay (NMD) process is intricately regulated by its phosphorylation status, which is mediated by the serine/threonine kinase SMG1[3]. Hyperphosphorylated UPF1 interacts with RNA decay factors such as SMG6 and SMG5/7[4], facilitating the degradation of target RNAs. Subsequently, hyperphosphorylated UPF1 undergoes dephosphorylation by the enzyme PP2A, reverting to its hypophosphorylated form, hypo-UPF1[5]. This hypo-UPF1 pool is recycled for subsequent rounds of NMD. UPF1 recognizes premature termination codon (PTC)-containing transcripts with various NMD factors or initiates the degradation of long 3'UTR-containing transcripts with the help of miRNAs in the regulation of mRNA expression[6-9]. Notably, UV cross-linking RNA immunoprecipitation sequencing (CLIP-seq) demonstrated that UPF1 was also associated with a variety of lncRNAs[10], indicat-

ing that UPF1 has the potential to regulate cell fate by reducing the abundance of lncRNAs, although the detailed mechanism by which UPF1 degrades lncRNAs remains unknown.

Here, we investigated the role of UPF1 in HCC. Transcriptome analysis in UPF1-depleted cell lines showed that *lncRNA-HEIH* was commonly upregulated. Consistent with the effects of UPF1 depletion (enhanced HCC cell growth), exogenous *lncRNA-HEIH* promoted HCC tumorigenesis. Analysis of the public UPF1 CLIP-seq dataset and biochemical assays revealed that UPF1 binds to the double-stranded region in *lncRNA-HEIH* and that its degradation is dependent on UPF1 phosphorylation and SMG5. *LncRNA-HEIH* acts as a decoy of miR-194-5p, which targets the oncogene GNA13. Our findings demonstrate that UPF1 regulates *lncRNA-HEIH* levels in HCC, and this lncRNA recruits miR-194-5p and regulates GNA13 expression, ultimately demonstrating therapeutic potential in HCC.

## Chapter 2: Circular RNA in HCC

Circular RNA (circRNA) represents a unique class of RNA molecules distinguished by their closed-loop structure, a departure from the linear configuration typical of most RNA. This distinctive form arises through back-splicing, where a downstream splice donor site connects with an upstream splice acceptor site, resulting in a covalently closed loop devoid of free ends. CircRNAs, prevalent across diverse organisms, wield significant influence over gene expression modulation through diverse mechanisms, including serving as microRNA sponges, orchestrating transcriptional processes, engaging in protein interactions, and even generating peptides.

Emerging research underscores the pivotal role of circRNAs in HCC, where they demonstrate a propensity to thwart programmed cell death mechanisms by disrupting essential cellular signaling pathways or facilitating heightened invasion and metastasis. In this presentation, we aim to provide a succinct overview of the latest advancements in understanding HCC-specific circRNAs within our laboratory.

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**Kyun-Hwan Kim**

*Sungkyunkwan University*

## Self Introduction

Kyun-Hwan Kim is a molecular virologist, currently a Professor of Precision Medicine at Sungkyunkwan University Medical School. He initially trained in Korea, obtaining a BS/MS from the Seoul National University and a Ph.D. at the Yonsei University, followed by postdoctoral studies at Brown University. He returned to Korea in 2005 to establish a Virology research laboratory at the Konkuk University in Seoul. He moved to Sungkyunkwan University in Mar 2020. He serves as an academic editor at PLoS ONE, Frontier in Immunology, and World Journal of Gastroenterology.

## Research Interests

The Kyun-Hwan Kim's lab works in the fields of hepatitis B virus, influenza virus, corona virus, and virus-related diseases, attempting to decipher the molecular and cellular mechanisms that control viral replication, life-cycle, and virus-induced pathogenesis. Current interests and investigations include the viral evasion against host immune systems, drug resistance, and development of antivirals.

## Representative Publications

1. Shin GC, Lee MH, Kim N, et al., & Kim KH*. Paraoxonase-2 agonist vutiglabridin promotes autophagy activation and mitochondrial function to alleviate non-alcoholic steatohepatitis. Br J Pharmacol. 2024. In press.
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# Dysregulation of Liver Regeneration by Hepatitis B Virus Infection: Impact on Development of HCC

**Kyun-Hwan Kim** *Sungkyunkwan University*

The liver is unique in its ability to regenerate in response to damage. The complex process of liver regeneration consists of multiple interactive pathways. About 2 billion people worldwide have been infected with hepatitis B virus (HBV), and HBV causes 686,000 deaths each year due to its complications. Long-term infection with HBV which causes chronic inflammation, leads to serious liver-related diseases including cirrhosis and hepatocellular carcinoma. HBV infection has been reported to interfere with the critical mechanisms required for liver regeneration.

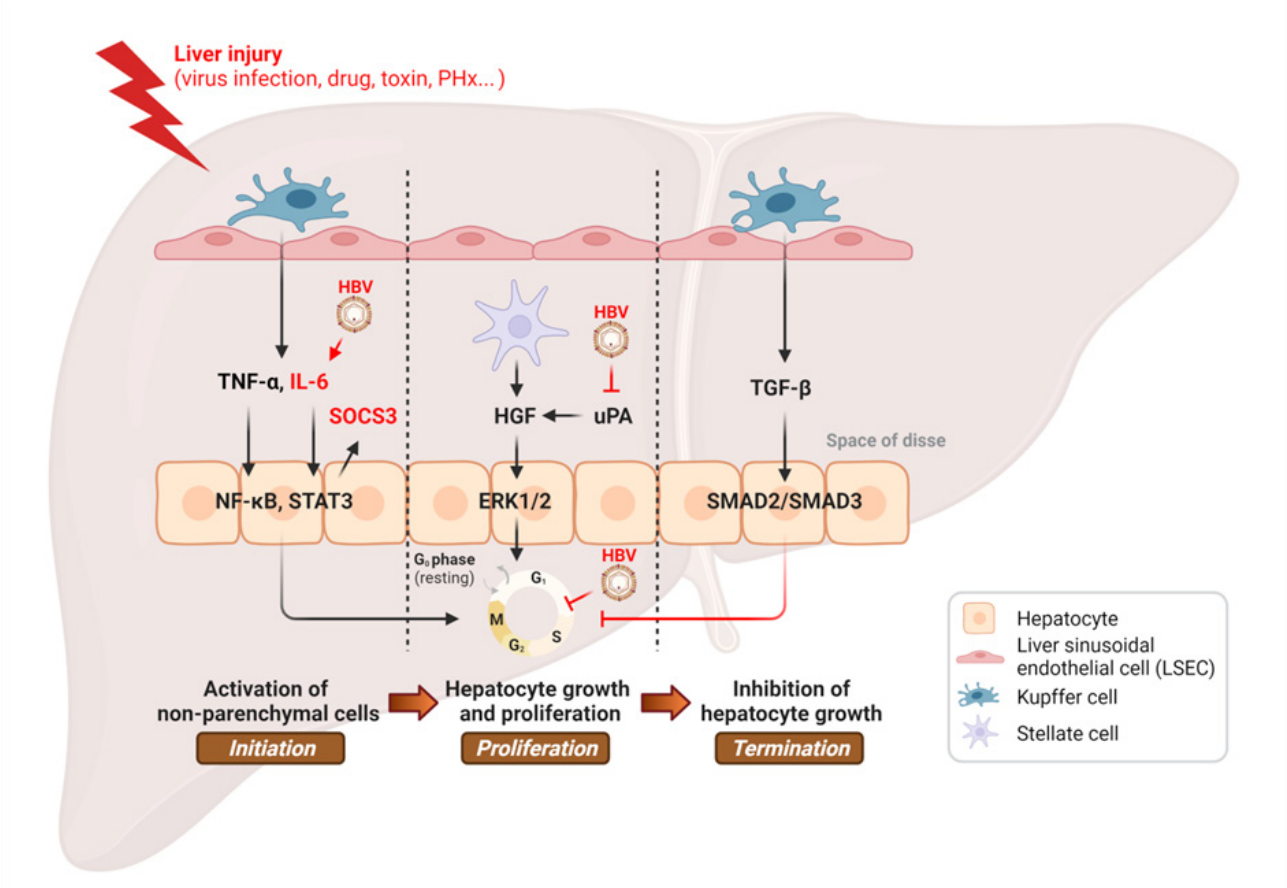


**Figure 1.** Inhibition of the hepatic regenerative pathway by HBV infection. PHx, partial hepatectomy.

In this presentation, the studies on liver tissue characteristics and liver regeneration mechanisms are summarized. Moreover, the inhibitory mechanisms of HBV infection in liver regeneration are investigated. Finally, the association between interrupted liver regeneration and hepatocarcinogenesis, both triggered by HBV infection, is outlined. Understanding the fundamental and complex liver regeneration process is expected to provide significant therapeutic advantages for HBV-associated hepatocellular carcinoma.

**Keyword:** Hepatitis B virus (HBV), Liver, Liver regeneration, HBV-related hepatocellular carcinoma

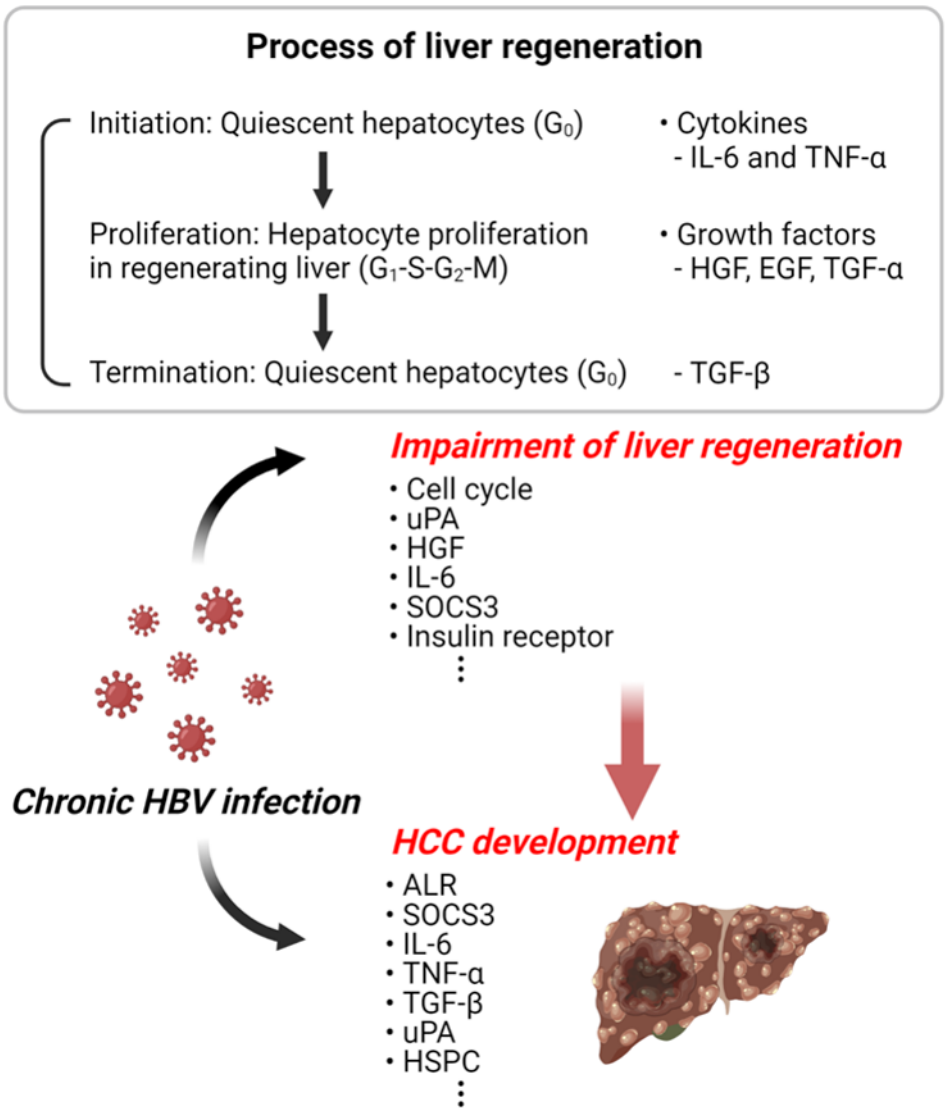


**Figure 2.** Schematic diagram of HBV-related liver regeneration and HCC. The illustration represents the increased incidence of liver cancer due to the abnormal liver regeneration caused by HBV infection.


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**Keun-Gyu Park**

*Kyungpook National University*

## Self Introduction

Prof. Keun-Gyu Park is a Professor of the Department of Internal Medicine, Kyungpook National University School of Medicine and is currently holding a Director of division of Endocrinology and Metabolism Kyungpook National University Hospital.

Prof. Park graduated from Keimyung University School of Medicine with his medical degree in 1996 and completed his internship and residency at the Department of Internal Medicine at Keimyung University Dongsna Hospital, receiving his diploma in Internal Medicine in 2022.

## Research Interests

Cancer Metabolism, Fatty liver, Diabetes

## Representative Publications

1. Kim DH, Knag YN, Jin J, Park M, Kim D, Yoon G, Yun JW, Lee J, Park SY, Lee YR, Byun JK, Choi YK, Park KG*. Glutamine-derived aspartate is required for eIF5A hypusination-mediated translation of HIF-1alpha to induce polarization of tumor-associated macrophages. Experimental and Molecular Medicine2024 May 1. Online ahead of print. PMID: 38689086
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# Modulation of Amino Acid Metabolism as a Therapeutic Target of Liver Cancer

**Keun-Gyu Park** *Kyungpook National University*

Proliferating cancer cells rely largely on glutamine for survival and proliferation. Glutamine serves as a carbon source for the synthesis of lipids and metabolites via the TCA cycle, as well as a source of nitrogen for amino acid and nucleotide synthesis. To date, many studies have explored the role of glutamine metabolism in cancer, thereby providing a scientific rationale for targeting glutamine metabolism for cancer treatment. In this symposium, I will briefly summarize the previous our study demonstrating that glutamine metabolism has a pivotal role in anti-tumor response of CD8 T cells and further discuss the recent our study showing the role of glutamine metabolism in polarization of tumor associated macrophages (TAMs), which are major players in tumor immune microenvironment.

TAMs are vital contributors to the growth, metastasis, and therapy resistance of various cancers, including hepatocellular carcinoma (HCC). However, the exact phenotype of TAMs, and the mechanisms underlying their modulation for therapeutic purposes, remain unclear. Here, we present compelling evidence that glutamine-derived aspartate in TAMs stimulates spermidine production through the polyamine synthesis pathway, thereby increasing the translation efficiency of HIF-1$\alpha$ via eIF5A hypusination. Consequently, augmented translation of HIF-1$\alpha$ drives TAMs to increase glycolysis and develop a metabolic phenotype distinct from that of M2 macrophages. Finally, eIF5A levels in tumor stromal lesions were higher than in non-tumor stromal lesions. Additionally, the degree of tumor stromal eIF5A hypusination was significantly associated with a higher tumor grade. Taken together, the data highlight the potential of inhibiting hypusinated eIF5A by targeting glutamine metabolism in TAMs, thereby opening up a promising avenue for development of novel therapeutic approaches to HCC.


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THE LIVER WEEK 2024

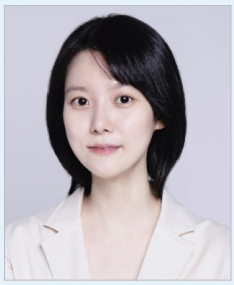
DAY 2: June 28 (Fri)

# Data Science Camp 1

## Statistical Methodologies in Clinical Research

**Chairs:**

**Geum-Youn Gwak** (Sungkyunkwan Univ.)
**Sangwook Kang** (Yonsei Univ.)



**Danbee Kang**

*Sungkyunkwan University*

## Self Introduction

Prof. Danbee Kang is an Assistant Professor of Department of Clinical Research Design & Evaluation, SAIHST, Sungkyunkwan University and is an Assistant Professor of Center for Clinical Epidemiology, Samsung Medical Center, simultaneously.

## Research Interests

Clinical epidemiology; Real world data

## Representative Publications

1. Kang D, Cho J, Zhao D, Kim J, Kim N, Kim H, Kim S, Kim JY, Park YH, Im YH, Guallar E, Ahn JS. Scalp Cooling in Preventing Persistent Chemotherapy-Induced Alopecia: A Randomized Controlled Trial. J Clin Oncol. 2024 Jun 6:JCO2302374. doi: 10.1200/JCO.23.02374
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3. Sinn DH, Kang D, Kang M, Guallar E, Hong YS, Lee KH, Park J, Cho J, Gwak GY. Nonalcoholic fatty liver disease and accelerated loss of skeletal muscle mass: A longitudinal cohort study. Hepatology. 2022 Dec;76(6):1746-1754. doi: 10.1002/hep.32578 (co-first)
4. Sinn DH, Kang D, Jang HR, Gu S, Cho SJ, Paik SW, Ryu S, Chang Y, Lazo M, Guallar E, Cho J, Gwak GY. Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: A cohort study. J Hepatol. 2017 Dec;67(6):1274-1280. doi: 10.1016/j.jhep.2017.08.024 (co-first)
5. Sinn DH, Kang D, Jang HR, Gu S, Cho SJ, Paik SW, Ryu S, Chang Y, Lazo M, Guallar E, Cho J, Gwak GY. Non-alcoholic fatty liver disease and progression of coronary artery calcium score: a retrospective cohort study. Gut. 2017 Feb;66(2):323-329. doi: 10.1136/gutjnl-2016-311854 (co-first)

# Practical Approach for Causal Inference

**Danbee Kang** *Sungkyunkwan University*

**Background/Aim:** Causal inference is the term used for the process of determining whether an observed association truly reflects a cause-and-effect relationship. Although well-conducted randomized clinical trials remain the preferred approach for answering causal questions, methods for observational studies have advanced such that causal interpretations of the results of well-conducted observational studies may be possible when strong assumptions hold. Thus, this presentation aims to introduce a framework for comparative effectiveness research.

**Methods:** Causal inference from large observational databases can be viewed as an attempt to emulate a randomized experiment—the target experiment or target trial—that would answer the question of interest. Target trial emulation is a 2-step process.

The first step is articulating the causal question in the form of the protocol of a hypothetical randomized trial that would provide the answer. The protocol must specify certain key elements that define the causal estimands (eligibility criteria, treatment strategies, treatment assignment, the start and end of follow-up, outcomes, causal contrasts) and the data analysis plan.1 The randomized trial described in the protocol becomes the target study for the causal inference of interest.

The second step is explicitly emulating the components of that protocol using the observational data: finding eligible individuals, assigning them to a treatment strategy compatible with their data, following them up from assignment (time zero) until outcome or end of follow-up, and conducting the same analysis as the corresponding target trial, except that there is adjustment for baseline confounders in an attempt to emulate random treatment assignment.

**Conclusion(s):** Adoption of the proposed frame work to identify when causal interpretation is appropriate in observational studies promises to facilitate better communication between authors, reviewers, editors, and readers.

**Seo Young Park**

*Korea National Open University*

## Self Introduction

### *Education*

| | | | |
|---|---|---|---|
| 2000-2004 | Seoul National University, Seoul, Korea | BSc | Statistics and Mathematics |
| 2005-2010 | University of North Carolina at Chapel Hill Chapel Hill, NC, USA<br>Advisor: Yufeng Liu, PhD | PhD | Statistics |

### *Appointments and Positions*

| | |
|---|---|
| 2009-2009 | Research Intern, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Ct, USA |
| 2010-2011 | Research Associate (Assistant Professor), Department of Health Studies, Biostatistics Lab, University of Chicago, Chicago, IL, USA |
| 2011-2017 | Assistant Professor |
| 2017-2018 | Associate Professor, Department of Medicine, Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA, USA |
| 2018-2021 | Research Associate Professor, Department of Clinical Epidemiology and Biostatistics, University of Ulsan, Asan Medical Center, Seoul, Korea |
| 2021-Present | Assistant Professor, Department of Statistics and Data Science, Korea National Open University, Seoul, Korea |

## Representative Publications

1. Kim JE, Park JE, Park SY, Kim YH, Hong CK, Kim JH, Kim HS. Defining subventricular zone involvement to predict the survival of patients in isocitrate dehydrogenase-wild type glioblastoma: validation in a prospective registry. Eur Radiol. 2023 Sep;33(9):6448-6458. doi: 10.1007/s00330-023-09625-w. Epub 2023 Apr 15. PubMed PMID: 37060448.
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# Advanced Survival Analysis

**Seo Young Park** *Korea National Open University*

Survival analysis technique has wide application in medical and clinical research. While basic survival analysis methods such as Kaplan-Meier curve, log-rank test or Cox proportional hazards model offer valuable insights into the relationship between risk factors and clinical time-to-event outcome, there are situations where these methods are not applicable due to violation of underlying assumptions, or these methods are bound to give biased estimates. In this talk, we briefly review the fundamental concepts in survival analysis and introduce some of the advanced survival analysis techniques: stratified Cox model, Cox model with time-dependent covariates, and landmark analysis. Illustrative examples and R programming demonstrations showcase the practical implementation of these approaches.

**Sehee Kim**

*University of Ulsan*

## Self Introduction

Dr. Sehee Kim is a Research Associate Professor of the Department of Clinical Epidemiology and Biostatistics, University Ulsan College of Medicine and Asan Medical Center.

Dr. Kim joined the Asan Medical Center in 2020. She received her PhD in Biostatistics from the University of North Carolina. She then worked as a research fellow at the Harvard School of Public Health from 2010 to 2012. She was also a professor of Biostatistics at the University of Michigan from 2012 to 2020, when she moved to the Asan Medical Center.

## Research Interests

Dr. Kim's methods work has primarily focused on joint modeling of longitudinal and time-to-events data, analysis of complicated time-to-event outcomes (including recurrent events, left-truncated data, cure-rate models, and competing risks analyses, etc), and risk score development and model discrimination. Collaboratively, Dr. Kim aims to improve biomedical science and public health science by bridging the gap between researchers, the statistical methods needed and applied to studies, and the communication of results.

## Representative Publications

1. Lee JH*, Kim S*, Oh Y. (2023). A prediction scoring model for the effect of withdrawal or addition of inhaled corticosteroids in patients with Chronic Obstructive Pulmonary Disease. International J of Chronic Obstructive Pulmonary Disease, 18:113-127. (* Co-first author)
2. Hartman N#, Kim S, He K, Kalbfleisch JD. (2023). Concordance indices with left-truncated and right-censored data. Biometrics, 79(3):1624-1634. (# Student under my supervision)
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6. Kim S, Schaubel DE, McCullough KP. (2018). A C-index for recurrent event data: Application to hospitalizations among dialysis patients. Biometrics, 74(2):734-743.

# Development of Clinical Prediction Models

**Sehee Kim** *University of Ulsan*

Clinical prediction models are pivotal tools in modern medicine, aiding in decision-making, risk stratification, and personalized care. This seminar will outline the comprehensive process of developing such models using medical data. It begins with defining the clinical question and identifying the primary outcome. Data collection and preparation, emphasizing data quality and data processing, are critical initial steps. Variable selection involves identifying relevant predictors through clinical knowledge and exploratory analyses, followed by feature engineering to transform raw data into meaningful features.

Model development includes choosing appropriate statistical or machine learning techniques, such as logistic regression, Cox regression, or random forests, and validating the model through training and cross-validation. Model evaluation employs performance metrics such as sensitivity and specificity, ROC-AUC or C-index for model discrimination, and calibration plots. We will also discuss ways of addressing overfitting issues using cross-validation and regularization techniques.

Model interpretation focuses on understanding predictor effects through raw regression coefficients, odds ratios, or hazard ratios and feature importance. Validation and calibration are crucial, involving internal techniques like bootstrapping and external validation on independent datasets to ensure generalizability.

Case studies illustrate practical applications of these models: one on fibrosis-4 (FIB-4) predicting fibrosis progression in patients with HIV/HCV, and another on predicting hepatocellular carcinoma (HCC) risk in patients with non-alcoholic fatty liver disease (NAFLD)-cirrhosis.

Challenges in data quality, model complexity, and clinical integration are acknowledged, with future directions pointing towards incorporating genomics and real-time data processing.

In conclusion, the structured development of clinical prediction models holds significant promise for enhancing patient care through informed, data-driven decision-making. This seminar will serve as a guide for clinicians to understand and apply predictive analytics in their practice, fostering collaboration between clinicians and data scientists for improved healthcare outcomes.

**Seungbong Han**

*Korea University*

## Self Introduction

Prof. Seungbong Han is a Associate Professor of the Department of Biostatistics, Korea University College of Medicine and is holding a joint position at the Graduate School of Public Health in Korea University.

Prof. Han graduated from the Department of Statistics at the University of Wisconsin-Madison in USA with Ph.D degree and Master's degree.

Prof. Han has been taking a number of roles, including medical technology reevaluation advisory group member from the National Evidence-based healthcare Collaborating Agency (2018-2024), advisory committee member for Clinical Trials from the Medical Device Safety Bureau, Korea Food and Drug Administration (2012-2017), and currently as Statistical Reviewer for Journal of Clinical Neurology (2023- ).

## Research Interests

- His research interest includes Survival Analysis, Causal Inference, Big Data Analysis and Prediction Model Building.
- Recently, he works on developing model performance measure for completing risks survival data.

## Representative Publications

1. Five-year on-treatment variables-based PPACS model predicts subsequent hepatocellular carcinoma in entecavir/tenofovir-treated patients. International Journal of Cancer 2023
2. Simulation study for the machine learning models and evaluation measures in survival data, Journal of the Korean Data Information Science Society, 2023
3. Loco-regional therapies competing with radiofrequency ablation in potential indications for hepatocellular carcinoma : a network meta-analysis. Clinical and Molecular Hepatology 2023
4. Comprehensive Prediction of Subclinical Coronary Atherosclerosis in Subjects Without Traditional Cardiovascular Risk Factors. Am J Cardiol. 2023
5. Prediction of the 10-year risk of atherosclerotic cardiovascular disease in the Korean population. EPIDEMIOLOGY AND HEALTH 2023

# Various Model Performance Measures

**Seungbong Han** *Korea University*

Predictive performance measures in survival analysis are essential for evaluating the accuracy and reliability of survival models. We discuss the definition, interpretation, and application of each measure. This presentation offers an exploration of various predictive performance measures commonly employed in survival modeling. Key measures include the concordance index (C-index), integrated Brier score (IBS), time-dependent area under the receiver operating characteristic curve (AUC), calibration plot and a net benefit curve. By comprehensively understanding these performance metrics, researchers can make informed decisions regarding model selection and refinement, ultimately enhancing the utility and applicability of survival analysis in diverse fields.


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THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# Data Science Camp 2

## Harnessing Health Data in Medicine

**Chairs:**

**Sung Bum Cho** (Chonnam National Univ.)
**Seungbong Han** (Korea Univ.)


## Seng Chan You

*Yonsei University*


## Self Introduction

Seng Chan You, MD, Ph.D. obtained his medical degree from Yonsei University College of Medicine in Seoul, South Korea, and completed his internal medicine residency at Severance Hospital. Dr. You's academic pursuits continued at the Department of Biomedical Informatics at Ajou University, where he began his journey in the field of biomedical informatics.

His work is prominently affiliated with the Observational Health Data Sciences and Informatics (OHDSI) program, where he's recognized as a key collaborator. His dedication and innovative research approach were honored in 2021 with the Young Scientist Award of the Wunsch Medical Award.

With a research focus on data standardization, the generation of real-world evidence, and the application of artificial intelligence in healthcare, He actively supports the standardization and expansion of healthcare data in various countries, including the Asia Pacific region. By leveraging advanced data science and rigorous methodologies, he is committed to producing reliable, reproducible, and transparent real-world evidence. Additionally, he is engaged in artificial intelligence research that has the potential to be applied in medical practice and benefit patients directly.

## Research Interests

Medical Big Data, A.I., and Observational Study

## Representative Publications


1. Ranitidine Use and Incident Cancer in a Multinational Cohort. Jama Network Open, v.6, no.9, pp.e2333495, 2023.09.
2. The Evolution of Evidence-Based Medicine: When the Magic of the Randomized Clinical Trial Meets Real-World Data. CIRCULATION, v.145, no.2, pp.107-109. 2022.01.
3. Comprehensive Comparative Effectiveness and Safety of First-Line $\beta$-Blocker Monotherapy in Hypertensive Patients: A Large-Scale Multicenter Observational Study. HYPERTENSION, v.77, no.5, pp.1,528-1,538. 2021.05.
4. Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. JAMA, 324(16):1640-1650. 2020.10.

# Common Data Model (CDM) for Observational Research

**Seng Chan You** *Yonsei University*

In recent years, the landscape of observational research has transformed significantly with the advent of the Common Data Model (CDM). This presentation delves into the application and impact of CDM in observational research, highlighting its role in enhancing data standardization, scalability, and international collaboration. Specifically, it focuses on the Observational Health Data Sciences and Informatics (OHDSI) network and its utilization of the OMOP CDM to facilitate systematic and reproducible research across diverse health databases worldwide.

Observational research traditionally grapples with challenges related to data heterogeneity, lack of standardization, and limited generalizability. These issues are particularly pronounced when attempting to aggregate and analyze data from various sources. The CDM approach addresses these challenges by providing a standardized data structure and common terminology, thus enabling more efficient data integration and analysis.

The presentation begins by outlining the core principles and structure of the CDM, with a particular emphasis on the OMOP CDM. It describes how the OMOP CDM accommodates a vast array of data elements, facilitating broader terminology coverage and interoperability. This standardization is crucial for enabling large-scale observational studies that are both scalable and reproducible.

A significant portion of the presentation is dedicated to the OHDSI network, an international collaborative consortium that applies open-source data analytic solutions based on the OMOP CDM. The mission and objectives of OHDSI, such as fostering innovation, reproducibility, and openness, are discussed in detail. The network's commitment to community collaboration and beneficence ensures that the generated evidence promotes better health decisions and care.

The presentation highlights several key advantages of using CDM in observational research:

1. Scalability: CDM facilitates systematic research across the world, allowing for the integration of diverse health databases from multiple countries.
2. Data Standardization: By standardizing data, CDM enables more accurate and reliable analysis, reducing the risk of bias and improving the validity of research findings.

3. International Collaboration: The CDM approach supports global research efforts, fostering collaboration among researchers from different regions and institutions.

Several case studies are presented to illustrate the practical applications of CDM in observational research. These examples demonstrate how CDM has been used to address complex research questions and generate robust evidence. For instance, studies leveraging the OHDSI network's capabilities have provided insights into the safety and efficacy of various treatments, contributing to better healthcare outcomes.

Despite its advantages, the implementation of CDM in observational research is not without challenges. The presentation acknowledges issues such as data privacy concerns, the need for continuous updates to the data model, and the complexities of integrating data from different healthcare systems. However, it also highlights ongoing efforts to address these challenges, including advancements in data security, the development of more comprehensive data models, and increased international collaboration.

In conclusion, the adoption of the Common Data Model represents a significant advancement in the field of observational research. By providing a standardized framework for data integration and analysis, CDM enhances the scalability, reproducibility, and generalizability of research findings. The OHDSI network's application of the OMOP CDM exemplifies the potential of this approach to transform healthcare research and improve patient outcomes globally. Future efforts should focus on expanding the adoption of CDM, addressing remaining challenges, and fostering greater international collaboration to realize the full potential of observational research.


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**Kyu-Hwan Jung**

*Sungkyunkwan University*

## Self Introduction

Kyu-Hwan Jung serves as an assistant professor at both Sungkyunkwan University's Samsung Advanced Institute for Health Science and Technology (SAIHST) and the Research Institute for Future Medicine at Samsung Medical Center, positions he has held since August 2022.

Previously, he co-founded VUNO Inc. and served as Chief Technology Officer from January 2015 to August 2022, where he played a crucial role in developing medical decision support solutions using deep learning algorithms. Before his tenure at VUNO, Dr. Jung was a research staff member at Samsung Advanced Institute of Technology (SAIT) from March 2014 to December 2014. He also worked as a manager at SK Planet's Institute of Platform Technology from October 2011 to February 2014, and at SK Telecom's Institute of Platform Technology from January 2011 to September 2011.

Dr. Jung is actively involved in professional organizations related to his field. He has been a Planning Board Member of the Korean Society of Artificial Intelligence in Medicine (KoSAIM) since January 2019 and a Scientific Board Member of the Korean Society of Imaging Informatics in Medicine (KSIIM) since March 2019.

Kyu-Hwan Jung received his B.S. in Industrial and Management Engineering from POSTECH (Pohang University of Science and Technology) in August 2005 and continued his studies at POSTECH, earning a Ph.D. in the same field in August 2010.

## Research Interests

Machine Learning, Deep Learning, Artificial Intelligence, Clinical Decision Support System, Software as a Medical Device

## Representative Publications

1. Jaeyoung Kim et al., "Key Feature Replacement of In-Distribution Samples for Out-of-Distribution Detection", AAAI 2023
2. Seo Taek Kong et al., "A Neural Pre-Conditioning Active Learning Algorithm to Reduce Label Complexity", NeuIPS 2022
3. Jinkyeong Sung et al., "Added Value of Deep Learningbased Detection System for Multiple Major Findings on Chest Radiographs: A Randomized Crossover Study", Radiology, 2021
4. Jeonghyuk Park et al., "A prospective validation and observer performance study of a deep learning algorithm for pathologic diagnosis of gastric tumors in endoscopic biopsies", Clinical Cancer Research, 2021
5. Jaemin Son et al., "Development and Validation of Deep Learning Models for Screening Multiple Abnormal Findings in Retinal Fundus Images", Ophthalmology, 2020.

# AI's Role in Diagnosis and Prognosis

**Kyu-Hwan Jung** *Sungkyunkwan University*

The rapid advancement and implementation of Artificial Intelligence (AI) in the medical field, hold significant promise for improving the quality and efficiency of clinical workflows. This review examines the current status and future prospects of AI in healthcare, emphasizing the regulatory approvals of various commercial solutions across different countries (Esteva et al., 2019). AI technologies have already begun to make substantial impacts in areas such as diagnostic imaging, personalized treatment, and patient monitoring. The discussion extends to the ongoing development of technical approaches and services poised to revolutionize clinical workflows in the near future (Topol, 2019).

One of the critical aspects covered is the methodological strategies aimed at overcoming the present limitations of medical AI algorithms. Current AI systems often face challenges related to data quality, interpretability, and generalizability. Addressing these limitations involves integrating robust validation methods, incorporating diverse datasets, and enhancing algorithm transparency (Amann et al., 2020). Additionally, the integration of cutting-edge technologies from diverse fields is highlighted as a means to enhance the synergy between human physicians and AI, thereby augmenting clinical decision-making and patient outcomes (Jiang et al., 2017).

Special attention is given to generative AI, recognized for its capability to generate or predict new data. This technology is gaining traction in areas such as disease diagnosis, medical image analysis, and drug discovery. Generative AI models, such as Generative Adversarial Networks (GANs) and variational autoencoders (VAEs), have shown promise in generating realistic medical images and predicting disease progression (Chen et al., 2020). This lecture introduce recent advancements in generative AI technologies, including large language models (LLMs) (Brown et al., 2020), diffusion models, and vision language models, as well as large multimodal models (LMMs) that handle various data types and enable simultaneous user interaction (Ramesh et al., 2022).

Furthermore, the talk underscores the ethical and regulatory challenges posed by these generative AI technologies in healthcare. The application of AI in medicine raises significant concerns about data privacy, algorithmic bias, and the transparency of decision-making processes (Morley et al., 2020). It is crucial to establish frameworks and guidelines that address these ethical and regulatory issues to ensure the responsible deployment of AI in clinical settings. This includes developing standards for data gover-

nance, creating mechanisms for accountability, and fostering an environment of continuous monitoring and evaluation of AI systems (Naylor et al., 2021).

Overall, this talk highlights the transformative potential of AI in the medical field while acknowledging the challenges and limitations that need to be addressed. By advancing methodological approaches, integrating novel technologies, and addressing ethical and regulatory concerns, AI can significantly enhance the capabilities of healthcare systems, ultimately improving patient care and outcomes.

## References


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# Big Data in Healthcare: Research and Applications

**So-Ryoung Lee**

*Seoul National University*


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June 27-29, 2024 | Walkerhill, Seoul, Korea

**Hyo Jung Park**

*University of Ulsan*

## Self Introduction

Prof. Hyo Jung Park graduated from University of Ulsan College of Medicine with her medical degree in 2013 and completed her intership and residancy at Asan Medical Center, receiving her diploma in Radiology in 2018. She obtained a master's degree in 2022 and a doctoral degree in 2022. She is an Assistant Professor of the Department of Radiology, University of Ulsan College of Medicine.

## Research Interests

Liver Imaging, Biliopancreatic imaging, Cancer imaging, Personalized medicine

## Representative Publications

1. Park HJ, Shin K, You M-W, et al. Deep Learning–based Detection of Solid and Cystic Pancreatic Neoplasms at Contrast-enhanced CT. Radiology 2023 Jan 306(1):140–149
2. Park HJ, Kim KW, Won SE, et al. Definition, Incidence, and Challenges for Assessment of Hyperprogressive Disease during Cancer Treatment with Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Netw Open 2021; 4(3) e211136
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# Guide for Radiomics Study to Clinical Researchers

**Hyo Jung Park** *University of Ulsan*

Imaging plays a pivotal role in evaluating various liver diseases, including screening, surveillance, diagnosis, and prognostication of diffuse liver disorders and hepatic neoplasms. Recent advancements in imaging techniques have enabled the identification of non-invasive imaging surrogates for patients' clinical outcomes. Particularly, advances in computer science have facilitated the clinical application of computer-assisted analysis in imaging examinations, including radiomics.

Radiomics is a set of techniques that utilize high-dimensional features extracted from images for diagnostic and predictive tasks. This approach is based on the hypothesis that a radiologic phenotype may reflect genetic alterations in carcinogenesis and tumor biology, and thus may predict the biological behavior of the tumor. It has gained attention as a method for supporting clinical decision-making and precision medicine. With this methodology, the role of imaging may expand beyond traditional visual image analysis.

Radiomics is an evolving field of research and has the potential to substitute invasive and expensive genetic tests. It can also be used to predict treatment response and prognosis, as well as guide personalized treatment options. However, the pitfalls of radiomics must also be acknowledged, including laborious and time-consuming processes, high dependency on the technical aspects of image preprocessing and feature extraction, and limited generalizability.

For radiomics to become a valid clinical tool, its processes must be standardized, and its performance must be validated through properly conducted clinical tests. Future research endeavors need to address the clinical impact of radiomics and determine how these techniques can be incorporated into real-world clinical practice.

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THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# KASL Branch EMW 3 [Gangwon]

## Research Journey of Gangwon Branch of KASL: Cirrhosis and Its Complications

**Chair:**

**Gab Jin Cheon** (Univ. of Ulsan)

**Seul Ki Han**

*Yonsei University Wonju*

## Self Introduction

Prof. Han graduated from Yonsei University Wonju College of Medicine with his medical degree in 2015 and completed his internship and residency at the Department of Internal medicine at Wonju Severance Christian Hospital.

## Research Interests

Liver cirrhosis, Portal hypertension, Alcoholic liver disease.

## Representative Publications

1. Han, S. K., Kim, M. Y., Kang, S. H., & Baik, S. K. (2022). Application of ultrasound for the diagnosis of cirrhosis/portal hypertension. Journal of Medical Ultrasonics, 49(3), 321-331.
2. Han, S. K., Kang, S. H., Kim, M. Y., Na, S. K., Kim, T., Lee, M., ... & Baik, S. K. (2022). Outcome of Intermittent Thoracentesis versus Pigtail Catheter Drainage for Hepatic Hydrothorax. Journal of Clinical Medicine, 11(23), 7221.
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# History and Clinical Indications of NSBB

**Seul Ki Han** *Yonsei University Wonju*

## History and Clinical Indications of NSBB

### *1. History of NSBB:*

In 1980, the Lebrec group first reported that non-selective beta-blockers (NSBB) were effective in preventing gastrointestinal bleeding.

### *2. Indications:*

- Compensated Cirrhosis and CSPH (Clinically Significant Portal Hypertension): NSBBs are beneficial in preventing the progression to decompensated cirrhosis.
- Variceal Bleeding Prevention: Effective for both primary and secondary prophylaxis in patients with high-risk varices.
- Advanced Cirrhosis: May be beneficial with proper dose adjustment.

### *3. Limitations:*

- Ineffective in preventing the development of new varices.
- Many side effects and low tolerance.
- High doses associated with higher mortality rates.
- Difficult to maintain maximum titrated dose in clinical practice; dose adjustments are often necessary based on the patient's condition.

## Real-Life Data from Korea

### *1. LONG Study in Gangwon-do:*

- Compared low-dose (≤80mg) and high-dose (>80mg) NSBB.
- Low-dose NSBB was significantly associated with improved survival, especially in patients with moderate/severe ascites.
- NSBB treatment reduced HVPG (Hepatic Venous Pressure Gradient), contributing to reduced ascites occurrence and improved survival rates.

## Propranolol vs. Carvedilol

### *1. Comparison of Effects:*

- Carvedilol is more effective than propranolol in reducing portal pressure and is effective at low doses.
- Carvedilol has the additional benefit of intrahepatic vasodilation.
- High doses of Carvedilol can have significant side effects, thus low doses are recommended.

## Summary

### *1. Who and When to Use NSBB:*

- No clear benefit for early fibrosis with mild portal hypertension.
- Beneficial for compensated cirrhosis with CSPH and high-risk varices.
- Potentially beneficial for advanced cirrhosis with ascites with proper dose adjustment.

### *2. Which Drug:*

- Portal pressure reduction: propranolol < carvedilol.
- Clinical outcomes: more research needed.

NSBBs play a crucial role in preventing variceal bleeding and improving survival in cirrhosis patients. However, due to their side effects and the necessity for dose adjustments, careful individualized use is essential.


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**Tae-Suk Kim**

*Kangwon National University*

## Self Introduction

| | |
|---|---|
| 2013.03-2020.08 | Ph.D. in Clinical Medical Science Kangwon National University College of Medicine, Chuncheon-si, Korea |
| 2010.03-2012.08 | M.S. in Clinical Medical Science Kangwon National University College of Medicine, Chuncheon-si, Korea |
| 2003.03-2008.02 | M.D. in Medicine Kangwon National University College of Medicine, Chuncheon-si, Korea |
| 2016.03-2019.08 | Assistant clinical professor, Division of Gastroenterology, Department of Internal Medicine, Kangwon National University Hospital, Chuncheon, South Korea |
| 2022.03-present | Assistant Professor, Division of Gastroenterology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, South Korea |

## Research Interests

- Alcoholic liver disease
- Liver cirrhosis
- Hepatocellular carcinoma
- Abdominal US

## Representative Publications

1. Kim, Tae Suk, et al. "Metformin and dichloroacetate suppress proliferation of liver cancer cells by inhibiting mTOR complex 1." International Journal of Molecular Sciences 22.18 (2021): 10027.
2. Kim, Tae Suk, et al. "Reappraisal of sepsis-3 and CLIF-SOFA as predictors of mortality in patients with cirrhosis and infection presenting to the emergency department: A multicenter study." Clinical and molecular hepatology 28.3 (2022): 540.
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# New Insights of SEPSIS-3

**Tae-Suk Kim** *Kangwon National University*

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. During sepsis, the liver has essential roles, such as immune defense and metabolic adaptation to inflammation. In addition, it is a target for sepsis-related injury, including hypoxic hepatitis, cholestasis, drug-induced liver injury, and secondary sclerosing cholangitis in critically ill patients.

Our group's research aimed to compare the predictive abilities of the Sepsis-3 criteria and Chronic Liver Failure-SOFA (CLIF-SOFA) scores for in-hospital mortality in cirrhotic patients admitted to the emergency department (ED) for infections. A total of 1,622 cirrhosis patients who were admitted to the ED for infections were assessed retrospectively. We analyzed their demographic, laboratory, and microbiological data upon diagnosis of the infection. The primary endpoint of our study was the in-hospital mortality rate. We evaluated the predictive performances of baseline CLIF-SOFA, Sepsis-3, and qSOFA scores for in-hospital mortality. The CLIF-SOFA score was found to be significantly better at predicting in-hospital mortality than both the Sepsis-3 and qSOFA scores.

In cirrhotic patients presenting with infections at the ED, CLIF-SOFA scores demonstrated a superior ability to predict mortality compared to both the Sepsis-3 criteria and qSOFA scores. Therefore, the CLIF-SOFA score can be a useful tool for risk stratification in cirrhotic patients who require timely intervention for infection.


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THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# KASL Branch EMW 4 [Gyeonggi-Incheon]

**Chair:**

**Soon Woo Nam** (The Catholic Univ. of Korea)

**Min Kyung Park**

*Seoul National University*

## Self Introduction

### *Education*

Prof. Park holds a Ph.D. in Stem Cell Biology from Seoul National University College of Medicine (2021-2023). She also obtained an M.D. Master Degree of Medicine from the same institution (2013-2017) and a B.S. in Biology from Seoul National University (2008-2012).

Prof. Park completed a medical internship (2017-2018) and a residency in Internal Medicine (2018-2021) at Seoul National University Hospital. She served as a Research and Clinical Fellow at the Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine (2018-2022). Following this, she became a Clinical Assistant Professor at the Department of Internal Medicine, Seoul National University Hospital (2022-2023), and currently holds the same position at Seoul National University Bundang Hospital (2023- ).

## Research Interests

Prof. Park is deeply interested in all aspects of hepatology. Her primary research areas include investigating the pathogenesis, treatment, and prevention of hepatitis B and C in the context of viral hepatitis, as well as exploring the mechanisms, diagnosis, and therapeutic approaches for metabolic dysfunction-associated steatotic liver disease (MASLD) in the field of fatty liver disease.

## Representative Publications

1. Park MK*, Hur MH*, Moon HS*, et al. Extrahepatic malignancies in metabolic dysfunction-associated fatty liver disease: A nationwide cohort study. Liver Int. Published online January 17, 2024. (* co-first authors)
2. Park MK*, Lee DH*, Hur BY, et al. Effectiveness of US Surveillance of Hepatocellular Carcinoma in Chronic Hepatitis B: US LI-RADS Visualization Score. Radiology. 2023;307(5):e222106. (* co-first authors)
3. Hur MH*, Park MK*, Cheuk-Fung Yip T*, Chen CH*, Lee HC*, Choi WM*, et al. Personalized antiviral drug selection in chronic hepatitis B patients using a machine learning model: a multinational study. [published online ahead of print, 2023 Mar 7]. Am J Gastroenterol. (* co-first authors)
4. Park MK, Lee YB, Moon H, Choi NR, Kim MA, Jang H, Nam JY, Cho EJ, Lee JH, Yu SJ, Kim YJ, Yoon JH. Effectiveness of Lenvatinib Versus Sorafenib for Unresectable Hepatocellular Carcinoma in Patients with Hepatic Decompensation. Dig Dis Sci. 2022 Jan 20. (First authors)
5. Chung SW*, Park MK*, Cho YY*, et al. Effectiveness of Transarterial Chemoembolization-First Treatment for Advanced Hepatocellular Carcinoma: A Propensity Score Matching Analysis. J Hepatocell Carcinoma. 2021;8:587-598. Published 2021 Jun 15. (* co-first authors)

# Medical Perspectives on Transjugular Intrahepatic Portosystemic Shunt (TIPS)

**Min Kyung Park** *Seoul National University*

## Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is a minimally invasive procedure employed in the management of complications arising from portal hypertension, including refractory ascites and variceal bleeding. As a bridge to liver transplantation or as a definitive treatment, TIPS has gained prominence due to its effectiveness in reducing portal pressure and associated morbidity. This abstract aims to present the current medical perspectives on TIPS, focusing on its indications, procedural aspects, and clinical outcomes.

## Indications

TIPS is primarily indicated in patients with complications of portal hypertension unresponsive to conventional medical therapies.[1] These include refractory variceal hemorrhage, refractory ascites, hepatic hydrothorax, and Budd-Chiari syndrome. Additionally, TIPS is considered for patients with hepatopulmonary syndrome and as a bridge to liver transplantation in those with end-stage liver disease.[2]

## Procedural Aspects

The procedure involves the creation of a tract between the hepatic vein and the portal vein using an intravascular stent, thereby reducing portal pressure. This is achieved under fluoroscopic guidance, ensuring minimal invasiveness and reduced recovery time compared to surgical shunts. Advances in imaging techniques and stent technology have significantly improved the success rates and safety profile of TIPS.

## Clinical Outcomes

Clinical outcomes following TIPS are influenced by patient selection and the underlying liver function. The procedure effectively controls variceal bleeding and reduces ascites in the majority of patients. However, post-TIPS hepatic encephalopathy (PSE) remains a significant complication, occurring in up to 30% of patients.[3] Careful patient selection, pre-procedural risk assessment, and post-procedural management strategies are crucial in mitigating these risks.[4] Long-term patency of the shunt is another

critical factor, with advancements in stent design improving durability and reducing the need for re-intervention.[5]

## Conclusion

TIPS represents a pivotal advancement in the management of portal hypertension-related complications. While it offers significant benefits in terms of symptom control and quality of life improvement, careful patient selection and comprehensive post-procedural care are essential to optimize outcomes. Future directions include the refinement of patient selection criteria, enhancement of stent technology, and development of strategies to manage and prevent post-TIPS complications. Continued research and clinical trials will further delineate the role of TIPS in hepatic disease management, ensuring its optimal application in clinical practice.

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2. Larrey E, Cluzel P, Rudler M, Goumard C, Damais-Thabut D, Allaire M. TIPS for patients with early HCC: A bridge to liver transplantation. Clin Res Hepatol Gastroenterol 2022;46:101790.
3. Ahmed Z, Hassan M, Arif SF, et al. Comparative Efficacy of Treatment Options for the Prevention of Post-TIPS Hepatic Encephalopathy: A Systematic Review and Network Meta-analysis. J Gastrointestin Liver Dis 2023;32:70-76.
4. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406-460.
5. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2021;74:1014-1048.


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**Tae Won Choi**

*Ajou University*

## Self Introduction

Prof. Taewon Choi is a Professor of the Department of Radiology, Ajou University School of Medicine with a subspecialty in interventional radiology.

Prof. Choi graduated from Seoul National University College of Medicine with his medical degree in 2012 and completed his internship and residency at the Department of Radiology at Seoul National University Hospital, receiving his diploma in Radiology in 2017. Prof. Choi completed his interventional radiology fellowship at Seoul National University Hospital in 2020.

## Research Interests

Transarterial chemoembolization, Radiation protection

## Representative Publications

1. Choi TW, Chung JW, Kwon Y. Modified design of x-ray protective clothing to enhance radiation protection for interventional radiologists. Med Phys. 2023 Jun;50(6):3825-3832.
2. Choi TW, Joo I, Kim HC. Association of dysmorphic intratumoral vessel with high lung shunt fraction in patients with hepatocellular carcinoma. Sci Rep. 2022 Aug 21;12(1):14248.
3. Choi TW, Chung JW, Kim HC, Lee M, Choi JW, Jae HJ, et al. Anatomic Variations of the Hepatic Artery in 5625 Patients. Radiol Cardiothorac Imaging. 2021;3(4):e210007.
4. Choi TW, Chung JW, Cha BK, Choi KN, Park S, Son JW, et al. Feasibility of dosimetric measurements using Al2O3:C OSL dosimeter during fluoroscopy-guided procedures. J Radiol Prot. 2020;40(4).
5. Choi TW, Chung JW, Kim HC, Choi JW, Lee M, Hur S, et al. Aberrant gastric venous drainage and associated atrophy of hepatic segment II: computed tomography analysis of 2021 patients. Abdom Radiol (NY). 2020;45(9):2764-71.

# Before and After TIPS: Practical Insights from the Perspective of Radiology

**Tae Won Choi** *Ajou University*

## Contraindication for TIPS

- Significant pulmonary hypertension
- Heart failure or severe cardiac valvular insufficiency
- Rapidly progressive liver failure
- Severe or uncontrolled hepatic encephalopathy
- Uncontrolled systemic infection or sepsis
- Unrelieved biliary obstruction
- Polycystic liver disease (though successful cases reports exist)
- Extensive primary or metastatic hepatic malignancy

## Procedural complications

- Arrhythmias
- Wedge hepatic venography-related liver injury
- Extrahepatic portal vein puncture
- Hepatic arterial injury
- Liver capsule transgression

## Anatomical consideration

- The relative position of the right portal vein and right hepatic vein
- Small liver volume
- Prominent hepatic artery

Visualization of the portal vein

- Wedge hepatic venography
- Balloon-occluded venography
- $CO_2$ venography
- Real-time US

## Anticoagulation / antiplatelet after TIPS: meta-analyses

- Front. Pharmacol. 14:1116177
  - Anticoagulant or antiplatelet therapy may prevent new portal vein thrombosis
  - No significant difference: patency rate, bleeding, death
- Medicine 2022;101:26(e29742)
  - Anticoagulation: lower incidence of portal vein thrombosis
  - No significant difference: stent dysfunction, bleeding, hepatic encephalopathy

## Follow-up

- No standardized modality or interval
  - Doppler US
  - Every 6–12 months
- Who needs to be followed up?
  - Bare metal vs. covered stent
  - TIPS indication: bleeding patient
  - Biliary-venous fistula
  - Suboptimal stent position or configuration

## Hepatic encephalopathy after TIPS

- Incidence
  - New or worsened: 13–36%
  - Refractory: 8%
- Risk factors
  - Older age
  - Higher Child–Pugh and MELD score
  - History of hepatic encephalopathy pre-TIPS
  - Low portosystemic pressure gradient
  - Sarcopenia
  - Proton pump inhibitors
- Endovascular Treatment for Post-TIPS hepatic encephalopathy
  - TIPS Reduction
  - Spontaneous Portosystemic Shunts Embolization

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THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# KLTS-KAHBPS-KLCA Joint Symposium

## Multidisciplinary Approaches for HCC with Bile Duct Invasion

**Chairs:**

**Yi-Hsiang Huang** (National Yang Ming Chiao Tung Univ., Taiwan),
**Kyung-Suk Suh** (Seoul National Univ.)

**Yuri Cho**

*National Cancer Center*

## Self Introduction

- Seoul National University College of Medicine, 2008
- Master's degree of Medicine, 2013, Seoul National University
- Doctor's degree of Medicine, 2017, Seoul National University
- Research Fellow, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 2013-2016
- Assistant Professor, Department of Internal Medicine, CHA Gangnam Medical Center, CHA University School of Medicine, 2016-2021
- Center for Liver and Pancreatobiliary Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea, 2021-

## Research Interests

- Hepatocellular carcinoma
- Metabolic-dysfunction associated steatohepatitis
- Hepatitis B virus drug developmemt

## Representative Publications

1. Asian Pacific Association for the Study of the Liver clinical practice guidelines on liver transplantation. Kim DS, Yoon YI, Kim BK, Choudhury A, Kulkarni A, Park JY, Kim J, Sinn DH, Joo DJ, Choi Y, Lee JH, Choi HJ, Yoon KT, Yim SY, Park CS, Kim DG, Lee HW, Choi WM, Chon YE, Kang WH, Rhu J, Lee JG, Cho Y, Sung PS, Lee HA, Kim JH, Bae SH, Yang JM, Suh KS, Al Mahtab M, Tan SS, Abbas Z, Shresta A, Alam S, Arora A, Kumar A, Rathi P, Bhavani R, Panackel C, Lee KC, Li J, Yu ML, George J, Tanwandee T, Hsieh SY, Yong CC, Rela M, Lin HC, Omata M, Sarin SK; for Asian Pacific Association for Study of Liver (APASL). Hepatol Int. 2024 Apr;18(2):299-383. doi: 10.1007/s12072-023-10629-3. Epub 2024 Feb 28.
2. Transarterial chemoembolization for hepatocellular carcinoma: 2023 Expert consensus-based practical recommendations of the Korean Liver Cancer Association. Cho Y, Choi JW, Kwon H, Kim KY, Lee BC, Chu HH, Lee DH, Lee HA, Kim GM, Oh JS, Hyun D, Lee IJ, Rhim H; Research Committee of the Korean Liver Cancer Association. Clin Mol Hepatol. 2023 Jul;29(3):521-541.
3. Overview of Asian clinical practice guidelines for the management of hepatocellular carcinoma: An Asian perspective comparison. Cho Y, Kim BH, Park JW. Clin Mol Hepatol. 2023 Apr;29(2):252-262.
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5. Lee D, Kang JA, Lim C, Bae S, Choi J, Park M, Kim YC, Cho Y(co-corresponding), Park SG, Seo J. Entry inhibition of hepatitis B virus using cyclosporin O derivatives with peptoid side chain incorporation. Bioorg Med Chem. 2022 Aug 15;68:116862. doi: 10.1016/j.bmc.2022.116862. Epub 2022 Jun 6. PMID: 35691131
6. Choi SI, Cho Y (co-first), Ki M, Kim BH, Lee IJ, Kim TH, Kim SH, Koh YH, Kim HB, Hong EK, Kim CM, Park JW. Better survival of patients with hepatitis B virus-related hepatocellular carcinoma in South Korea: Changes in 16-years cohorts. PLoS One. 2022 Mar 24;17(3):e0265668. doi: 10.1371/journal.pone.0265668. eCollection 2022.
7. Cho Y, Cho EJ, Yoo JJ, Chang Y, Chung GE, Choi IY, Park SH, Han K, Kim YJ, Yoon JH, Shin DW, Yu SJ. The Importance of Metabolic Syndrome Status for the Risk of Non-Viral Hepatocellular Carcinoma: A Nationwide Population-Based Study. Front Oncol. 2022 May 4;12:863352. doi: 10.3389/fonc.2022.863352. eCollection 2022.

# Cases of HCC with Bile Duct Invasion

**Yuri Cho** *National Cancer Center*

## [Case 1]

The patient with hepatitis B virus-related liver cirrhosis (HBV-LC) classified as Child-Pugh class A5, on a regimen of tenofovir disoproxil fumarate (TDF) since May 3, 2022. The patient also has a history of hypertension (HTN) and diabetes mellitus (DM). The patient underwent right hemihepatectomy for hepatocellular carcinoma (HCC) in 2005 in Germany. First, TARE was planned. In May 2022, a 10.7 cm multinodular confluent HCC at liver segment 4 (S4) was diagnosed. The initial patient's Child-Pugh class deteriorated to A6. Celiac arteriography was performed on May 12, 2022, revealing bile duct invasion, leading to developing obstructive jaundice. Subsequently, percutaneous transhepatic biliary drainage (PTBD) was conducted from June 13, 2022, to November 22, 2022. Sequential treatment with Atezolizumab/Bevacizumab (AtezoBev) combinations was administered, with partial response (PR) achieved until cycles #13-15 (March 27, 2023, to April 17, 2023), indicating near complete remission (CR). Maintenance chemotherapy (molecular complete response by modified RECIST v1.1) was continued with cycles #16-17 (May 8, 2023, to May 30, 2023). Open peripheral segmentectomy of liver segment 4 (S4) was performed on August 3, 2023.

## [Case 2]

The patient was diagnosed as histology-confirmed infiltrative hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) (Vp3, right). A combination therapy of Atezolizumab + Bevacizumab (AtezoBev) was administered from September 30, 2022, to January 2, 2023, for 5 cycles. Concurrently, proton therapy was administered, including treatment for Rt. portal vein tumor thrombosis and S8/5 tumor from October 5, 2022, to October 18, 2022 (5000cGy/10Fx).

On January 5, 2023, the patient presented to the emergency room with intermittent epigastric pain and soreness starting four days prior. Blood tests and abdominal CT revealed acute pancreatitis, hemobilia, and a hematoma-filled distended gallbladder (GB). Precutaneous endoscopic sphincterotomy was performed, followed by supportive care, leading to improvement in pain and cholestasis, and subsequent discharge. Due to a serious adverse event of hemobilia, AtezoBev was discontinued, and from January 27, 2023, the patient started the 2nd line sorafenib therapy at a dose of 600mg bid. Subsequently, due

to continued mild epigastric soreness, the dose of sorafenib was reduced to 400mg qd starting from February 7, 2023.

On February 20, 2023, the patient presented to the emergency room with acute abdominal pain starting one day prior. CT revealed a hematoma in the common bile duct (CBD), leading to the insertion of an endoscopic nasobiliary drainage (ENBD) on February 21, 2023. Following ENBD drainage and antibiotic treatment, improvement in abdominal pain and cholestasis was observed, and the patient was discharged on February 23, 2023.

On March 20, 2023, percutaneous transhepatic gallbladder drainage (PTGBD) was inserted due to acute cholecystitis, followed by PTGBD tube change on March 23, 2023, and insertion of percutaneous catheter drainage (PCD) for a perihepatic abscess resulting from gallbladder rupture.

Following proton therapy and AtezoBev anticancer treatment, there was no tumor progression, and surgical resection, including cholecystectomy, was planned for the state requiring cholecystectomy, including infiltrative HCC. Right tri-sectionectomy and cholecystectomy were performed on April 3, 2023.

Liver MRI on May 6, 2023, Dynamic Liver CT on July 21, 2023, Liver MRI on September 2, 2023, revealed no signs of hepatocellular carcinoma recurrence. Chronic hepatitis C was treated with Glecaprevir/Pibrentasvir for a total of 8 weeks from May 30, 2023, to July 25, 2023, confirming SVR12. The patient is currently under observation in a state of complete remission of hepatocellular carcinoma.


www.theliverweek.org
June 27-29, 2024 | Walkerhill, Seoul, Korea

**Jae Geun Lee**

*Yonsei University*

## Self Introduction

I am Liver transplantation Surgeon in Yonsei University College of Medicine, Severance hospital. I underwent resident program for Surgery and fellowship program for Transplant Surgery in Severance hospital. I graduated Yonsei University College of Medicine in 2009 and acquired Master of Science in Nano Science and Technology in 2015. I have worked as Assistant Prof. in Yonsei University College of Medicine since 2015.3.

Member of Academic committee in Korean Liver Cancer Association
Member of Academic committee in Korean Association of HBP surgery
Member of Academic committee in Korean Transplantation Society
Member of International collaboration committee in Korean Liver Transplantation Society
Member of Academic committee in International Living Donor Liver Transplantation Society
Member of Academic committee in International Society of Liver Surgeons

## Research Interests

- Liver transplantation
- HCC
- Immuosuppresant
- Infection

## Representative Publications

1. Entecavir versus tenofovir on the recurrence of hepatitis B–related HCC after liver transplantation: A multicenter observational study. Liver Transpl. 2023 Dec 1;29(12):1272-1281.
2. Risk factors for late-onset Pneumocystis jirovecii pneumonia in liver transplant recipients. Int J Infect Dis. 2023 Jun:131:166-172. Epub 2023 Apr 11.
3. Effect of statins on the recurrence of hepatocellular carcinoma after liver transplantation: An illusion revealed by exposure density sampling. Liver Int. 2023 Sep;43(9):2017-2025.
4. Tacrolimus Monotherapy within 12 Months after Liver Transplantation in the Era of Reduced Tacrolimus and Mycophenolate Mofetil: National Registry Study. J Clin Med . 2022 May 17;11(10):2806.
5. Renal safety of tenofovir disoproxil fumarate and entecavir with hepatitis B immunoglobulin in liver transplant patients. J Viral Hepat. 2020 Aug;27(8):818-825
6. Functions of human liver CD69(+)CD103(-)CD8(+) T cells depend on HIF-2alpha activity in healthy and pathologic livers. J Hepatol. 2020 Jun;72(6):1170-1181
7. Outcomes of Robotic Living Donor Right Hepatectomy From 52 Consecutive Cases: Comparison With Open and Laparoscopy-assisted Donor Hepatectomy. Ann Surg. 2022 Feb 1;275(2):e433-e442

# Case Presentation 2. (Surgery)

**Jae Geun Lee** *Yonsei University*

**Sang Hyub Lee**

*Seoul National University*

## Self Introduction

Prof. Sang Hyub Lee is a Professor of the Department of Internal medicine, Seoul National University Hospital.
Prof. Lee graduated from Seoul National University College of Medicine with his medical degree in 1997 and completed his internship and residency at the Department of Internal medicine at Seoul National University Hospital, receiving his diploma in Internal medicine in 2002.

Since 2021, Prof. Lee has been taking a number of roles, including Director of the Scientific Committee of Society of Gastrointestinal Intervention (2021-2023), Director of the Research Group for Endoscopic Ultrasound of Korean Society of Gastrointestinal Endoscopy (2021-2023), Director of the Scientific Committee of Korean Pancreatobiliary Association (2022-2024), and currently as Director of the Scientific Committee of Korean Society of Gastrointestinal Cancer Research (2024- ).

## Research Interests

- The clinical and translational study for biliary and pancreatic diseases
- The endoscopic intervention and new therapeutic agent development for the pancreato-biliary malignancy

## Representative Publications

1. Oh D, Han SY, Lee SH, et al. Comparison of long-term outcomes of endoscopic ultrasound-guided hepaticogastrostomy and choledochoduodenostomy for distal malignant biliary obstruction: a multicenter retrospective study. Therap Adv Gastroenterol 2024;17:17562848241239551.
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4. Kim JS, Paik WH, Lee SH, et al. Clinical Significance of Venous Thromboembolism in Patients with Advanced Cholangiocarcinoma. Gut Liver 2024;18:165-73.
5. Cho IR, Lee SH, Choi JH, et al. Diagnostic Performance of Endoscopic Ultrasound Elastography for Differential Diagnosis of Gallbladder Polyp. Gastrointest Endosc 2024.
6. Ahn DW, Lee SH, Choi JH, et al. Optimal Follow-up of Incidental Pancreatic Cystic Lesions without Worrisome Features: Clinical Outcome after Long-term Follow-up. Gut Liver 2024;18:328-37.
7. Son JH, Choi YH, Lee SH, Paik WH, Ryu JK, Kim YT. Flavokawain B Inhibits Growth of Cholangiocarcinoma Cells by Suppressing the Akt Pathway. In Vivo 2023;37:1077-84.
8. Park JM, Park N, Lee SH, et al. A population-based cohort study on risk factors for acute pancreatitis: A comparison by age group. Pancreatology 2023;23:321-9.
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10. Paik WH, Jang DK, Cho S, et al. Acute Pancreatitis and the Risk of Dementia in Diabetes: A Nationwide Cohort Study Using Korean Healthcare Claims Database. J Alzheimers Dis 2023;94:205-16.

# Endoscopic and Percutaneous Biliary Decompression

**Sang Hyub Lee** *Seoul National University*

## Introduction

Jaundice is a common symptom of HCC which occurs in about 5% to 44% of HCC patients at initial diagnosis and it occurs more in the later stages of the disease.[1-6] This occurs mostly in relation to liver parenchymal insufficiency due to liver cirrhosis or destruction of the liver parenchyma by the tumor.[7] On the other hand, obstructive jaundice is less common and has reported that it accounts for about 0.5% to 13% of HCC patients.[8-10] However, obstructive jaundice still has great clinical significance in HCC patients because it can be improved through appropriate biliary drainage.[8,11]

## Characteristics of bile duct obstruction due to hepatocellular carcinoma

### *Classification of Biliary Obstruction*

Biliary duct obstruction caused by hepatocellular carcinoma can be divided into extrahepatic and intrahepatic depending on the location of the obstruction and it can be classified into type 1, intraluminal obstructions; type 2, hemobilia; and type 3, extraluminal obstruction by the mechanism of obstruction according to cholangiographic feature.

### *Impact of obstructive jaundice on HCC patients and role of drainage*

Although there is not much evidence, obstructive jaundice in HCC patients is associated with a poor prognosis, which is due to more portal vein thrombi, unresectability and worse liver function. There have been several retrospective studies showing that biliary drainage improves the prognosis of HCC patients, and the results are relatively consistent. In one retrospective study, obstructive jaundice was observed in 88 of 247 patients with HCC with bile duct invasion, which was associated with a shorter overall survival.[12] In the same study, biliary drainage was performed in 54.5% of patients and successful biliary drainage was associated with better overall survival.

In addition to improving the survival rate, biliary drainage has theoretical advantages that can improve the quality of life and improve liver function. Also, with successful biliary drainage, it can provide an opportunity for additional anti-cancer treatment. Choi et al. showed that the survival rate of HCC patients was improved after successful biliary drainage compared to who failed the biliary drainage. And the

survival rate was further improved when transarterial chemoembolization of tumor was performed after successful drainage.[13] Therefore, biliary drainage should always be considered as a treatment option when jaundice occurs in HCC patients.

## Endoscopic Management of Obstructive Jaundice in HCC patients

Biliary drainage can be largely divided into percutaneous and endoscopic approach. The choice of which drainage method to use depends on the patient's general medical condition, and location and mechanisms of biliary obstruction. The advantages of endoscopic retrograde biliary drainage (ERBD) over percutaneous transhepatic biliary drainage (PTBD) are that it is less invasive and more physiological because bile is drained internally, and the patient feels less discomfort due to the absence of an extracorporeal tube.[14] The disadvantage is that the procedure is more complicated using endoscope, and complications such as intestinal perforation and post-ERCP pancreatitis may occur. It also lacks an external tube, making flushing of catheter is not possible and requires frequent stent replacement.

### *Efficacy of Endoscopic Retrograde Biliary Drainage in HCC patients*

Studies have shown that ERBD has a technical success rate of 95% to 100%, and a clinical success rate of 40% to 80%.[11,13,15,16] Complication rate was about 20-30%,[11,15] which seems higher than those of studies with periampullary cancer or cholangiocarcinoma patients (4.2 – 7%).[17-19] This high complication rate is probably due to the hypervascular nature of HCC and frequently accompanied liver cirrhosis and hepatic insufficiency. According to the most recent study, ERBD was performed on 107 HCC patients with biliary obstruction. The technical success rate was 98.1% and the clinical success rate was 81%. The successful biliary drainage was associated with a good prognosis for patients.[20]

## Conclusions

Obstructive jaundice accounts for a small percentage of all jaundice in HCC patients but, it is very important to distinguish it from jaundice caused by liver failure. Endoscopic drainage, like other cancers, is still an effective drainage method in HCC patients. The drainage method should be decided in consideration of the patient's liver function or the location of the biliary obstruction.

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**Dongho Hyun**

*Sungkyunkwan University*

## Self Introduction

### *Education*

| | | |
|---|---|---|
| 1997.03-2003.02 | Bachelor's degree | Soonchunhyang University, College of Medicine, College of Medicine, ChungcheongnamDo, South Korea |
| 2008.03-2010.08 | Master's degree | Ulsan University, College of Medicine, Radiology, Ulsan City, South Korea |
| 2014.03-present | Doctor's degree | Soonchunhyang University, College of Medicine, Radiology, ChungcheongnamDo, South Korea |

### *Career*

| | |
|---|---|
| 2003.03-2004.02 | Internship in Asan Medical Center, Seoul, South Korea |
| 2004.04-2007.04 | Military service in 17th infantry Division, Gyeonggi province, South Korea |
| 2007.05-2011.02 | Radiology, Resident training in Asan Medical Center, Seoul, South Korea |
| 2011.03-2012.02 | Radiologist in Osan Hankook Hospital, Gyeonggi province, South Korea |
| 2012.03-2014.02 | Interventional radiology fellowship in Samsung Medical Center, Seoul, South Korea |
| 2014.03-2015.02 | Instructor, Samsung Medical Center, Seoul, South Korea |
| 2015.03-2017.02 | Clinical Assistant professor, Samsung Medical Center, Seoul, South Korea |
| 2017.03-2019.02 | Assistant professor, Samsung Medical Center, Seoul, Korea |
| 2019.03-Present | Associate professor, Samsung Medical Center, Seoul, Korea |

## Research Interests

Transarterial treatment of hepatocellular carcinoma (cTACE, TARE, combination treatment), lymphatic intervention, LT-related intervention, portal hypertension-related intervention, EVAR

## Representative Publications

1. Cha DI, Lee MW, Hyun D, Ahn SH, Jeong WK, Rhim H. Combined Transarterial Chemoembolization and Radiofrequency Ablation for Hepatocellular Carcinoma Infeasible for Ultrasound-Guided Percutaneous Radiofrequency Ablation: A Comparative Study with General Ultrasound-Guided Radiofrequency Ablation Outcomes. Cancers (Basel). 2023 Oct 28;15(21):5193. doi: 10.3390/cancers15215193. PMID: 37958370; PMCID: PMC10650828.
2. Yu JI, Park HC, Shin H, Park H, Shin SW, Cho SK, Hyun D, Shin J, Goh MJ, Choi MS, Park B, Yoon SM, Jung J. External validation of subclassification system and progression pattern analysis in hepatocelluar carcinoma with macroscopic vascular invasion. Radiother Oncol. 2023 Oct;187:109841. doi: 10.1016/j.radonc.2023.109841. Epub 2023 Aug 4. PMID: 37543052.
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5. Lee HN, Hyun D. Complications Related to Transarterial Treatment of Hepatocellular Carcinoma: A Comprehensive Review. Korean J Radiol. 2023 Mar;24(3):204-223. doi: 10.3348/kjr.2022.0395. Epub 2023 Jan 19. PMID: 36788765; PMCID: PMC9971838.

# Transarterial Intervention Treatments

**Dongho Hyun** *Sungkyunkwan University*

**Xiao Xu**

*Zhejiang University, China*

## Self Introduction

Professor Xu graduated and got his Ph.D and M.D degree from Zhejiang University in 2002, under the supervision of Professor Shusen Zheng and Professor Sheung Tat Fan. From then on, he has served as a transplant and HBP surgeon for more than 20 years in the Department of Hepatobiliary & Pancreatic Surgery. As the Director of the Zhejiang Provincial Key Laboratory of Integrated Oncology and Intelligent Medicine, he mainly focuses on transplant oncology and precision diagnosis and treatment for HPB malignancies. Professor Xu has hosted multiple scientific research programs, which funded by National Hightech R&D Program of China (863 Program), National Science and Technology Major Project of China, Key Program of National Natural Science Foundation of China, etc. He has published over 240 papers in SCI journals such as Gut and Journal of Hepatology. For his outstanding work, he was elected as the President-elect of Chinese Society of Organ Transplantation.

## Research Interests

Transplant oncology, Precision diagnosis and treatment for hepato-pancreato-biliary malignancies

## Representative Publications

1. Xu X, Lu D, Ling Q, Wei X, Wu J, Zhou L, Yan S, Wu L, Geng L, Ke Q, Gao F, Tu Z, Wang W, Zhang M, Shen Y, Xie H, Jiang W, Wang H, Zheng S. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. Gut. 2016
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5. Wang S, Wang R, Xu N, Wei X, Yang Y, Lian Z, Cen B, Shen C, Li W, Wang J, Zhang Z, Tang L, Wei Q, Lu D, Xu X*. SULT2B1-CS-DOCK2 axis regulates effector T-cell exhaustion in HCC microenvironment. Hepatology. 2023

# Liver Resection and Transplantation

**Xiao Xu** *Zhejiang University, China*

**Purpose:** Long-term outcomes of liver transplantation (LT) for hepatocellular carcinoma (HCC) with bile duct tumor thrombus (BDTT) remain controversial. This study aimed to analyze the overall survival and recurrence after LT in patients with HCC with BDTT and to compare the prognosis of LT for HCC with PVTT.

**Patients and Methods:** The study was conducted in 50 patients with BDTT and 176 patients with PVTT but without BDTT, after selection from four transplantation centers of 2024 adult LT cases. Based on Cheng's classification of BDTT, the patients were divided into two groups: type 1 BDTT (38 patients) and type 2 BDTT (12 patients). The characteristics and long-term outcomes of the included patients were compared after propensity score matching (PSM).

**Results:** Kaplan-Meier analysis revealed that the 1-, 3-, and 5-year OS rates of patients who underwent LT for HCC with BDTT were 81.42%, 48.65%, and 45.09%, respectively, which were lower than the rates of 92.86%, 81.03%, and 71.23%, patients without BDTT, after PSM ($P<0.05$). However, the OS rate of patients with BDTT was comparable to that of patients with PVTT ($P>0.05$). Nevertheless, patients who underwent LT for HCC with type 1 BDTT showed superior OS and RFS compared to those with type 2 BDTT (OS, $P<0.001$; RFS, $P=0.002$).

**Conclusions:** The results of this study showed that HCC patients with BDTT had a poor prognosis after LT, but there was no significant difference in prognosis compared to PVTT or BDTT with PVTT. HCC patients with type 1 BDTT had superior outcomes than those with type 2 BDTT. Therefore, further large-scale prospective studies are warranted to evaluate the survival of these patients, which may provide new insights into LT in HCC patients with BDTT.

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2. Lee JS, Kim J, Rhu J, Choi GS, Joh JW. Long-Term Outcomes of Liver Transplantation in Hepatocellular Carcinoma with Bile Duct Tumor Thrombus: A Comparison with Portal Vein Tumor Thrombus. Cancers (Basel).

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THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# Health Insurance and Policy Forum

**Chairs:**

**In Hee Kim** (Jeonbuk National Univ.)
**Hyun Woong Lee** (Yonsei Univ.)

**Panelist:**

**Jin Sun Yang** (Korea Disease Control and Prevention Agency)

**Nam Young Kim**

*Health Insurance Review & Assessment Service*

## Self Introduction

Director Kim Nam-young joined the Health Insurance Review and Assessment Service in 2001. Since then she has worked on reviewing claims and developing the criteria of claims review and quality assessment. She assumed her position as the director of the Cancer Assessment Division, Quality Assessment Administration Department. Now she's responsible for the assessment of the five cancers-colorectal, breast, lung, stomach, and liver cancer, and Intensive Care Unit (ICU).

# Quality Assessment of Liver Cancer Care in Korea: A Comprehensive Approach and Future Challenge

**Nam Young Kim** *Health Insurance Review & Assessment Service*

Cancer is one of the greatest social concerns in Korea, with the highest mortality rates among other diseases. To address this, quality assessment of cancer care has been conducted since 2011. Currently, Korea evaluates the five most prevalent cancers: colorectal, breast, lung, stomach, and liver cancer.

Historically, the assessment of cancer care quality in South Korea focused solely on patients who received surgical interventions. However, this limited perspective didn't fully capture the broader aspects of cancer care quality. With the rapid advancements in health technology and pharmaceuticals, there has been a proliferation of cancer treatment modalities, necessitating a more comprehensive evaluation approach. With this in mind, in 2020, we undertook a study to enhance cancer care quality assessment framework to better reflect the changing health care landscape, broaden the assessment scope of cancer care, and solidify performance-based cancer assessment.

In light of the research findings, we expanded the assessment scope from cancer surgery to the entire therapy process, from care planning and intervention to end-of-life care. Additionally, we introduced both common indicators across the five most common cancers-colorectal, breast, lung, stomach, and liver-and specific indicators for each type. Now the second cycle of the first evaluation is in progress, assessing the holistic cancer care from January to December 2023.

Despite liver cancer being the second leading cause of cancer mortality in South Korea, standardized therapy modalities were previously absent. Therefore, operative mortality, specifically from hepatectomy, represented the entire liver cancer evaluation outcome and was disclosed to the public. However, the study to enhance cancer care quality assessment framework published in 2020 has established a strong foundation for a shift towards assessing holistic liver cancer care.

Today, quality assessments for liver cancer encompass overall care, reflecting the unique characteristics of liver cancer therapies across different. This shift aims to provide the public with a clearer understanding of the quality of liver cancer therapy. Nevertheless, the inclusion of non-surgical liver cancer treatments in the assessment indicators still remains a future challenge.

**Mi Young Kang**

*Health Insurance Review & Assessment Service*

## Self Introduction

2024-present 건강보험심사평가원 약제관리실 약제기준부장 (약제 급여기준 관리 총괄)

# Process and Criteria for the Reimbursement of Oncologic Pharmacotherapies

**Mi Young Kang** *Health Insurance Review & Assessment Service*

**Young Chang**

*Soonchunhyang University*

## Self Introduction

Prof. Young Chang is an Assistant Professor of the Department of Internal Medicine, Soonchunhyang University College of Medicine.

Prof. Chang graduated from Seoul National University College of Medicine with her medical degree in 2011 and completed his internship and residency at the Department of Internal Medicine at Seoul National University Hospital, receiving his diploma in Internal Medicine in 2021.

Prof. Hong has been involved in a number of committees, and currently in Scientific Committee and Research Committee of the Korean Association of the Study of the Liver (2023-present), Publication Committee and Primary Liver Cancer Registry Committee of the Korean Liver Cancer Association (2023-present).

# Management Model after Screening for Viral Hepatitis B and C in Korea

**Young Chang** *Soonchunhyang University*

The World Health Organization aims to eliminate viral hepatitis globally by 2030 and has urged countries to implement targeted policies. While the prevalence of Hepatitis B in Korea has significantly decreased to about 2.4% due to vaccination and prevention programs, the disease still results in a high mortality rate of 18.9 per 100,000 persons. Additionally, the management rate for Hepatitis B is currently estimated at 39.4%, with a treatment rate of 67.3%, indicating a significant need for improvement to meet WHO elimination standards. Hepatitis C, despite its lower prevalence in Korea (antibody positivity rate of 0.7%), presents challenges with an annual incidence rate higher than WHO standards, requiring enhanced management and treatment rates. Given the current situation, raising public awareness of the severity of viral hepatitis and exploring effective strategies for linking diagnosis to treatment is crucial.

We conducted a study in collaboration with the Korea Disease Control and Prevention Agency and the Korean Association for Healthcare Management to develop a management model for chronic viral hepatitis B and C, structured into three parts. The first part focuses on managing and linking treatment for viral hepatitis patients identified through health screenings. The second part develops forms and models for managing and linking treatment for patients identified through national health screenings. The third part applies and analyzes a hepatitis testing and treatment linkage system for inmates in correctional facilities.

The findings indicate a significant reduction in the prevalence of Hepatitis B in Korea, but a high rate of new diagnoses persists. Public awareness regarding disease progression, management, and treatment remains inadequate. Therefore, maintaining current screening and vaccination efforts and enhancing public and medical awareness are essential. For Hepatitis C, improving public awareness and increasing screening for asymptomatic patients, alongside financial support for treatment, could expedite achievement of WHO elimination goals. Implementing reflex testing and direct communication methods for positive cases could improve management and treatment rates.

The study also discusses limitations in coordinating various national health screening systems and

suggests that linking patient information with the Korea Disease Control and Prevention Agency could enhance infectious disease management effectiveness. However, challenges persist in engaging participants in web-based surveys and assessing societal benefits, particularly among younger populations with lower Hepatitis B and C prevalence rates.

Finally, the study suggests that Hepatitis B vaccination may be necessary for vulnerable groups, such as inmates, who are not high-risk but exhibit low antibody rates, particularly among the young. Early diagnosis and treatment are crucial for high-risk groups like inmates and drug abusers for Hepatitis C, considering limited medical insurance coverage for medication costs. An early diagnosis-treatment program conducted in a Seoul-based prison demonstrates potential for broader application in other correctional facilities, pending exclusion of treatment drug costs.


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**Min-Ho Shin**

*Chonnam National University*

## Self Introduction

신민호 교수는 2006년부터 전남대학교 의과대학 예방의학 교수로 재직 중입니다. 신민호 교수는 1998년 전남대학교 의과대학을 졸업한 후, 같은 대학에서 예방의학 레지던트를 마치고 2002년에 예방의학 전문의를 취득했습니다. 신민호 교수는 2022년부터 전라남도 감염병지원단장으로 활동하고 있습니다.

# Local Government-Based Hepatitis C Elimination Project: Jeollanam-do Performance Report

**Min-Ho Shin** *Chonnam National University*

Hepatitis C virus (HCV) is a global health issue, with a 1.6% prevalence. In South Korea, the seroprevalence rate is 0.7% for both men and women. Chronic HCV infection can lead to severe liver damage, cirrhosis, and liver cancer. Many infected individuals are unaware of their condition, contributing to the virus's spread. While there is no HCV vaccine, effective treatments exist. However, about 40-50% of infected individuals in developed countries, including South Korea, are unaware of their infection. Direct-acting antiviral (DAA) drugs have a high cure rate of 95-99%, but their high cost results in a low treatment rate of about 50%. According to 2019 data from the National Health Insurance Service, approximately 380,000 people were estimated to have been diagnosed with hepatitis C, but only 47,546 received treatment, indicating that only about 20% of patients were diagnosed and treated. Therefore, broader screening, early diagnosis, and proactive treatment efforts are needed.

Since 2016, hepatitis C has been classified as a third-class infectious disease with mandatory reporting. High cumulative incidence rates from 2017 to 2022 were seen in Jeollanam-do, Busan, Gyeongnam, Incheon, and Jeju. The highest rates by county were in Jindo-gun (Jeollanam-do), Sunchang-gun (Jeollabuk-do), Namhae-gun (Gyeongnam), Shinan-gun (Jeollanam-do), and Seo-gu (Busan). From 2014-2018, the highest liver cancer rates were in Jeollanam-do, Gyeongnam, Jeju, Busan, and Gangwon. The highest county rates were in Shinan-gun and Jindo-gun (Jeollanam-do), Ulleung-gun (Gyeongbuk), Namhae-gun (Gyeongnam), and Sunchang-gun (Jeollabuk-do). These overlaps indicate a significant link between hepatitis C and liver cancer.

To address the high liver cancer incidence in Jeollanam-do and reduce regional disparities, Jeollanam-do has planned a hepatitis C eradication project targeting areas with high cumulative hepatitis C incidence. This community-based eradication program involves screening, diagnosis, and treatment. Starting in February 2023, pilot projects were conducted in six high-incidence counties (Jangheung, Gangjin, Haenam, Wando, Jindo, Shinan). The project activities included promoting through public health centers, using rapid diagnostic kits for HCV antibody testing, conducting awareness surveys for antibody-positive individuals, performing HCV RNA testing for positive cases, conducting genotype testing for RNA-positive individuals, linking confirmed patients to treatment, and providing follow-up management. The pilot project involved 2,455 participants, with 300-600 participants per county. Of

the 2,455 participants, 26 were antibody-positive, and 13 were RNA-positive, who received treatment cost support. In the second year of the project, starting in 2024, the project expanded to include Goheung-gun, targeting 7,814 participants in seven counties. Sixty-eight were antibody-positive, and 25 were RNA-positive, who will receive treatment cost support.

Reducing regional disparities in liver cancer incidence requires a comprehensive HCV elimination strategy, including prevention, diagnosis, and treatment through national and community programs. The hepatitis C eradication project in Jeollanam-do aims to serve as a model for public health by expanding to other regions in South Korea based on its successful outcomes.

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2. The White Paper on Liver Diseases of Koreans by the Korean Association for the Study of the Liver, 2023.
3. Cancer Incidence Statistics by Region (2014-2018), Korean Statistical Information Service (KOSIS): http://kosis.kr

THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

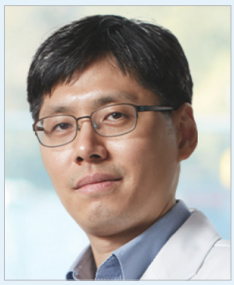
# KLTS-KAHBPS-KASL Joint Symposium

# Updates on Cystic Liver Disease

**Chairs:**

**Jin-Woo Lee** (Inha Univ.)

**Alfred Kow** (National Univ. of Singapore, Singapore)



**Beom Kyung Kim**

*Yonsei University*

## Self Introduction

### *Education*

| | |
|---|---|
| 1997-2003 | Yonsei University College of Medicine, Seoul, Republic of Korea |
| 2005-2007 | Master Degree, Graduate School, Yonsei University College of Medicine, Seoul, Republic of Korea |
| 2010-2013 | Ph.D., Graduate School, Yonsei University College of Medicine Seoul, Republic of Korea |

### *Professional Experience*

| | |
|---|---|
| 2003-2004 | Internship: Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea |
| 2004-2008 | Residency: Severance Hospital, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea |
| 2008-2011 | Military service as a doctor |
| 2011-2013 | Fellowship: Severance Hospital, Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea |
| 2013-2018 | Gastroenterology specialist: Severance Hospital, Seoul, Republic of Korea / Assistant clinical professor: Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea |
| 2018-2023 | Assistant professor/Associate: Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea |
| 2023- | Professor: Division of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea |

## Research Interests

Viral hepatitis, liver cirrhosis, and hepatocellular carcinoma
Molecular biology of hepatitis B virus

## Representative Publications

1. Kim BK, Bernstein N, Huang DQ, Tamaki N, Imajo K, Yoneda M, Sutter N, Jung J, Nguyen K, Nguyen L, Le T, Madamba E, Richards L, Valasek MA, Behling C, Sirlin CB, Nakajima A, Loomba R. Clinical and histologic factors associated with discordance between steatosis grade derived from histology vs. MRI-PDFF in NAFLD. Aliment Pharmacol Ther. 2023 Jul;58(2):229-237. doi: 10.1111/apt.17564. Epub 2023 Jun 2.
2. Kim DS, Kim BK, Lee JS, Lee HW, Park JY, Kim DY, Ahn SH, Pyrsopoulos N, Kim SU. Noninvasive risk assessment of hepatic decompensation in patients with hepatitis B virus-related liver cirrhosis. J Gastroenterol Hepatol. 2023 Aug;38(8):1372-1380. doi: 10.1111/jgh.16210. Epub 2023 May 15.
3. Kim BK. How to deliver palliative care for patients with management in decompensated cirrhosis. Hepatobiliary Surg Nutr. 2023 Aug 1;12(4):576-579
4. Kim BK, Ahn SH. Prediction model of hepatitis B virus-related hepatocellular carcinoma in patients receiving antiviral therapy. J Formos Med Assoc. 2023 Jun 15:S0929-6646(23)00198-5. doi: 10.1016/j.jfma.2023.05.029. Online ahead of print.
5. Kim BK, Bergstrom J, Loomba R, Tamaki N, Izumi N, Nakajima A, Idilman R, Gumussoy M, Oz DK, Erden A, Truong E, Yang JD, Noureddin M, Allen AM, Loomba R, Ajmera V. Magnetic resonance Elastography-Based prediction model for hepatic decompensation in NAFLD; a Multi-Center cohort study. Hepatology. 2023 May 22. doi: 10.1097/HEP.0000000000000470. Online ahead of print.

# Epidemiologic and Genetic Landscapes of Polycystic Liver Disease

**Beom Kyung Kim** *Yonsei University*

Polycystic liver disease (PLD), a rare condition, is caused by three genetic disorders: autosomal dominant polycystic liver disease (ADPLD), autosomal dominant polycystic kidney disease (ADPKD), and autosomal recessive polycystic kidney disease (ARPKD). While PLD typically does not affect liver function, severe cases may cause symptoms due to the enlarged liver pressing on surrounding organs or increasing intra-abdominal pressure. Diagnosis primarily relies on imaging techniques, with genetic testing reserved for complex cases. However, genetic testing can be beneficial for early treatment, prognosis prediction, and patient classification for genetic interventions. Although the precise genetic causes and mechanisms are not fully understood, research suggests that primary ciliopathy or defective ciliogenesis play significant roles. PLD mainly arises from faulty ciliogenesis and inadequate endoplasmic reticulum quality control. Mutations that result in loss of function in ciliogenesis-related genes such as Pkd1, Pkd2, Pkhd1, and Dzip1l lead to cyst formation in the liver and kidneys in ADPKD and ARPKD. Additionally, mutations in genes involved in endoplasmic reticulum quality control and protein folding, trafficking, and maturation—such as PRKCSH, Sec63, ALG8, ALG9, GANAB, and SEC61B—can impair the synthesis and function of polycystin 1 (PC1) and polycystin 2 (PC2), or promote their degradation, leading to isolated hepatic cysts or concurrent liver and kidney cysts. Recent studies indicate that mutations in LRP5, which disrupt canonical Wnt signaling, can also cause hepatic cysts. Current treatments for PLD include somatostatin analogs, percutaneous intervention, surgical fenestration, resection, and liver transplantation. Additionally, several experimental therapies targeting underlying molecular mechanisms and signaling pathways have shown promising results in preclinical studies.

**Seung Baek Hong**

*Pusan National University*

## Self Introduction

Prof. Seung Baek Hong is a Professor of the Department of Radiology, Pusan National University College of Medicine and is currently holding a position of assistant professor of Pusan National University Hospital.

Prof. Hong graduated from Pusan National University College of Medicine with his medical degree in 2012 and completed his internship and residency at the Department of Radiology at Pusan National University Hospital.

## Research Interests

Liver MRI

## Representative Publications

1. Multiple arterial-phase MRI with gadoxetic acid improves diagnosis of hepatocellular carcinoma ≤3.0 cm. Liver Int. 2023 Feb;43(2):462-470.
2. Surveillance failure in ultrasound for hepatocellular carcinoma: a systematic review and meta-analysis. Gut. 2022 Mar 1
3. MRI Features for Predicting Microvascular Invasion of Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Liver Cancer. 2021 Apr;10(2):94-106.
4. Modified CAIPIRINHA-VIBE without view-sharing on gadoxetic acid-enhanced multi-arterial phase MR imaging for diagnosing hepatocellular carcinoma: comparison with the CAIPIRINHA-Dixon-TWIST-VIBE. Eur Radiol. 2019 Jul;29(7):3574-3583
5. Pancreatic Cancer CT: Prediction of Resectability according to NCCN Criteria. Radiology. 2018 Dec;289(3):710-718.

# Radiological Diagnosis for Cystic Liver Disease

**Seung Baek Hong** *Pusan National University*

## Cystic lesions

- Developmental
- Inflammatory
- Neoplastic

## Cystic lesions

- Benign cystic lesions: common

## Developmental cyst

***- Simple hepatic cyst***

***- Biliary Harmatoma (von Meyenburg Complex)***

- Multiple, small (< 15 mm), round or irregular scattered cysts with a predilection for the subcapsular region.

***- Caroli disease***

- Characterized by the saccular dilatation of large intrahepatic bile ducts with an intact extrahepatic duct (EHD).
- Communication with the biliary system is observed on imaging studies such as MRCP
- A notable radiologic finding: "central dot sign."
  - The portal radicle, central enhancing component on CT and MRI

***- Polycystic liver disease.***

- Characterized by multiple hepatic cysts that are similar in characteristics to simple hepatic cysts.
- It is an autosomal-dominant condition often associated with Autosomal Dominant Polycystic Kidney Disease (ADPKD).

## Infectious lesions

### - *Pyogenic abscess*

- US Findings
  - Anechoic mass with well-defined or indistinct borders
  - Possibly contain echogenic debris or gas.
- CT Findings
  - Iso- to hypoattenuating compared with background liver on the unenhanced phase
  - Peripheral rim of enhancement, Double target sign, Thrombophlebitis, gas within the abscess cavity, or pneumobilia
- MRI Findings
  - The central portion of the lesion: low signal intensity on T1-WI and high signal intensity on T2-W
  - Peripheral halo of hyperintensity indicating edema on T2-weighted imaging.

### - *Fungal Micro-abscesses*

- Typically seen in immunocompromised patients.
- Small (< 2 cm) and disseminated throughout the liver and the spleen on US, CT, and MRI.

### - *Hydatid cyst (cystic echinococcosis)*

- Variable features
  - Simple cyst with no internal architecture
  - Cyst with daughter cysts
  - Calcified cyst or Complicated cyst
- Daughter cyst demonstrating a slightly different signal intensity than the mother cyst

## Neoplastic lesions

### - *Biliary cystadenoma and cystadenocarcinoma*

- Multilocular with enhancing walls, fine septations, and variable calcification, Biliary cystadenoma
  - DDX with simple hepatic cyst: interval septation, Bile duct dilatation, location in the left lobe (Hard to differentiate)
- Biliary cystadenocarcinoma
  - Enhancing mural nodules/internal soft tissue and irregular thickness of the septa

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2. Am J Gastroenterol. 2014 Sep;109(9):1328-47.
3. Radiographics. 2013 Sep-Oct;33(5):1419-33.

**Dong-Wan Seo**

*University of Ulsan*

## Self Introduction

Pf. Dong Wan Seo is a specialist on pancreatico-biliary endoscopy and EUS.

His current position is a full professor and Chairman of Department of Internal Medicine, University of Ulsan Medical College, Asan Medical Center which is the largest teaching hospital in South Korea.

He has created a lot of advanced endoscopy works to the World of GI Endoscopy including his own classification of cholangioscopic reading, EUS-guided treatment of pancreatic cystic tumors and EUS-guided ablation therapy of pancreatic solid tumor. He is actively conducting many studies related to interventional EUS including EUS-guided hepatic cyst ablation.

Prof. Seo served as Secretary General of World Endoscopy Organization (WEO) from 2013 to 2017, and Chairman of Steering Committee of World Congress of Endoscopy 2020 (ENDO 2020). Now he is serving as co-chair of ENDO 2024. He also served as Chairman of Educational Committee in Korean Society of Gastroenterology (KSG), Director of Gastroenterology Specialty Board in Korean Society of Internal Medicine (KSIM), and Secretary General of Society of Gastrointestinal Intervention (SGI). Pf. Seo started WEO International School of EUS (WISE) from 2018 to educate young endosonographers.

## Research Interests

- Pancreatobiliary disease
- Therapeutic endoscopy, ERCP
- Interventional EUS & EUS education

## Representative Publications

1. Cholangioscopy Koonja/Lippincott, 2002
2. Therapeutic Endoscopy in Gastroenterology (Co-author) Koonja publishing Co. 2004
3. Endoscopic Retrograde Cholangio-Pancreatography (co-author) Elsevier, 2008, 2013
4. Gastrointestinal Disease 3rd Ed. (Co-author) Iljogak 2011
5. Textbook of Endoscopic Ultrasonography (Co-author) Jin Publishing & Printing Co. 2011
6. Diagnostic & Therapeutic Procedures in Gastroenterology (Co-author)
7. Springer International Publishing Co 2018

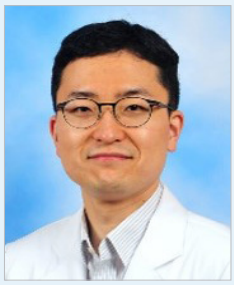
# EUS-Guided or Percutaneous Therapies for Cystic Liver Disease

**Dong-Wan Seo** *University of Ulsan*

Cystic liver diseases are comprised of wide sprectrum of diseases; simple hepatic cysts, polycystic liver disease, hydatid cyst and cystic neoplasms. Before deciding therapeutic strategy, it is critically important to differentiate benign hepatic cyst from cystic neoplasm. In most of cases, the differentiation of simple cyst from cystic neoplasm is not so difficult. However, in a small proportion of cystic disease, the differentiation can be difficult and eventually leads to unnecessary hepatic resection since the mainstay of therapy of cystic neoplasm until now is surgical resection. Another important factor to be considered before therapy is the presence of symptom or structural derangement because of the compression of huge cyst. Most of hepatic simple cyst is asymptomatic and incidentally detected during routine health check-up. In majority of cases, regular follow-up seems to be enough. Treatment is required in only small proportion of whole cystic liver disease.

Non-neoplastic hepatic cyst can be managed by non-surgical method and there are 2 main approaches to hepatic cyst; percutaneous and EUS-guided approach. Percutaneous approach means that the insertion of percutaneous drainage tube first, and then ethanol retention therapy after drainage cystic fluid. The amount of ethanol can be variable according to the size of hepatic cyst but it can be limited by systemic absorption and side effect. Generally less than 150 cc per cyst seems to be enough. Same treatment can be applied under EUS guidance and this means that the aspiration of cystic fluid after EUS-guided insertion of 19G needle and ethanol injection through the same needle. After retention time, injected ethanol can be re-aspirated under EUS-guidance. EUS-guided approach has the advantage of 1 step procedure and it is real time EUS-guidance. EUS-guided approach has higher procedural success rate compared to percutaneous approach. However, for huge hepatic cyst in which the amount of cystic fluid is more than 1000cc, the aspiration takes too much time. For right side hepatic cyst, especially right dome area, it is difficult to target by EUS-guidance since EUS scope is located in the stomach and liver is a large organ. In our study, the complete resolution of cyst was achieved in more than 90% of included patient and partial resolution of cyst was observed in less than 10% of included patients. Cyst recurrence was not observed in 66 months of study period.

Our conclusion is that percutaneous catheter-guided and EUS-guided ethanol retention therapy showed very good symptomatic and radiologic response and long-term outcome. It can be considered as a primary method of treatment of hepatic cysts given its high degree of technical feasibility and safety.




## Seoung Yoon Rho

*Yonsei University*


## Self Introduction

Prof. Seoung yoon Rho is a assistant Professor of the Department of Surgery, Yonsei University College of Medicine and is currently holding a position of Chief of Division of hepatobiliary pancreatic surgery in Yongin Severance hospital .

Prof. Rho graduated from Yonsei Wonju University College of Medicine with his medical degree in 2009 and completed his residency at the Department of Surgery at Yonsei University Severance Hospital, receiving his diploma in General Surgery in 2014.

After his military service of medical officer and fellowshiop training in HBP field in Severance hospital, Prof. Rho has been started his HBP professor career from severance hospital and Yongin Severance hospital since 2019.

## Research Interests

- Hepatocellular carcinoma
- MALFD
- Minimally invasive surgery in HBP

## Representative Publications


1. SY Rho, SH Lee, M Park, J Lee, SH Lee, HK Hwang, YK Paik, WJ Lee, CM Kang, Developing a preoperative serum metabolome-based recurrence-predicting nomogram for patients with resected pancreatic ductal adenocarcinoma. Sci Rep 2019;9;18634
2. SH Lee, GH Choi, DH Han, KS Kim, JS Choi, SY Rho, Chronological analysis of surgical and oncological outcomes after the treatment of perihilar cholangiocarcinoma, Ann Hepatobiliary Pancreat Surg 202;25;62-70
3. Chiow, A. K. H., SY Rho, I. J. Y. Wee, L. S. Lee, and G. H. Choi. "Robotic Icg Guided Anatomical Liver Resection in a Multi-Centre Cohort: An Evolution from "Positive Staining" into "Negative Staining" Method." [In eng]. HPB (Oxford) 23, no. 3 (Mar 2021): 475-8
4. SY Rho,., H. W. Lee, D. Y. Kim, and K. S. Kim. "Current Status of Therapeutic Choice and Feasibility for Patients with Hepatocellular Carcinoma Aged ≥ 70 Years: A Nationwide Cancer Registry Analysis." [In eng]. J Hepatocell Carcinoma 8 (2021): 321-32
5. SY Rho,., J. G. Lee, D. J. Joo, M. S. Kim, S. I. Kim, D. H. Han, J. S. Choi, and G. H. Choi. "Outcomes of Robotic Living Donor Right Hepatectomy from 52 Consecutive Cases: Comparison with Open and Laparoscopy-Assisted Donor Hepatectomy." [In eng]. Ann Surg 275, no. 2 (Feb 1 2022): e433-e4

# Surgical Treatments of Large Hepatic Cysts

**Seoung Yoon Rho** *Yonsei University*

Hepatic cystic lesions can be categorized embryologically, morphologically, and pathologically. Among them, simple hepatic cysts are one of the most common benign lesions in the liver. The prevalence is reported to be about 2.5% to 18%, and the size can be up to 30 cm. Most cystic lesions are asymptomatic and less than 3 cm in size. However, it is known that about 15% of all cysts have symptoms, and in those larger than 10 cm, symptoms such as pain, bloating, nausea, and a palpable mass may occur. Surgical treatment can be considered in cases where a simple hepatic cyst has symptoms, is compressing the surrounding vena cava or bile duct due to mass effect, is gradually increasing in size, or has a premalignant potential such as mucinous cystadenoma and differential diagnosis is not possible. According to the 2014 ACG guideline, laparoscopic de-roofing surgery can be considered preferentially over aspiration or sclerotherapy for symptomatic simple hepatic cysts, depending on local expertise. According to the 2022 EASL guideline, since there is no high-quality RCT yet, both sclerotherapy and de-roofing surgery should be considered volume-reducing therapies.

In recent meta-analysis, laparoscopic de-roofing has a higher rate of symptom relief than percutaneous aspiration, but the cyst recurrence rate was reported to be about 5.6%. In another meta-analysis, the overall complication rate was 10.8%, and the recurrence rate was 9.6%. In studies comparing quality of life, both the functional scale and symptom scale reported increased scores compared to before surgery. Efforts to reduce the occurrence of recurrence and complications after surgery include using surgical staplers, wall cauterization, and flaps of the omental or falciform ligament during surgery, but the effectiveness of these procedures is still debated.

When it comes to the status of hepatic cyst treatment in Korea, it is steadily increasing every year, with 139 cases of liver cyst marsupialization performed in 2022. Although there are no accurate statistics on hepatic cysts, percutaneous sclerotherapy (except head & neck) steadily increased until 2019 and then decreased over the past three year.

In conclusion, surgical treatment can be considered for symptomatic hepatic cysts, and several efforts are needed to reduce recurrence and complications. With the recent development of diagnostic technology, the prevalence of hepatic cysts is increasing, and the development of practical guidelines for this may be considered in near future.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THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# KASL Symposium 4

## Portal Hypertension and Its Repercussions in Hepatic Care

**Chairs:**

**Chang Wook Kim** (The Catholic Univ. of Korea)
**Jongman Kim** (Sungkyunkwan Univ.)

**Rakhi Maiwall**

*Institute of Liver and Biliary Sciences, India*

## Self Introduction

Dr. Rakhi Maiwall is currently working as a Professor of Hepatology at Institute of Liver and Biliary Sciences and is also Incharge of the Liver Intensive Care at ILBS. She is the Vice-secretary of the International club of ascites and has published original articles in indexed journals and has more than 160 publications and contributed 10 book chapters

## Research Interests

- AKI
- Acute and acute on chronic liver failure
- Critical care hepatology
- Extracorporeal Liver support

## Representative Publications

1. Maiwall R, Rao Pasupuleti SS, Hidam AK, Kumar A, Tevethia HV, Vijayaraghavan R, Majumdar A, Prasher A, Thomas S, Mathur RP, Kumar G, Sarin SK. A randomised-controlled trial (TARGET-C) of high vs. low target mean arterial pressure in patients with cirrhosis and septic shock. J Hepatol. 2023 Aug;79(2):349-361.
2. Maiwall R, Kumar A, Pasupuleti SSR, Hidam AK, Tevethia H, Kumar G, Sahney A, Mitra LG, Sarin SK. A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. J Hepatol. 2022 Sep;77(3):670-682.
3. Maiwall R, Rastogi A, Pasupuleti SSR, Hidam AK, Singh M, Kadyan S, Jain P, Kumar G, Sarin SK. Natural history, spectrum and outcome of stage 3 AKI in patients with acute-on-chronic liver failure. Liver Int. 2022 Dec;42(12):2800-2814
4. Maiwall R, Singh SP, Angeli P, Moreau R, Krag A, Singh V, APASL clinical practice guidelines on the management of acute kidney injury in acute-on-chronic liver failure. Hepatol Int. 2024 Jun;18(3):833-869
5. Maiwall R, Pasupuleti SSR, Hidam AK, Rastogi A, Thomas S, Kumar G, Kumar A, Sarin SK. Non-resolution of acute kidney injury in the first week portends the development of chronic kidney disease in critically ill patients with cirrhosis. Aliment Pharmacol Ther. 2023 Sep;58(6):593-610

# Personalized Approach to Albumin Replacement in Decompensated Cirrhosis

**Rakhi Maiwall** *Institute of Liver and Biliary Sciences, India*

Albumin is very commonly used for the management of decompensated cirrhosis. Intravenous albumin administration has multiple mechanisms by which it can improve clinical outcomes in patients with cirrhosis. Albumin can improve the effective hypovolemia and also improve the systemic inflammation, cause endothelial stabilization, and has immunomodulatory function. The outcomes of albumin in different clinical contexts have been reported to be different. In the context of stable decompensated cirrhosis, long-term albumin administration, has shown to improve outcomes in patients with uncomplicated ascites.[1-4] Albumin can improve the effective hypovolemia and is currently recognised as the most effective fluid for volume expansion especially in advanced decompensated cirrhosis with hypoalbuminemia and ascites. In the multicentric trial from Italy, the investigators demonstrated a benefit of regular long term albumin administration at 80 grams for 2 weeks followed by 40 grams every week for 18 months.[4] The dose of albumin was associated with increase in the serum albumin concentrations and a decrease in all the liver-related complications, a better control of ascites and also a survival benefit free of transjugular intrahepatic portosystemic shunt (TIPS) or liver transplantation (LT). In the MACHT study, a lower dose of albumin of 40 grams every two weeks was combined with alpha-adrenergic agonist midodrine the benefits of the combination was not observed in patients with ascites awaiting liver transplantation. However, majority of the patients got transplanted within 90 days after being enrolled in the trial. Therefore, the long-term benefits of albumin administration could not be identified.[5] The two studies used different doses of LTA, however, whether all patients with decompensated cirrhosis and uncomplicated ascites require 40grams/ week is not known.[5] Therefore, a personalized approach could guide the right dose in these patients. The on-treatment serum albumin could be used to guide the appropriate dose of albumin in these patients. In an elegant post-hoc analysis from the same study the authors made some important observations. The first finding from this analysis suggested a lower serum albumin was associated with high mortality at 18-months. Long term albumin administration was able to efface the relationship of serum albumin and mortality. A delta increase of 0.75 gm/dl was observed in more than 90% of patients at one-month. Each gm/dl increase or decrease in serum albumin was associated with improved versus worsening survival. Patients who achieved a target level of albumin of 4 gm/dl had better outcomes compared to those who did not.[6] Patients who achieved the target serum albumin between 2.5-4 gm/dl still had better outcomes compared to the standard medi-

cal treatment. Therefore, on-treatment serum albumin could in a way guide a personalized approach to LTA.

However, when in the context of hospitalized patients with cirrhosis, in the ATTIRE study, the investigators targeted a serum albumin above 3 gm/dl in hospitalized patients with cirrhosis and did not observe any benefit.[7] Rather more patients in the targeted albumin group developed pulmonary complications. In the context of critically ill patients with cirrhosis with sepsis-induced hypotension 20% albumin was an independent predictor of more pulmonary complications compared to plasmalyte.[8] In patients with cirrhosis with sepsis, organ failures, a personalized approach possibly targeting the effective albumin concentration may be better. The dynamic indices and cardiopulmonary assessment using the point of care ultrasound could guide a personalized approach to albumin treatment.[9-11]

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9. Bernardi M. Effective albumin - A novel paradigm in the management of decompensated liver cirrhosis. J Transl Int Med. 20237;11:11-14
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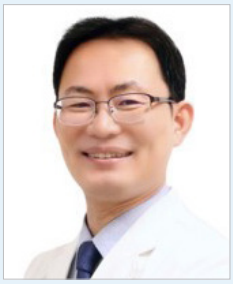


**Sejoong Kim**

*Seoul National University*

## Self Introduction

I completed their Bachelor's, Master's, and Ph.D. degrees at Seoul National University College of Medicine. I also completed a postdoctoral program in Biomedical Engineering at the University of Michigan. Currently, they are working in the Nephrology Department at Seoul National University Bundang Hospital and serving as the director of the Center for Artificial Intelligence in Healthcare there. Additionally, they hold a professorship in internal medicine at Seoul National University College of Medicine. Their primary research areas include microphysiological systems, artificial intelligence, drug development, and clinical trials. They have published over 200 peer-reviewed papers and are actively involved in treating patients with acute kidney injury, chronic kidney disease, hemodialysis, and kidney transplantation.

## Representative Publications

1. Evidence-based hyponatremia management in liver disease. Ryu JY, Baek SH, Kim S. Clin Mol Hepatol. 2023 Oct;29(4):924-944.
2. Korean Society of Nephrology 2022 Recommendations on controversial issues in diagnosis and management of hyponatremia. Lee Y, Yoo KD, Baek SH, Kim YG, Kim HJ, Ryu JY, Paek JH, Suh SH, Oh SW, Lee J, Jhee JH, Suh JS, Yang EM, Park YH, Kim YL, Choi M, Oh KH, Kim S. Kidney Res Clin Pract. 2022 Jul;41(4):393-411.
3. Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients With Symptomatic Hyponatremia: The SALSA Randomized Clinical Trial. Baek SH, Jo YH, Ahn S, Medina-Liabres K, Oh YK, Lee JB, Kim S. JAMA Intern Med. 2021 Jan 1;181(1):81-92.
4. Real-Time Clinical Decision Support Based on Recurrent Neural Networks for In-Hospital Acute Kidney Injury: External Validation and Model Interpretation. Kim K, Yang H, Yi J, Son HE, Ryu JY, Kim YC, Jeong JC, Chin HJ, Na KY, Chae DW, Han SS, Kim S.J Med Internet Res. 2021 Apr 16;23(4):e24120.
5. Pharmacokinetic profile that reduces nephrotoxicity of gentamicin in a perfused kidney-ona-chip. Kim S, LesherPerez SC, Kim BC, Yamanishi C, Labuz JM, Leung B, Takayama S. Biofabrication. 2016 Mar 24;8(1):015021.

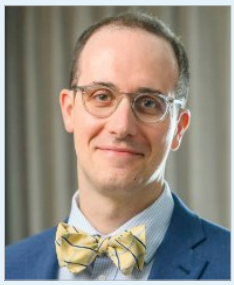
# Correction and Prevention of Hyponatremia in Cirrhotic with Ascites

**Sejoong Kim** *Seoul National University*

The lecture on "Correction and Prevention of Hyponatremia in Cirrhotic Patients with Ascites" by Sejoong Kim delves into managing this complex condition in liver cirrhosis patients. It discusses the pathophysiology, involving ascites and hormonal imbalances, and outlines a systematic diagnostic approach that includes confirming hypotonicity and assessing symptoms. The presentation highlights treatment strategies for both acute and chronic hyponatremia and emphasizes the necessity of cautious correction to prevent complications like osmotic demyelination. The lecture encourages a tailored approach to each patient's condition and the importance of prevention strategies and continual medical education to enhance patient outcomes.

## References

1. Evidence-based hyponatremia management in liver disease.
2. Ryu JY, Baek SH, Kim S. Clin Mol Hepatol. 2023 Oct;29(4):924-944.
3. Korean Society of Nephrology 2022 Recommendations on controversial issues in diagnosis and management of hyponatremia.
4. Lee Y, Yoo KD, Baek SH, Kim YG, Kim HJ, Ryu JY, Paek JH, Suh SH, Oh SW, Lee J, Jhee JH, Suh JS, Yang EM, Park YH, Kim YL, Choi M, Oh KH, Kim S. Kidney Res Clin Pract. 2022 Jul;41(4):393-411.
5. Risk of Overcorrection in Rapid Intermittent Bolus vs Slow Continuous Infusion Therapies of Hypertonic Saline for Patients With Symptomatic Hyponatremia: The SALSA Randomized Clinical Trial.
6. Baek SH, Jo YH, Ahn S, Medina-Liabres K, Oh YK, Lee JB, Kim S. JAMA Intern Med. 2021 Jan 1;181(1):81-92.



**Elliot B. Tapper**

*University of Michigan, USA*

## Self Introduction

Elliot Tapper MD is Associate Professor at University of Michigan where he directs the Michigan Cirrhosis Program. He is editor-in-chief of Hepatology Communications. His research program is focused on improving quality of life in patients with cirrhosis. He trained in medicine, gastroenterology, and transplant hepatology at Beth Israel Deaconness in Boston.

## Research Interests

1. Patient reported outcomes. Research seeks to define unmet needs and deploy clinical trials which improve symptom burden.
2. Hepatic encephalopathy. Previous work defined epidemiology, developed risk scores for incident HE, and created models to improve hospital readmissions. Currently leading a multicenter trial of primary prophylaxis of HE.

## Representative Publications

1. Tapper EB, Parikh ND. Diagnosis and Management of Cirrhosis and Its Complications: A Review. Jama. 2023 May 9;329(18):1589-602.
2. Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999-2016: observational study. bmj. 2018 Jul 18;362.
3. Tapper EB, Lok AS. Use of liver imaging and biopsy in clinical practice. New England Journal of Medicine. 2017 Aug 24;377(8):756-68.
4. Tapper EB, Parikh ND, Sengupta N, Mellinger J, Ratz D, Lok AS, Su GL. A risk score to predict the development of hepatic encephalopathy in a population - based cohort of patients with cirrhosis. Hepatology. 2018 Oct;68(4):1498-507.
5. Tapper EB, Finkelstein D, Mittleman MA, Piatkowski G, Chang M, Lai M. A quality improvement initiative reduces 30-day rate of readmission for patients with cirrhosis. Clinical Gastroenterology and Hepatology. 2016 May 1;14(5):753-9.

# Diagnostic Test and Available Therapy for Covert vs. Overt Hepatic Encephalopathy

**Elliot B. Tapper** *University of Michigan, USA*

Elliot Tapper MD, Chief of Hepatology at the University of Michigan, will discuss the diagnosis and management of hepatic encephalopathy (HE). We will begin by defining covert and overt HE. We will focus on the bedside diagnosis of covert HE and then tools to carefully initiate lactulose therapy. We will discuss therapies and supportive care for overt HE and touch on 'out of the box' interventions for the prevention of overt HE episodes.

**Eileen L. Yoon**

*Hanyang University*

## Self Introduction

Prof. Eileen Yoon is an Associate Professor of the Department of Internal Medicine, Hanyang University College of Medicine.

Prof. Yoon graduated from Korea University College of Medicine with her medical degree in 2006 and completed her residency at the Department of Internal Medicine at Korean University Hospital, receiving his diploma in Gastroenterology in 2013.

Since 2014, Prof. Yoon has been taking a number of roles, including members of Insurance Committee of the Korean Association of the Study of the Liver (2020- Present) and Korean association of Gastroenterology (2022- Present), and currently as Director of Insurance Committee of the Korean Liver Cancer Association (2024- Present).

## Research Interests

Metabolic-associated fatty liver disease, Alcohol-related liver disease, Liver cirrhosis

## Representative Publications

1. Lee CM, Yoon EL, Kim M, et al. Prevalence, distribution, and hepatic fibrosis burden of the different subtypes of steatotic liver disease in primary care settings. Hepatology. 2024;79(6):1393-400. Epub 20231101.
2. Park H, Kim M, Kim HL, et al. Diagnostic performances of Fibrosis-4 index and nonalcoholic fatty liver disease fibrosis score in metabolic dysfunction-associated steatotic liver disease in Asian primary care clinics. Hepatol Res. 2024. Epub 20240504.
3. Park H, Yoon EL, Chung GE, et al. Genetic and Metabolic Characteristics of Lean Nonalcoholic Fatty Liver Disease in a Korean Health Examinee Cohort. Gut Liver. 2024;18(2):316-27. Epub 20230810.
4. Park H, Yoon EL, Kim M, et al. Comparative evaluation of non-invasive tests for risk stratification for cause specific mortality in at-risk population of hepatic fibrosis. Sci Rep. 2024;14(1):7189. Epub 20240326.
5. Park H, Yoon EL, Kim M, et al. Cost-effectiveness study of FIB-4 followed by transient elastography screening strategy for advanced hepatic fibrosis in a NAFLD at-risk population. Liver Int. 2024;44(4):944-54. Epub 20240130.

# Blood Products and Pharmacologic Agents and Their Indications for Hepatic Coagulopathy

**Eileen L. Yoon** *Hanyang University*

## Abstract

Alterations in the results of conventional hemostasis tests are common in patients with liver cirrhosis. Common features of bleeding in liver cirrhosis have made the clinicians transfuse the blood products to correct the laboratory abnormalities. However, hemostatic rebalance in patients with liver cirrhosis is widely accepted although it is fragile. Tests which truly reflect the balance of procoagulant, and anticoagulant factors in vivo are lacking. Most bleeding in patients with liver cirrhosis is portal hypertension-driven and it is unrelated to hemostasis. Therefore, routine use of blood products to correct hemostatic laboratory abnormalities are not recommended in the prophylaxis of bleeding prior to procedure. Thrombopoietin receptor agonists can be good alternatives to platelet transfusion.

## Introduction

Alterations in the results of conventional hemostasis tests are common in patients with liver cirrhosis. Common features of bleeding in liver cirrhosis have made the clinicians transfuse the blood products to correct the laboratory abnormalities. However, hemostatic rebalance in patients with liver cirrhosis is widely accepted although it is fragile.[1] In line with this, incidence of procedure-related bleeding and major bleeding in decompensated liver cirrhosis patients is as low as 6.9% and 2.3% per admission.[2] Liberal transfusion of bleed products carries risks of volume overload which may aggravate portal hypertension, immunologic and infectious risk, and possibility of clotting.[3] Especially fresh frozen plasma is usually transfused to patients with volume of 10mL/kg which may exacerbate the portal hypertensive-driven bleeding. Additionally, anemia, infection, and renal failure also affect coagulation in patients with liver cirrhosis. Fresh frozen plasma, prothrombin complex concentrates, and platelet concentrate should not be routinely used as a preventive measure in LC patients undergoing invasive procedures[3]. Thrombopoietin receptor agonists, avatrombopag or lusutrombopag are approved for thrombocytopenic liver cirrhosis patients undergoing an invasive procedure.[4,5] Although it requires 5 to 7 days to elevate platelet levels prior to procedure, they can be used to decrease the rate of platelet transfusion in patients undergoing high-risk procedures in whom local hemostasis is not possible and platelet is very low (< 20 X $10^9$/L).[3] For portal pressure-driven bleeding, measures to lower portal pressure are the main-

stay of the treatment. For non-portal hypertensive causes of bleeding, local measures, interventional radiologic treatment, treatment for other contributing factors such as renal failure, infection, correction for anemia should be sought. There is no evidence for correction of prothrombin time or platelet or to use tranexamic acids in patients with abnormalities in thrombolytic system and correction of hemostasis may be considered on a case-by-case basis.

## Conclusions

Hemostatic rebalance is achieved in patients with liver cirrhosis. However, it is fragile with extrahepatic variables. Tests which truly reflect the balance of procoagulant and anticoagulant factors in vivo are lacking. Most bleeding in patients with liver cirrhosis is portal hypertension-driven and it is unrelated to hemostasis. Therefore, routine use of blood products to correct hemostatic laboratory abnormalities are not recommended in the prophylaxis of bleeding prior to procedure. Thrombopoietin receptor agonists can be good alternatives to platelet transfusion.

## References

1. Tripodi A, Primignani M, Lemma L, et al. Evidence that low protein C contributes to the procoagulant imbalance in cirrhosis. J Hepatol. 2013;59(2):265-70. Epub 20130411.
2. Intagliata NM, Rahimi RS, Higuera-de-la-Tijera F, et al. Procedural-Related Bleeding in Hospitalized Patients With Liver Disease (PROC-BLeeD): An International, Prospective, Multicenter Observational Study. Gastroenterology. 2023;165(3):717-32. Epub 20230602.
3. EASL Clinical Practice Guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol. 2022;76(5):1151-84. Epub 20220315.
4. Hidaka H, Kurosaki M, Tanaka H, et al. Lusutrombopag Reduces Need for Platelet Transfusion in Patients With Thrombocytopenia Undergoing Invasive Procedures. Clin Gastroenterol Hepatol. 2019;17(6):1192-200. Epub 20181128.
5. Terrault N, Chen YC, Izumi N, et al. Avatrombopag Before Procedures Reduces Need for Platelet Transfusion in Patients With Chronic Liver Disease and Thrombocytopenia. Gastroenterology. 2018;155(3):705-18. Epub 20180517.

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SINCE 2014

THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# State-of-the-Art Lecture

**Chair:**

**Joo Hyun Sohn** (Hanyang Univ.)

**Rohit Loomba**

*University of California San Diego, USA*

## Self Introduction

Dr. Rohit Loomba is a Professor of Medicine (with tenure), Chief, Division of Gastroenterology and Hepatology, at the University of California at San Diego. He is an internationally recognized thought leader in translational research and innovative clinical trial design in nonalcoholic steatohepatitis (NASH), and non-invasive assessment of liver disease using advanced imaging modalities.

Dr. Loomba is the founding director of the UCSD MASLD Research Center, which fosters collaborative team science where a multi-disciplinary team of researchers are conducting cutting edge research in all aspects of NAFLD including non-invasive biomarkers, genetics, epidemiology, clinical trial design, imaging end-points, and integrated OMICs using microbiome, metabolome and lipidome. This integrated approach has led to several innovative applications such as establishment of MRI-PDFF as a non-invasive biomarker of treatment response in early phase trials in NASH, which has now been adopted in more than 100 clinical trials conducted worldwide. He holds several patents on non-invasive biomarkers of NASH and fibrosis.

His research is funded by the National Institutes of Health as a Principal Investigator including two R01s, three U01 (two NIDDK and one from NIAAA), clinical core director of P30 (NIDDK) and project director P01 (NHLBI) grant mechanisms, Foundation of NIH, as well as several large multicenter, multi-million dollar investigator initiated research projects funded by the industry. He is the Principal Investigator, UCSD, for the NIDDK-sponsored NASH Clinical Research Network and the Liver Cirrhosis Network. He also serves as on the Scientific Advisory Board of numerous biotechnology and large pharmaceutical companies and guides clinical drug development and biomarker discovery programs globally.

He serves on the Editorial Board of Gastroenterology, Journal of Hepatology, GUT and Nature Reviews in Gastroenterology and Hepatology. He recently completed a 5-year term as the Deputy Editor of HEPATOLOGY, the official journal of the AASLD. Currently, he serves as the co-Editor of Alimentary Pharmacology and Therapeutics, an international journal in the field of gastroenterology and Hepatology. Dr. Loomba has published more than 500 manuscripts and has an H-index of 131. He has been consistently listed among the top 1% of the globally highly cited scientists across all fields since 2019 by Web of Science. He is an elected member of the American Society of Clinical Investigation (ASCI), and the Association of American Physicians (AAP).

### *Education*

| | |
|---|---|
| 08/05-05/07 | Masters of Health Science in Clinical Research (NIH-Duke University Combined Program)<br>Duke University School of Medicine, Durham, NC |
| 08/93-03/99 | M.B.B.S. (equivalent of MD) The Armed Forces Medical College, Pune University India |

## Representative Publications

1. Loomba R. Autoimmune hepatitis: a clinical challenge. Nov 2002, Resident Rept J, published by AGA.
2. Loomba R and Liang TJ. Novel approaches to new therapies for hepatitis B virus infection. Antivir ther 2006; 1: 1-16.
3. Lutchman G, Modi A, Pomrat K, Kleiner D, Ghany MG, Heller T, Loomba R, Park Y, Liang TJ, Hoofnagle JH. The effects of discontinuing pioglitazone in patients with nonalcoholic steatohepatitis. Hepatology 2007;46(2): 424-9.
4. Loomba R and Ghany MG. Diagnosis and treatment of chronic HBeAg-negative hepatiis B. Curr Hepatitis Rept 2007; 6:146-153.
5. Loomba R and Liang TJ. Treatment of chronic hepatitis B. Antivir Ther 2007; 12 Suppl 3:H33-41.

# Advances in Non-Invasive Assessment of MASH

**Rohit Loomba** *University of California San Diego, USA*


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THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# President's Choice Lecture

**Chair:**

**Yoon Jun Kim** (Seoul National Univ.)

**Tim F. Greten**

*National Cancer Institute, USA*

## Self Introduction

Tim F. Greten, M.D., received his medical training at the Christian Albrechts University in Kiel, Germany. He did his internship in Munich followed by a 3-year postdoctoral fellowship at the Johns Hopkins University (Baltimore, Maryland), where he initiated his work in the field of tumor immunology. In 1999, Dr. Greten returned to Hannover Medical School, where he finished his training in Internal Medicine (2003), Medical Oncology (2004) and Gastroenterology (2007). He held an Associate Professor position in the Department of Gastroenterology, Hepatology and Endocrinology in Hannover Medical School. In February 2010, Dr. Greten joined CCR's Medical Oncology Branch as the head of the Gastrointestinal Malignancy Section and was promoted as a tenured Senior Investigator in 2015 and Deputy Branch Chief in 2018 and CCR Deputy Director in 2023.

Dr. Greten has published more than 250 peer-reviewed papers in different journals including Science, Nature, Cell, Cancer Cell, Cancer Discovery and New England Journal of Medicine. In 2023 Dr. Greten was awarded the NCI and CCR Director's Award for Outstanding Mentorship.

## Research Interests

Immunotherapy of Liver Cancer

## Representative Publications

1. Ma, C., et al., NAFLD causes selective CD4(+) T lymphocyte loss and promotes hepatocarcinogenesis. Nature, 2016. 531(7593): p. 253-7.
2. Duffy, A.G., et al., Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. J Hepatol, 2017. 66(3): p. 545-551.
3. Ma, C., et al., Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science, 2018. 360(6391): p. eaan5931.
4. Ma, C., et al., Platelets control liver tumor growth through P2Y12-dependent CD40L release in NAFLD. Cancer Cell, 2022. 40(9): p. 986-998 e5.
5. Ruf, B., et al., Tumor-associated macrophages trigger MAIT cell dysfunction at the HCC invasive margin. Cell, 2023. 186(17): p. 3686-3705 e32.

# Innovative Immunotherapy Concepts for Liver Cancer

**Tim F. Greten** *National Cancer Institute, USA*

Despite the recent approval of immune checkpoint inhibitor therapies for patients with hepatocellular carcinoma, the majority of patients with HCC do not respond to this treatment and overall survival time remains limited. Our group has been studying the tumor specific immune microenvironment environment for many years and this has resulted in potential new treatment options, which are either being studied or could be potentially studied in the future.

In my presentation I will focus on four different aspects, which illustrate my vision of innovation in HCC:
1. Identification of potential biomarkers in HCC.
2. New combination therapies using already approved drugs
3. Adoptive T cell therapy
4. The role of the gut microbiome and neuro-immune interactions.


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DAY 3: June 29 (Sat)

# KASL Symposium 5

## Personalized Approaches to Liver Disease

**Chairs:**

**Byung-Cheol Song** (Jeju National Univ.)
**Mark Muthiah** (National Univ. Hospital, Singapore)

**Won Sohn**

*Sungkyunkwan University*

## Self Introduction

### *Education*

| | |
|---|---|
| 1995.3-2002.2 | M.D., Hanyang University, Seoul, Korea |
| 2004.3-2006.2 | M.Sc., Hanyang University, Seoul, Korea |
| 2011.3-2013.2 | Ph.D., Hanyang university, Seoul, Korea |

### *Professional Experience*

| | |
|---|---|
| 2002.3-2003.2 | Internship, Hanyang University Hospital |
| 2003.3-2007.2 | Residentship, Department internal medicine, Hanyang University Hospital |
| 2007.3-2010.4 | Attending Physician, Department of internal medicine, In-kok Jae Hospital. |
| 2010.5-2012.2 | Clinical Fellowship, Division of Gastroenterology, Hanyang University Hospital |
| 2012.3-2013.2 | Attending Physician, Division of Gastroenterology, Hanyang University Hospital |
| 2013.3-2015.2 | Research Fellowship, Division of Gastroenterology, Samsung Medical Center |
| 2015.3-2017.2 | Attending Physician, Liver Center and Internal Medicine, Bundang Jesaeng Hospital |
| 2017.3-2019.2 | Assistant Professor, Division of Gastroenterology, Wonkwang University Sanbon Hospital |
| 2019.3- | Associate Professor, Division of Gastroenterology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine |

## Research Interests

- Liver fibrosis
- Steatotic liver disease
- Hepatocellular carcinoma

## Representative Publications

1. Sohn W, Park SY, Lee TH, et al. Effect of direct-acting antivirals on disease burden of hepatitis C virus infection in South Korea in 2007–2021: a nationwide, multicentre, retrospective cohort study. eClinicalMedicine. 2024;7:102671
2. Sohn W, Chang Y, Cho YK, et al. Isolated Hepatitis B core antibody positivity and long-term liver-related mortality in Korea: A cohort study. Am J Gastroenterol. 2023;118(1):95-104.
3. Sohn W, Kang D, Kang M, et al. Impact of nationwide hepatocellular carcinoma surveillance on the prognosis in patients with chronic liver disease. Clin Mol Hepatol. 2022;28(4):851-863.
4. Sohn W, Kwon HJ, Chang Y, et al. Liver fibrosis in Asians with metabolic dysfunction-associated fatty liver disease. Clin Gastroenterol Hepatol. 2022 May;20(5):e1135-e1148
5. Sohn W, Cho JY, Kim JH, et al. Risk score model for the development of hepatocellular carcinoma in treatment-naïve patients receiving oral antiviral treatment for chronic hepatitis B. Clin Mol Hepatol.2017;23(2):170-178.

# Effectiveness and Challenges of Etiology-Based Surveillance Approaches for HCC

**Won Sohn** *Sungkyunkwan University*

Hepatocellular carcinoma (HCC) is indolent and asymptomatic at an early stage, and approximately half of HCC cases are diagnosed at an advanced tumor stage. Thus, it is necessary to determine and monitor the high-risk groups for liver disease-related complications, including HCC, through surveillance programs aimed at reducing liver-related mortality. A meta-analysis revealed that HCC surveillance was beneficial in detecting early-stage tumors, increasing the chance of curative therapy, and improving overall survival in cirrhotic patients.

Surveillance is the repeated screening of patients with the at-risk population. An intervention is considered effective if it provides an increase in longevity of about 100 days, i.e., about 3 months. Although the levels were set years ago, and may not be appropriate today, interventions that can be achieved at a cost of less than about $50,000/year of life gained are considered cost-effective. HCC surveillance is recommended based on the cost-effectiveness considering threshold incidence for efficacy of surveillance according to the etiology of chronic liver disease and presence of cirrhosis (below table). Most guidelines recommend HCC surveillance in high risk groups (cirrhosis of any cause or chronic hepatitis B [CHB]) using ultrasonography and/or serum alpha-fetoprotein (AFP) every 6 months. However, there is a lack of existing clinical evidence on the effect of HCC surveillance on chronic liver disease prognosis, and

**Table 3. Groups for whom HCC surveillance in recommended or in whom the risk of HCC is increased, but in whom efficacy of surveillance has not been demonstrated**

| Surveillance recommended | | |
|---|---|---|
| **Population group** | **Threshold incidence for efficacy of surveillance (> .25 LYG)(%/year)** | **Incidence of HCC** |
| Asian male hepatitis B carriers over age 40 | 0.2 | 0.4-0.6%/year |
| Asian female hepatitis B carriers over age 50 | 0.2 | 0.3-0.6%/year |
| Hepatitis B carrier with family history of HCC | 0.2 | Incidence higher than without family history |
| African/North American Blacks with hepatitis B | 0.2 | HCC occurs at a younger age |
| Cirrhotic hepatitis B carriers | 0.2-1.5 | 3-8%/yr |
| Hepatitis C cirrhosis | 1.5 | 3-5%/yr |
| Stage 4 primary biliary cirrhosis | 1.5 | 3-5%/yr |
| Genetic hemachromatosis and cirrhosis | 1.5 | Unknown, but probably > 1.5%/year |
| Alpha 1-antitrypsin deficiency and cirrhosis | 1.5 | Unknown, but probably > 1.5%/year |
| Other cirrhosis | 1.5 | Unknown |
| **Surveillance benefit uncertain** | | |
| Hepatitis B carriers younger than 40 (males) or 50 (females) | 0.2 | < 0.2%/yr |
| Hepatitis C and stage 3 fibrosis | 1.5 | < 1.5%/yr |
| Non-cirrhotic NAFLD | 1.5 | < 1.5%/yr |

there are only two randomized clinical trials on HCC surveillance in Chinese patients with CHB. Besides, one of those randomized trials used serum AFP only for HCC surveillance and did not show a reduction in mortality in patients who underwent surveillance. In addition, the adherence to HCC surveillance is poor even in high risk groups.

## 1. Chronic hepatitis B

Hepatitis B virus (HBV) infection is a global health concern that causes acute and chronic infections that can progress to liver cirrhosis, HCC, and liver failure, with eventual death. To increase the early detection of HCC, reduce complications among the patients with CHB, and improve overall survival. HCC surveillance is recommended for CHB patients with high risk group which consisted of cirrhosis or Asians aged over 40 years. This is because the annual incidence of HCC in Asian patients with CHB irrespective of cirrhosis begins to exceed 0.2% after age 40 when surveillance for HCC is cost-effective.

The risk of HCC in CHB depends on viral activity (HBeAg, HBV DNA), disease activity (ALT level), fibrotic burden, and host factors (age, gender, family history, diabetes, alcohol, and smoking). The prediction of HCC risk in patients with CHB has been stratified using the risk score models based on above-mentioned factors.

Most of risk prediction scores for HCC in untreated patients were derived from Asian cohorts. Host factors (age and gender) were included in all models in untreated patients. Fibrotic burden was also included in all models. However, fibrotic burden was assessed in various method such as presence of cirrhosis, platelet count, albumin level, liver stiffness measurement (LSM), and spleen size. Viral factors (high level of HBV DNA, and HBeAg positivity), and disease activity (high level of ALT) were included in the risk prediction model in untreated patients. The accuracy of prediction for HCC development over 5-10 years ranged between 0.76 and 0.92, which was presented by the area under the receiver operating characteristic curve (AUROC).

Nowadays, use of oral antiviral agents (nucleos(t)ide analogue, NA) has been established as the standard treatment for CHB. The use of antiviral agents suppresses HBV replication and decreases hepatic inflammation. Furthermore, long-term use of antiviral agents can improve advanced fibrosis or cirrhosis in the histologic findings. There is no question about the role of preventive effect of antiviral agents on the reducing risk of HCC in patients with CHB. The use of antiviral agents significantly reduces the risk of HCC in CHB compared to patients with no use of antiviral agents.

There are several prediction models for HCC risk in CHB patients receiving antiviral agents. Most of them were derived from Asia, but PAGE-B model was made based on Caucasian patients. Host factors (age and gender) and fibrotic burden were included in all models in CHB patients receiving antiviral agents. Some models included However, viral factors (HBV DNA, and HBeAg), and disease activity (ALT) are not included in the models with use of antiviral agents. The AUROC for HCC development over 5-10 years

ranged between 0.76 and 0.86.

## 2. Chronic hepatitis C

Recently, a paradigm shift from interferon-based to direct-acting antiviral (DAA) treatments for chronic hepatitis C (CHC) occurred. Recent meta-analyses have shown that DAA therapy reduces the risk of HCC, decompensation, and mortality in patients with CHC. Sustained virological response (SVR) to DAA treatment in cirrhotic patients with CHC improved portal hypertension and reduced the hepatic venous pressure gradient. SVR to DAA treatment decreased the risk of HCC in patients with CHC.

There is no doubt of HCC surveillance in CHC patients with cirrhosis in terms of cost-effectiveness. However, there is a lack of HCC surveillance in non-cirrhotic patients achieving SVR. Some studies showed that HCC surveillance might be useful in patients with advanced fibrosis (F3). However, liver biopsy is invasive and not widely used in real practice. It is needed to determine high risk group in non-cirrhotic patients using noninvasive fibrosis marker. A study showed that the post SVR state with FIB-4 index with > 3.25 had 2.16% of HCC incidence which had cost-effectiveness for HCC surveillance.

## 3. Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease, which is defined as intrahepatic triglyceride content of >5%. It has become widespread with the increasing prevalence of obesity and metabolic syndrome. The spectrum of NAFLD includes simple steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. It's reasonable to include NASH-cirrhosis as an at-risk population for HCC surveillance. However, HCC can develop in NAFLD without advanced fibrosis or cirrhosis. A study reported that 30% of NAFLD-HCC developed in the background of no cirrhosis. Unlike viral hepatitis, the risk factors for HCC development is unclear in patients with NAFLD/NASH.

Recent studies showed that genetic polymorphisms (*PNPLA3, MBOAT7, TM6SF2*, and *GCKR*) that are associated with hepatic fat content predicted HCC development in patients with NAFLD. Polygenic risk score which consists of several genetic polymorphisms was suggested as a prediction model for NAFLD-HCC development. However, the diagnostic accuracy is still not high. Further studies are needed to clarify the precise risk factors for NAFLD-HCC. It is not difficult to determine an at-risk population for HCC development in patients with non-cirrhotic NAFLD.

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3. Sohn W, Kang D, Kang M, Guallar E, Cho J, Paik YH. Impact of nationwide hepatocellular carcinoma surveillance on the prognosis in patients with chronic liver disease. Clin Mol Hepatol. 2022 Oct;28(4):851–63.
4. Papatheodoridis GV, Voulgaris T, Papatheodoridi M, Kim WR. Risk Scores for Hepatocellular Carcinoma in

Chronic Hepatitis B: A Promise for Precision Medicine. Hepatology. 2020 Dec;72(6):2197–205.
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**Wai-Kay Seto**

*The University of Hong Kong, Hong Kong*

## Self Introduction

Prof. Wai-Kay Seto is currently a specialist in Gastroenterology and Hepatology and Clinical Professor in the Department of Medicine; Principal Investigator of the State Key Laboratory of Liver Research, The University of Hong Kong; and Assistant Dean (Research), LKS Faculty of Medicine, The University of Hong Kong. Prof. Seto is ranked annually by Clarivate Analytics in the top 1% worldwide by research since 2020. He has published more than 290 international journal articles and book chapters, including first- or corresponding-authored articles in the Lancet, Journal of Clinical Oncology, Lancet Global Health, Journal of Hepatology, Gut, and Hepatology, majority related to research on chronic liver diseases. Prof. Seto has been awarded the American Gastroenterological Association Fellowship (2021); the Asia-Pacific Digestive Week Emerging Leader from the APDW Federation (2018); Guangdong Province Outstanding Young Medical Talent Award (2017); and the Outstanding Young Research Award (2016-2017) from The University of Hong Kong.

## Research Interests

Viral Hepatitis; Liver Fibrosis; Hepatocellular Carcinoma; Biotechnology Related to Chronic Liver Disease

## Representative Publications

1. Zhang S, Chau HT, Tun HM, Huang FY, Wong DK, Mak LY, Yuen MF, Seto WK. Virological response to nucleos(t)ide analogues treatment in chronic hepatitis B patients is associated with Bacteroides-dominant gut microbiome. EBioMedicine 2024 in press
2. Mao X, Peng C, Mak LY, Cheng HM, Fung J, Peleg N, Leung H, Kumar R, Lee JH, Shlomai A, Yuen MF, Seto WK. Steatosis, HBV-related hepatocellular carcinoma, cirrhosis and HBsAg seroclearance: a systematic review and meta-analysis. Hepatology 2023 77(5):1735-1745
3. Mak LY, Hui RW, Lee CH, Mao X, Cheung KS, Wong DK, Lui DT, Fung J, Yuen MF, Seto WK. Glycemic burden and the risk of adverse hepatic outcomes in chronic hepatitis B patients with type 2 diabetes. Hepatology 2023 77(2):606-618
4. Su S, Wong WC, Zou Z, Cheng DD, Ong JJ, Chan P, Ji F, Yuen MF, Zhaung G, Seto WK*, Zhang L. Cost-effectiveness of universal screening for chronic hepatitis B virus infection in China: an economic evaluation. Lancet Glob Health 2022 10(2):e278-287
5. Seto WK, Liu KS, Mak LY, Cloherty G, Wong DK, Gersch J, Lam YF, Cheung KS, Chow N, Ko KL, To WP, Fung J, Yuen MF. Role of serum HBV RNA and hepatitis B surface antigen levels in identifying Asian chronic hepatitis B patients suitable for entecavir cessation. Gut 2021 70:775-783

# Virologic and Immunologic Biomarkers to Guide Treatment of Chronic Hepatitis B

**Wai-Kay Seto** *The University of Hong Kong, Hong Kong*

Despite the World Health Organization's objectives to achieve global viral hepatitis B elimination, the diagnostic and treatment coverage of many countries and regions remain at low levels. Based on current epidemiological estimates, HBV-related mortality has remained constant in countries of high sociodemographic index, and in the coming future will be expected to increase in the Western Pacific. In additional to traditional viral markers, hepatitis B core-related antigen (HBcrAg) and hepatitis B virus RNA (HBV RNA) are increasingly applied to predict the natural course of disease as well as long-term outcomes. Serum HBcrAg is an antigen associated with viral activity, and it is able predict HBV-related hepatocellular carcinoma development especially in patients with intermediate viral activity. Recent development include the point-of-care lateral flow HBcrAg test which is able to establish patient for treatment eligibility in a out-of-clinic setting and may be suitable for rural communities. Serum HBV RNA is an important viral intermediate that unlike HBV DNA, has a more gradual decrease during nucleoside analogue therapy. One use of HBV RNA is to predict virological relapse after nucleoside analogue cessation. The latest HBV RNA assays also offer a better transcriptional reflection of intrahepatic covalently closed circular DNA. While there is emerging evidence of biomarkers reflecting the immune response toward HBV, it remains hindered by accessibility and practicality. Novel biomarkers are still unmentioned in international HBV disease guidelines. That being said, its future role will probably be in the prediction of viral kinetics for emerging novel therapies aiming at a functional cure of the disease.

**Barjesh Chander Sharma**

*Govind Ballabh Pant Hospital, India*

## Research Experience

1. Papers published : 270
2. Submitted for publication : 8
3. Papers presented/abstracted : 300
4. Conferences/Workshops attended : 75

## Journal Editor, Member and Office Bearer of Scientific Committees and Societies

1. President of APASL.
2. Secretary General of APASL
3. Member of Steering Committee of APASL.
4. Chairman of Guidelines Committee of APASL
5. Member of Executive Council of APASL.
6. Member of Executive Council of Indian Association for Study of Liver Diseases.
7. Member of Indian Society of Gastroenterology.
8. Member of Society of Gastrointestinal Endoscopy.
9. Member of Indian Association for Study of Liver Diseases.
10. Member of Asian Pacific Association for Study of the Liver
11. Editor
    - Journal of Gastroenterology and Hepatology 2004; 19: Supplement
    - Postgraduate course and current reviews in Hepatology, 14th Biennial Conference of Asian Pacific Association for the study of the Liver
12. Assistant Editor for Journal "Hepatology Intennational"
13. Member of Editorial Board of ' World Journal of Gastroenterology'.
14. Member of Editorial Board og J Gastroenterol Hepatol.
15. Member of Editorial Board of Journal of Clinical and Experimental

# Role of Combination Therapy in Hepatic Encephalopathy

**Barjesh Chander Sharma** *Govind Ballabh Pant Hospital, India*

Hepatic encephalopathy (HE) is characterized by wide spectrum of neurological and psychiatric alterations resulting due to advanced liver malfunction. It is a neurological ailment related to hepatic insufficiency and/or portosystemic shunts. Its clinical features include neuropsychiatric dysfunction, ranges from subclinical changes to coma. Overt HE is found in 30-45% of patients with cirrhosis and 10-50% of patients with a transjugular intrahepatic portosystemic shunt (TIPS). Recurrence of HE is seen in 47-57% of patients by the end of one year despite being on treatment. Occurrence of each bout of HE results in increased morbidity, hospitalization, health care burden, poor prognosis and increased mortality. Combination of rifaximin with lactulose has favourable effect on patients with recurrent HE who have recurrent bouts of HE despite on lactulose. Thus, rifaximin along with lactulose should be considered for preventing the recurrent episodes of HE. With use of rifaximin as addition to lactulose for the prophylaxis of third and further episodes of HE, cost can be saved both from a hospital and healthcare payer's perspective. From healthcare payer's view, costs raise by adding rifaximin to lactulose is reduced due to improved survival with rifaximin causing relatively low drug and liver transplant related costs. Combination of lactulose plus albumin is also more effective than lactulose alone in the management of overt HE with more decrease in the levels of arterial ammonia, interleukin-6, interleukin-18, tumor necrosis factor-alpha, and endotoxins. Triple combination of L-ornithine L aspartate (LOLA) with lactulose and rifaximin is more efficacious than only lactulose and rifaximin in improving grades of HE, recovery time from HE and with reduced 28-days mortality. In cirrhotic patients with advanced HE adjuvant treatment with LOLA along with lactulose and metronidazole is safe and associated with fast improvement and reduced hospital stay. In conclusion combination therapy including lactulose, rifaximin, albumin and LOLA is effective in the management and prevention of recurrent HE.

**Jean-Charles Nault**

*Sorbonne Université, France*

## Self Introduction

Jean-Charles Nault received is MD and PhD from Paris Descartes University. He is currently professor in the liver unit of the Avicenne Hospital in Bobigny, France with a high priority on early detection of primary liver tumors and on therapeutic innovation. He is also an active member of the laboratory of "functional genomics of solid tumors" in Cordeliers Research Center.

## Research Interests

His research is dedicated to translational research, in particular the identification of new driver genes in hepatocellular adenoma and hepatocellular carcinoma, of new therapeutic targets and of the molecular determinants of hepatocellular carcinoma's prognosis. He has discovered the role of mutation in the promoter of telomerase in liver carcinogenesis, identified a new virus responsible (adeno associated virus type 2) of development of HCC on normal liver and new therapeutic targets in advanced HCC.

## Representative Publications

1. Molecular-based targeted therapies in patients with hepatocellular carcinoma and hepato-cholangiocarcinoma refractory to atezolizumab/bevacizumab. Limousin W, Laurent-Puig P, Ziol M, Ganne-Carrié N, Nahon P, Ait-Omar A, Seror O, Sidali S, Campani C, Blanc P, Lermine A, Marisa L, Zucman-Rossi J, Nault JC. J Hepatol. 2023 Dec;79(6):1450-1458.
2. Body weight changes and duration of estrogen exposure modulate the evolution of hepatocellular adenomas after contraception discontinuation. Demory A, Péron JM, Calderaro J, Selves J, Mokrane FZ, Amaddeo G, Paradis V, Ziol M, Sutter O, Blaise L, Ganne-Carrié N, Vilgrain V, Cauchy F, Zucman-Rossi J, Ronot M, Nault JC. Hepatology. 2023 Feb 1;77(2):430-442.
3. Systemic Treatments with Tyrosine Kinase Inhibitor and Platinum-Based Chemotherapy in Patients with Unresectable or Metastatic Hepatocholangiocarcinoma. Gigante E, Hobeika C, Le Bail B, Paradis V, Tougeron D, Lequoy M, Bouattour M, Blanc JF, Ganne-Carrié N, Tran H, Hollande C, Allaire M, Amaddeo G, Regnault H, Vigneron P, Ronot M, Elkrief L, Verset G, Trepo E, Zaanan A, Ziol M, Ningarhari M, Calderaro J, Edeline J, Nault JC. Liver Cancer. 2022 Jun 14;11(5):460-473
4. Percutaneous radiofrequency ablation for hepatocellular carcinoma developed on non-alcoholic fatty liver disease. Nguyen N, Rode A, Trillaud H, Aubé C, Manichon AF, Hocquelet A, Paisant A, Dao T, Nahon P, Ganne-Carrié N, Blaise L, Cauchy F, Sutter O, Séror O, Nault JC. Liver Int. 2021 Dec 11.
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# Molecular-Based Strategy for Atezo/Bev-Failed HCC: The 2025 French Medicine Genomic Program

**Jean-Charles Nault** *Sorbonne Université, France*

Hepatocarcinogenesis is a multistep process starting with the exposure to different risk factors, followed by the development of a chronic liver disease and cirrhosis precede in the vast majority of the cases the development of HCC. Several lines of evidence have underlined the pivotal role of telomere maintenance in both cirrhosis and HCC pathogenesis. TERT promoter mutations were identified as the most frequent genetic alterations in hepatocellular carcinoma with an overall frequency around 60%. In contrast, acquisition of genomic diversity through mutations of classical oncogenes and tumor suppressor genes (TP53, CTNNB1, ARID1A…) occurred only in progressed HCC. Moreover, genomic analysis is currently used in innovative research program in France for patients with advanced HCC in order to match the genetic alterations with targeted therapy. In this lecture, the main mechanism involved in tumor progression during liver carcinogenesis will be detailed as well as the potential translation in clinical practice specially for the identification of new therapeutic targets based on Whole genome sequencing and RNA sequencing in patients with advanced HCC refractory atezolizumab-bevacizumab.


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# KASL-AASLD Morning Workshop

## Impact of Early TIPS for the Management of Variceal Bleeding

**Chairs:**

**Grace L. Su** (Univ. of Michigan, USA)
**June Sung Lee** (Inje Univ.)

**Eun Sun Jang**

*Seoul National University*

## Self Introduction

Prof. Eun Sun Jang is a professor of the Department of Internal Medicine, Seoul National University Bundang Hospital since 2011. She earned her medical, Master's, and Doctoral degrees from Seoul National University College of Medicine, where she also completed her internship and residency in Internal Medicine. Pf. Jang further enhanced her expertise as a visiting fellow at the National Institute of Diabetes and Digestive and Kidney Diseases, part of the National Institutes of Health in the USA, from 2022 to 2023. Currently, she actively contributes as an executive member of the scientific committee and a member of the policy committee of the Korean Association for the Study of the Liver.

## Research Interests

Chronic viral hepatitis, Autoimmune liver disease, Liver cirrhosis, Hepatocellular carcinoma

## Representative Publications

1. Jang ES, Choi GH, Kim YS, Kim IH, Lee YJ, Cho SB, Kim YT, Jeong SH. Prevalence, incidence, and outcomes of hepatitis E virus coinfection in patients with chronic hepatitis C. Sci Rep. 2023;13(1):13632
2. Kim KA, Choi HY, Ki M, Jang ES, Jeong SH. Epidemiological trends and outcomes of primary biliary cholangitis in South Korea between 2009 and 2019. J Gastroenterol. 2023;58(7):682-692.
3. Choi GH, Jang ES, Kim YS, Lee YJ, Kim IH, Cho SB, Lee HC, Jang JW, Ki M, Choi HY, Baik D, Jeong SH. Hepatocellular carcinoma, decompensation, and mortality based on hepatitis C treatment: A prospective cohort study. World J Gastroenterol. 2022;28(30):4182-4200.
4. Song IA, Jang ES, Oh TK. Validation of Dynamic Aspartate-to-Alanine Aminotransferase Ratio for Predicting Liver Disease Mortality. Hepatol Commun. 2022 Apr;6(4):740-749.
5. Kim SH, Cho EJ, Jang BO, Lee K, Choi JK, Choi GH, Lee JH, Yu SJ, Kim YJ, Lee YB, Yoon JH, Kim JW, Jeong SH, Jang ES. Comparison of biochemical response during antiviral treatment in patients with chronic hepatitis B infection. Liver Int. 2022;42(2):320-329.

# Case and Topic Presentation

**Eun Sun Jang** *Seoul National University*

Variceal bleeding represents a life-threatening complication in patients with decompensated liver cirrhosis, usually managed with beta-blockers and endoscopic techniques. While the Transjugular Intrahepatic Portosystemic Shunt (TIPS) effectively reduces portal hypertension, its invasiveness and associated risks, such as encephalopathy, have limited its widespread use. However, recent studies suggest the potential benefits of implementing early TIPS to reduce treatment failures and more effectively improve the overall survival of patients with high-risk varices. This session will explore the advantages and challenges of early TIPS through a case-based discussion, evaluating its role in contemporary therapeutic strategies.

**Guadalupe Garcia-Tsao**

*Yale University, USA*

## Self Introduction

Dr. Garcia-Tsao is Professor of Medicine at Yale University School of Medicine and at the VA-Connecticut Healthcare System. She is Chair of the Baveno (International Portal Hypertension) Cooperation and Director of the Clinical Core of the NIH-funded Yale Liver Center. Dr. Garcia-Tsao was on the Governing Board of the American Association for the Study of Liver Diseases (AASLD) from 2008 to 2013 and was its President in 2012. Dr. Garcia-Tsao was Associate Editor of Journal of Hepatology from 2001 to 2004, Associate Editor of Hepatology from 2011 to 2016 and has been Associate Editor of the New England Journal of Medicine since 2019. Dr. Garcia-Tsao has contributed to the science and practice of cirrhosis, portal hypertension and its complications, having authored over 300 original articles, including 24 practice guidelines (h-index 110). She has received numerous awards including the International Recognition Award (from EASL), the Distinguished Clinician Educator and Mentor Award (from AASLD) and the Distinguished Scientific Achievement Award (from the American Liver Foundation).

## Research Interests

Dr. Garcia-Tsao's investigation focuses on cirrhosis, portal hypertension and related complications, specifically varices and variceal hemorrhage, ascites and acute kidney injury. Interest in cirrhosis includes staging of the disease: compensated, decompensated and further decompensated as well as the new stage of recompensation. She has has authored over 300 original research publications in addition to several society guidelines and position papers in the field.

## Representative Publications

1. D'Amico G, Zipprich A, Villanueva C, Sordà JA, Morillas RM, Garcovich M, García Retortillo M, Martinez J, Calès P, D'Amico M, Dollinger M, García-Guix M, Gonzalez Ballerga E, Tsochatzis E, Cirera I, Albillos A, Roquin G, Pasta L, Colomo A, Daruich J, Canete N, Boursier J, Dallio M, Gasbarrini A, Iacobellis A, Gobbo G, Merli M, Federico A, Svegliati Baroni G, Pozzoni P, Addario L, Chessa L, Ridola L, Garcia-Tsao G. Further decompensation in cirrhosis. Results of a large multicenter cohort study supporting Baveno VII statements. Hepatology. 2023 Nov 2. Online ahead of print. PMID: 37916970
2. Kaplan DE, Bosch J, Ripoll C, Thiele M, Fortune BE, Simonetto DA, Garcia-Tsao G. AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 2023 Oct 23. Online ahead of print. PMID: 37870298
3. Garcia-Tsao G, Abraldes JG, Rich NE, Wong VW. AGA Clinical Practice Update on the Use of Vasoactive Drugs and Intravenous Albumin in Cirrhosis: Expert Review. Gastroenterology. 2023 Nov 17:S0016 5085(23)05143-0. doi: 10.1053/j.gastro.2023.10.016. Online ahead of print. PMID: 37978969\
4. Rabiee A, Deng Y, Ciarleglio M, Chan JL, Pons M, Genesca J, Garcia-Tsao G. Noninvasive predictors of clinically significant portal hypertension in NASH cirrhosis: Validation of ANTICIPATE models and development of a lab-based model. Hepatol Commun. 2022; 6(12):3324-3334. PMID:36214066
5. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol. 2022 Apr;76(4):959-974. PMID: 35120736

# Better

**Guadalupe Garcia-Tsao** *Yale University, USA*

- Variceal hemorrhage (VH) is an acute complication of cirrhosis associated with significant short-term morbidity and mortality
- Standard initial management is based on a combination of:
  - o splanchnic vasoconstrictors (octreotide, terlipressin) that decrease portal pressure by decreasing portal venous inflow
  - o antibiotics (norfloxacin) that decrease bacterial translocation that increases with hemorrhage, worsening splanchnic vasodilation and can lead to infections;
  - o endoscopic variceal ligation that will directly control bleeding at the variceal rupture site
- In general, Child A (mostly compensated) patients and Child B ("early" decompensated patients with moderately altered liver function) who are not actively bleeding at the time of endoscopy respond favorably to this treatment strategy. However, in patients with Child C cirrhosis (further decompensated and with altered liver function) standard therapy often fails and patients often rebleed despite standard initial therapy. Rebleeding in this setting is associated with a high mortality
- Ultimately, the therapy that will lead to a rapid reduction in portal pressure with cessation of bleeding, is placement of the transjugular intrahepatic porto-systemic shunt (TIPS). However, by shunting blood away from the liver it can be associated with porto-systemic encephalopathy (PSE) and even liver failure, particularly in already decompensated patients.
- TIPS was previously considered as salvage therapy, i.e. its use was reserved to patients in whom standard therapy had failed. However, given that such failure occurs mostly in Child C patients, salvage TIPS was associated with a very high mortality (>80%)
- A landmark multicenter study by Garcia-Pagan et al showed that early (within 72 hours of admission) placement of TIPS (placed in anticipation of rebleed, that is, preemptive placement of TIPS or pTIPS) in patients identified as having a high risk of rebleeding (Child C or B (7-8 score) was associated with decreased rebleeding and mortality without significantly increasing the risk of hepatic encephalopathy. The benefits of p-TIPS were also described in an RCT by Lv et al that included Child C and B patients. In contrast, the survival benefit of p-TIPS was not observed in an RCT by Dunne et al with a higher risk of

HE. \

- In a post-hoc analysis by Trebicka et al of 380 patients with acute-on-chronic liver failure included in a larger cohort of patients with VH showed that p-TIPS was associated with a decreased risk of 6-week rebleeding and mortality
- Meta-analyses of studies on pTIPS differ in their conclusions (Nicoara-Farcau et al; Hussain et al)
- Most of these studies have included patients bleeding from esophageal varices. Data regarding the efficacy of pTIPS in the prevention of rebleeding and death in patients with fundal varices is being explored in a multicenter trial (GAVAPROSEC) that uses glue obliteration as a comparator
- A large multicenter randomized trial (REACT-AVB) comparing pTIPS with the standard of care in patients with CPT scores 7–13 is underway in the United Kingdom. The results will hopefully clarify effect on survival and, importantly, the patient population that most benefits from pTIPS
- Also, different prognostic scores are being developed to best select patient who will most benefit from pTIPS
- Nevertheless, and unless these ongoing studies conclude differently,
  - o Baveno consensus recommendations state: pre-emptive TIPS with polytetrafluoroethylene (PTFE)-covered stents within 72 h (ideally <24 h) is indicated in patients bleeding from esophageal varices who meet any of the following criteria: Child-Pugh class C <14 points or Child-Pugh class B >7 with active bleeding at initial endoscopy or HVPG >20 mmHg at the time of hemorrhage. In patients fulfilling the criteria for pre-emptive TIPS, ACLF, hepatic encephalopathy at admission and hyperbilirubinemia at admission should not be considered contraindications.
  - o AASLD guidance recommends: In patients with CTP class B score >7 and active bleeding on endoscopy or CTP class C score 10–13, preemptive TIPS creation (within 72 hours and ideally within 24 hours of initial upper endoscopy) should be recommended in absence of absolute contraindications to TIPS. If TIPS is not locally available, transfer to a center with the capacity to intervene should be considered.

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2. Lv Y, Yang Z, Liu L, et al. Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial. Lancet Gastroenterol Hepatol 2019;4(8):587–598. PMID:31153882.
3. Dunne PDJ, Sinha R, Stanley AJ, et al. Randomised clinical trial: standard of care versus early-transjugular intrahepatic porto-systemic shunt (TIPSS) in patients with cirrhosis and oesophageal variceal bleeding. Aliment Pharmacol Ther 2020;52(1):98–106. PMID:32452561

4. Nicoară-Farcău O, Han G, Rudler M, Angrisani D, Monescillo A, Torres F, et al. Effects of Early Placement of Transjugular Portosystemic Shunts in Patients With High-Risk Acute Variceal Bleeding: a Meta-analysis of Individual Patient Data. Gastroenterology 2021;160(1):193–205
5. Hussain I, Wong YJ, Lohan R, et al. Does preemptive transjugular intrahepatic portosystemic shunt improve survival after acute variceal bleeding? Systematic review, meta-analysis, and trial sequential analysis of randomized trials. J Gastroenterol Hepatol 2022;37(3):455–463. PMID:34665473
6. Trebicka J, Gu W, Ibáñez-Samaniego L et al. Rebleeding and mortality risk are increased by ACLF but reduced by pre-emptive TIPS. J Hepatol 2020;73(5):1082–1091
7. De Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022;76(4):959–974.
8. Kaplan DE, Ripoll C, Thiele M, Fortune BE, Simonetto DA, Garcia-Tsao G, Bosch J. AASLD Practice Guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology. 2024 May 1;79(5):1180-1211. PMID 37870298

**Yeon Seok Seo**

*Korea University*

## Self Introduction

### *Medical Licenses and Board Certifications*

| | |
|---|---|
| 1996.03 | Korean License of Medical Doctor (License Number, 58571) |
| 2001.02 | Korean Board Certification of Internal Medicine (License Number, 7516) |
| 2006 | Korean Board Certification of Gastroenterology (License Number, 1-06-910) |

### *Educational Backgrounds and Degree*

| | |
|---|---|
| 1990.03-1996.02 | M.D. & Bachelor in Medical Science: Korea University College of Medicine, Seoul, Korea |
| 1997.09-1999.08 | Master in Internal Medicine, Graduate School of Korea University, Seoul, Korea<br>Title of Master Thesis: Effect of 12 month lamivudine therapy in patients with HBeAg positive chronic hepatitis B<br>Director: Prof. Chang Hong Lee, M.D., PhD. |
| 1999.09-2006.02 | Doctor of Philosophy in Internal Medicine, Graduate School of Korea University, Seoul, Korea<br>Title: Comparison of antiviral efficacy between adefovir dipivoxil in lamivudine (LMV) resistant status and LMV in nucleoside naïve status in chronic hepatitis B patients<br>Director: Prof. Jong Eun Yeon, M.D., PhD. |

### *Lists of Training, Employments and Military Service*

| | |
|---|---|
| 1996. 03-1997.02 | Full rotating Internship Training |
| 1997. 03-2001.02 | Residency Training of Internal Medicine |
| 2001. 04-2004.04 | Military Service for 36 months (Medical officer, Captain) |
| 2004. 05-2005.02 | Gastroenterology Fellowship, Korea University Guro Hospital, Seoul, Korea |
| 2005. 03-2006.02 | Clinical Assistant Professor, Korea University Guro Hospital, Seoul, Korea |
| 2006. 03-2007.02 | Clinical Assistant Professor, Korea University Anam Hospital, Seoul, Korea |
| 2007. 03-2010.02 | Assistant Professor, Korea University College of Medicine, Seoul, Korea |
| 2010. 03-2011.02 | Associate Professor, Korea University College of Medicine, Seoul, Korea |
| 2011. 03-2012.11 | Research fellowship, Mayo Clinic, Rochester, MN, USA |
| 2012. 12-2016.02 | Associate Professor, Korea University College of Medicine, Seoul, Korea |
| 2012. 12-Present | Professor, Korea University College of Medicine, Seoul, Korea |

### *Awards*

- Best Presentation Award: The Korean Association for the Study of the Liver (2006)
- Best Poster Award: The Asian Pacific Association for the Study of the Liver (2008)
- Best Poster Presentation Award: Seoul International Liver Symposium (2009)

### *Professional Affiliations*

- Member, Korean Medical Association (1996.3-present)
- Member, Korean Association of Internal Medicine (2001.3-present)
- Member, Korean Society of Gastrointestinal Endoscopy (2005. 8-present)
- Member, Korean Association for the Study of the Liver (2006. 10-present)
- Member, Korean Liver Cancer Study Group (2006. 10-present)
- Member, Korean Society of Gastroenterology (2006. 10-present)

# Worse

**Yeon Seok Seo** *Korea University*


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THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# KLCA-TLCA Joint Symposium

## East Meets Excellence: Exploring HCC Guidelines of Korea and Taiwan

**Chairs:**

**Jong Young Choi** (The Catholic Univ. of Korea)

**Yi-Hsiang Huang** (National Yang Ming Chiao Tung Univ., Taiwan)

**YoungRok Choi**

*Seoul National University*

## Self Introduction

### *Education*

| | |
|---|---|
| 1999-2003 | Busan National University College of Medicine, |
| 2007-2012 | M.S., College of Medicine, Seoul National University |
| 2014- | Ph.D. candidate, College of Medicine, Seoul National University |

### *Training*

| | |
|---|---|
| 2003.3-2004.2 | Intern-ship, Busan National University Hospital, Busan, Korea |
| 2004.3-2008.2 | Resident-ship in Department of Surgery, Seoul National University Hospital, Seoul, Korea |

## Research Interests

- Graft DSA in liver transplantation
- Bile exome excretion after liver transplantation
- Bile duct ischemia

## Representative Publications

1. Long-term outcomes of liver transplantation using grafts from donors with active hepatitis B virus replication: a multicenter cohort study, Annals of Surgical Treatment and Research 104 (4), 183
2. Total robot-assisted recipient's surgery in living donor liver transplantation: First step towards the future, J hepatobiliary pancreas science, https://doi.org/10.1002/jhbp.1327
3. Changes in Awareness Toward Minor's Organ Donation Through Structured Information; Survey, Transplant Int https://doi.org/10.3389/ti.2023.10795
4. Long - term outcomes of laparoscopic versus open liver resection for intrahepatic combined hepatocellular - cholangiocarcinoma with propensity score matching, Annals of Gastroenterological Surgery 6 (4), 562-568
5. Changes in Indices of Steatosis and Fibrosis in Liver Grafts of Living Donors After Weight Reduction, Front. Surg. 2022;9: 827526

# Biomarkers-Guided Liver Transplantation for Advanced HCC in Korea

**YoungRok Choi** *Seoul National University*

Historically, liver transplantation for HCC faced significant challenges due to poor survival rates. During the 1980s, broad indications for liver transplantation in HCC patients resulted in a five-year survival rate of less than 40%, leading to HCC being considered a relative contraindication for liver transplantation for a time. However, advancements in both surgical techniques and criteria for patient selection have dramatically improved outcomes.

The Milan criteria, introduced in the 1990s, marked a significant breakthrough by setting clear parameters: one lesion less than 5 cm or up to three lesions each smaller than 3 cm, with no extrahepatic manifestations and no gross vascular invasion. These criteria significantly improved post-transplant survival rates, achieving a five-year survival rate between 65-78%, comparable to patients undergoing liver transplantation for cirrhosis alone. Nonetheless, the limitations of these morphologic criteria soon became apparent, as they did not adequately account for the biological aggressiveness of the tumors.

Recognizing these limitations, various expanded criteria have been developed, incorporating serum biomarkers and the biological behavior of the tumors. Notable among these are the University of California, San Francisco (UCSF) criteria, the Tokyo criteria, and the Seoul National University criteria, each allowing for a broader range of tumor sizes and numbers, often in conjunction with serum markers like AFP and PIVKA-II. For instance, at Seoul National University, criteria include up to ten tumors, each less than 5 cm in diameter, with PIVKA-II levels $\leq$ 400 mAU/mL.

The role of living donor liver transplantation (LDLT) is particularly significant in regions like Korea and Taiwan, where deceased donor organs are less readily available. LDLT, despite its complexity and ethical considerations, offers a viable option, ensuring no waiting time and often resulting in better immediate quality of life post-transplant. The meticulous patient selection, thorough pre-transplant evaluation, and innovative use of bridging and downstaging therapies have all contributed to improving outcomes for patients with advanced HCC.

The integration of biomarkers such as alpha-fetoprotein (AFP) and other biological markers in the selection criteria for liver transplantation has shown promising results in identifying patients with advanced HCC who have better prognoses. Several studies have demonstrated that using these biomarkers,

alongside traditional imaging criteria, enhances the ability to select suitable candidates for liver transplantation. For instance, a study involving living donor liver transplantation (LDLT) for patients with portal vein tumor thrombosis (PVTT) and macrovascular invasion showed that those with lower AFP levels and good responses to downstaging therapies had significantly better survival rates. Patients with AFP levels below 100 ng/mL and favorable tumor responses had a five-year overall survival rate of 85% compared to those with higher AFP levels. This evidence suggests that incorporating biomarkers into the selection process can improve post-transplant outcomes, offering a more refined approach to managing advanced HCC.

In conclusion, biomarkers-guided liver transplantation represents a significant advancement in the treatment of advanced HCC. These expanded criteria and tailored approaches provide hope for improved survival and quality of life for patients battling this challenging disease. As these strategies continue to be refined and insights are shared across regions, the goal of providing excellence in care for all HCC patients becomes increasingly attainable.


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**Yi-Hsiang Huang**

*National Yang Ming Chiao Tung University, Taiwan*

## Self Introduction

Prof. Yi-Hsiang Huang is the President (2023-2027) of Taiwan Liver Cancer Association (TLCA), and the Director of Healthcare and Services Center at the Taipei Veterans General Hospital. He is also the Chair Professor for the Institute of Clinical Medicine, and the Director of the Department of Internal Medicine at the National Yang Ming Chiao Tung University. Completing his medical and PhD training at National Yang Ming University, he furthered his training as a research fellow at the Vaccine Branch of National Cancer Institute, National Institute of Health, USA from 2006 to 2007. Prof. Huang became a full professor at the Institute of Clinical Medicine, NYCU in 2011, and is now the Chair Professor at NYCU since Aug. 2022.

Prof. Huang has served as the council member of Asia-Pacific Primary Liver Cancer Expert Association (APPLE) since Jul. 2023; the executive committee member of Taiwan Association for the Study of the Liver (TASL) since Sep. 2023; the secretary general of the Chinese Medical Association (CMA) of Taiwan (2020-2026), the council member of the TLCA and the Taiwan Academy of Tumor Ablation (TATA).

## Research Interests

Prof. Huang's study interest is in the immunology of viral hepatitis and HCC, including HBV reactivation related to immunosuppressive treatment and immune checkpoint inhibitors; and HCC treatment across locoregional to systemic therapy.

## Representative Publications

1. Mon HC, Lee PC, Hung YP, Hung YW, Wu CJ, Lee CJ, Chi CT, Lee IC, Hou MC, Huang YH*. Functional Cure of Hepatitis B in Cancer Patients Undergoing Immune Checkpoint Inhibitors. J Hepatol 2024 (Accepted)
2. Hung YW, Lee IC, Chi CT, Lee RC, Liu CA, Chiu NC, Hwang HE, Chao Y, Hou MC, Huang YH*. Radiologic Patterns Determine the Outcomes of Initial and Subsequent Transarterial Chemoembolization in Intermediate-Stage Hepatocellular Carcinoma. Liver Cancer. 2024 Feb;13 (1): 29-40.
3. Lee PC, Wu CJ, Hung YW, Lee CJ, Chi CT, Lee IC, Yu-Lun K, Chou SH, Luo JC, Hou MC, Huang YH.*. Gut microbiota and metabolites associate with outcomes of immune checkpoint inhibitors-treated unresectable hepatocellular carcinoma. J Immunother Cancer 2022 Jun;10(6):e004779.
4. Chen MH, Lee IC, Chen MH, Hou MC, Tsai CY, Huang YH*. Abatacept is second to rituximab at risk of HBsAg reverse seroconversion in patients with rheumatic disease. Annals of Rheumatic Diseases 2021 Nov;80(11):1393-1399.
5. Chen MH, Chen MH, Chou CT, Hou MC, Tasi CY*, Huang YH*. Low but Long-lasting Risk of Reversal of Seroconversion in Patients With Rheumatoid Arthritis Receiving Immunosuppressive Therapy. Clin Gastroenterol Hepatol. 2020 Oct;18(11):2573-2581.

# AI Research of HCC in Taiwan

**Yi-Hsiang Huang** *National Yang Ming Chiao Tung University, Taiwan*

Artificial intelligence (AI), machine learning, deep learning and evolutional learning offer supervised or unsupervised algorithmic models through complex neural networks that can predictive more accurately than traditional models. For HCC research, AI has been applied for predicting the risk of HCC, survival outcome, tumor vascular invasion, and systemic treatment responses for HCC. Recently, the application of AI had been introduced into the field of HCC management in Taiwan. In our recent study, the risk of recurrence after surgical resection of HCC could be predicted by an evolutionary learning-derived clinical-radiomic "GARSL" models. This model can further discriminate the risk of recurrence either in high or low risk patients defined by IMbrave 050 study, indicating that the requirement of adjuvant immunotherapy after surgical resection of HCC can be determined by AI model in near future. TACE unsuitability is an emerging issue for intermediate stage HCC. We have recently proposed a novel 7-11 criteria to divide BCLC B HCC into low-, intermediate-, and high tumor burden; and define the outcomes of TACE through different radiologic patterns, both can assist decision making before TACE. By application if AI, the radiologic morphology could be classified through the assistance of AI. Dissimilarities in gut microbiome composition are associated with immune status and susceptibility to immunotherapy. We have identified the associated of gut microbiota and metabolites with outcome of HCC undergoing immune checkpoint inhibitors treatment. Due to the complexity of the gut microbiota, we have tried to apply AI for the classification of "preferable" and "unpreferable" gut microbiota to predict the outcome of HCC immunotherapy. All these studies are ongoing and may have clinical applications in the near future.

**Ji Hoon Kim**

*Korea University*

## Self Introduction

### *Current position*

| | |
|---|---|
| 2017.03 | Professor, Korea University Medical Center, Guro Hospital |

### *Previous position*

| | |
|---|---|
| 2008.03-2017.02 | Associate professor, Korea University Medical Center, Guro Hospital |
| 2011.09-2013.01 | Visiting Associate Professor, Systems Biology, MD Anderson Cancer Center, Houston, Texas, USA |
| 2008.03-2011.02 | Assistant professor, Korea University Medical Center, Guro Hospital |
| 2007.03-2008.02 | Clinical assistant professor, Korea University Medical Center, Guro Hospital |
| 2006.03-2007.02 | Clinical instructor, Liver Cnacer Center, National Cancer Center |
| 2005.05-2006.02 | Clinical instructor, Korea University Medical Center, Guro Hospital |
| 2002.03-2005.04 | Military Physician, Navy, Korea |
| 1998.03-2002.02 | Resident, Korea University Medical Center, Guro Hospital |
| 1997.03-1998.02 | Intern, Korea University Medical Center, Guro Hospital |
| 1991.03-1997.02 | Korea University, College of Medicine |

## Research Interests

My major interest is basic and clinical study for hepatocellular carcinoma, especially, biomarker study for HCC including genomics and proteomics

## Representative Publications

1. Hyun MH, Lee YS, Kim JH*, Lee CU, Jung YK, Seo YS, Yim HJ, Yeon JE, Byun KS. Hepatic Resection Compared to Chemoembolization in Intermediate to Advanced Stage Hepatocellular Carcinoma: A Meta-analysis of High-Quality Studies. Hepatology. 2018 Sep;68(3):977-993. PMID: 29543988
2. Kim JH, Sohn BH, Lee HS, Kim SB, Yoo JE, Park YY, Jeong W, Lee SS, Park ES, Kaseb A, Kim BH, Kim WB, Yeon JE, Byun KS, Chu IS, Kim SS, Wang XW, Thorgeirsson SS, Luk JM, Kang KJ, Heo J, Park YN, Lee JS Genomic predictors for recurrence patterns of hepatocellular carcinoma: model derivation and validation. PLoS Med. 2014 Dec 23;11(12):e1001770 PMID: 25536056
3. Jung ES, Kim JH*, Yoon EL, Lee HJ, Lee SJ, Suh SJ, Lee BJ, Seo YS, Yim HJ, Seo TS, Lee CH, Yeon JE, Park JJ, Kim JS, Bak YT, Byun KS. Comparison of the methods for tumor response assessment in patients with hepatocellular carcinoma undergoing transarterial chemoembolization. J Hepatol. 2013 Jun;58(6):1181-7. PMID: 23395691
4. Hyun MH, Lee YS, Kim JH*, Je JH, Yoo YJ, Yeon JE, Byun KS. Systematic review with meta-analysis: the efficacy and safety of tenofovir to prevent mother-to-child transmission of hepatitis B virus. Aliment Pharmacol Ther. 2017 Jun;45(12):1493-1505 PMID: 28436552
5. Lee YS, Seo YS, Kim JH*, Lee J, Kim HR, Yoo YJ, Kim TS, Kang SH, Suh SJ, Joo MK, Jung YK, Lee BJ, Yim HJ, Yeon JE, Kim JS, Park JJ, Um SH, Bak YT, Byun KS. Can More Aggressive Treatment Improve Prognosis in Patients with Hepatocellular Carcinoma? A Direct Comparison of the Hong Kong Liver Cancer and Barcelona Clinic Liver Cancer Algorithms. Gut Liver. 2018 Jan 15;12(1):94-101 PMID: 28873509

# Dissecting the Divergence: A Comparative Analysis of Stage-Specific HCC Treatment Approaches in Korea

**Ji Hoon Kim** *Korea University*

Hepatocellular carcinoma (HCC) is a highly aggressive and lethal form of liver cancer, accounting for a significant portion of cancer-related deaths worldwide. Despite advancements in diagnostic techniques and treatment strategies, HCC remains a significant global health burden, with a five-year survival rate of only 18%.

Liver transplantation, surgical resection, ablation therapy, transarterial chemo or radio embolization, radiation therapy and systemic targeted or imunooncologic therapy have been mainstay for the treatment of HCC HCC primarily affects and is affected with chronic liver diseases, such as cirrhosis, hepatitis B or C virus infection, and metabolic dysfunction-associated steatotic liver disease. Therefore, both the progression of tumor as well as underlying liver function should be considered to decide primary treatment of HCC in each individual. Consequently, although patients show similar tumor burden and liver function, divergent treatment have received according to institution and country. This is well known problems in HCC management to make the global comparison and standardization difficult.

In this KLCA-TLCA Joint Symposium, I will present the divergence of Korean experience of treatment of HCC patients in various HCC patient and I would like to make you think again about the differences between Taiwan and the world and seek a direction for improving prognosis of HCC patients.


## I-Cheng Lee

*National Yang Ming Chiao Tung University, Taiwan*


## Self Introduction

Dr. I-Cheng Lee is an Associate Professor at the School of Medicine, National Yang Ming Chiao Tung University in Taipei, Taiwan. He also serves as the Secretary General of the Taiwan Liver Cancer Association. Dr. Lee earned his medical degree from the National Yang-Ming University School of Medicine in 2004. He completed his residency in internal medicine, gastroenterology, and hepatology at Taipei Veterans General Hospital, Taiwan. In 2014, he obtained his Ph.D. from the Institute of Clinical Medicine, National Yang-Ming University. Dr. Lee furthered his expertise through basic research training in HBV virology, immunology, and carcinogenesis as a visiting scholar at Prof. James Ou's lab in the Department of Molecular Microbiology and Immunology, Keck School of Medicine, University of Southern California, in 2017. Currently, he serves as an attending physician at the Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital.

His clinical interests include the management of chronic hepatitis B, chronic hepatitis C, steatotic liver disease, cirrhosis and its complications, hepatocellular carcinoma (HCC), cholangiocarcinoma, radiofrequency ablation (RFA), microwave ablation (MWA), endoscopic retrograde cholangiopancreatography (ERCP), single-operator cholangioscopy and endoscopic stenting of the gastrointestinal tract.

## Research Interests

Dr. Lee's research focuses on clinical and translational aspects of chronic hepatitis B and HCC. He delves into host immune regulators and viral factors in their pathogenesis, natural history, and outcomes of chronic hepatitis B and HCC. Dr. Lee also focuses on integrating artificial intelligence (AI) into HCC research, encompassing AI-assisted image diagnosis of HCC and the development of AI-derived prognostic models.

## Representative Publications


1. Lee IC, Tsai YP, Lin YC, et al. A Hierarchical Fusion Strategy of Deep Learning Networks for Detection and Segmentation of Hepatocellular Carcinoma from Computed Tomography Images. Cancer Imaging 2024;24(1):43.
2. Lee IC, Huang JY, Chen TC, et al. Evolutionary Learning Derived Clinical-Radiomic Models for Predicting Early Recurrence of Hepatocellular Carcinoma After Resection. Liver Cancer 2021;10:572-582.
3. Hung YW, Lee IC*, Chi CT, et al. Redefining Tumor Burden in Patients with Intermediate Stage Hepatocellular Carcinoma: the Seven-Eleven Criteria. Liver Cancer 2021;10:629-640. (*Corresponding author)
4. Lee IC, Lei HJ, Chau GY, et al. Predictors of Long-term Recurrence and Survival After Resection of HBV-related Hepatocellular Carcinoma: The Role of HBsAg. Am J Cancer Res. 2021;11(7):3711-3725.
5. Lee IC, Hung YW, Liu CA, et al. A New ALBI-based Model to Predict Survival After Transarterial Chemoembolization for BCLC Stage B Hepatocellular Carcinoma. Liver Int. 201;39(9):1704-1712.

# Dissecting the Divergence: A Comparative Analysis of Stage-Specific HCC Treatment Approaches in Taiwan

**I-Cheng Lee** *National Yang Ming Chiao Tung University, Taiwan*

Hepatocellular carcinoma (HCC) remains a significant global public health issue, requiring tailored approaches to enhance patient outcomes in different regions. This topic focuses on comparing treatment strategies for different stages of HCC in Taiwan. Through a thorough review of literature and clinical practices, we aim to elucidate the subtle variations in treatment approaches across HCC stages. Additionally, we highlight the latest updates to the TLCA guidelines for HCC, emphasizing key revisions and innovative recommendations aimed at improving patient care. These updates cover a wide range of HCC management aspects, including surveillance methods, diagnostic approaches, staging criteria, and therapeutic interventions. We also address the existing disparity between clinical practices, TLCA guidelines, and national health insurance policies.

Through this exploration, we seek to identify divergences and commonalities in HCC management practices, shedding light on opportunities for refinement and optimization. This comparative analysis contributes to a deeper understanding of the multifaceted nature of HCC treatment approaches, facilitating informed decision-making and improved patient care in Taiwan and beyond.

## Reference

1. Management Consensus Guidelines for Hepatocellular Carcinoma: 2023 Update on Surveillance, Diagnosis, Systemic Treatment, and Posttreatment Monitoring by the Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan. Liver Cancer. Published online: February 12, 2024. DOI: 10.1159/000537686


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DAY 3: June 29 (Sat)

# KLCA-KASL Joint Symposium

## We Are Not Alone: Pioneering Combinational Approaches in HCC

**Chairs:**

**Kyung Sik Kim** (Yonsei Univ.)
**Han Chu Lee** (Univ. of Ulsan)

**Andrea Casadei Gardini**

*Vita-Salute San Raffaele University, Italy*

## Self Introduction

### *Work Experience*

- 2014.08-2015.10 Freelence contract at Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS
- 2015.10-2018.12 Permanent contract at Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS
- 2016.07-2018.12 Head phase 1 for gastrointestinal cancer at Istituto Scientifico Romagnolo per lo Studio e Cura dei Tumori (IRST) IRCCS
- 2017.03-2017.12 Fellowship. Clinica Universidad de Navarra, Unit of Hepatology; Pamplona, Spain. Mentory Prof Bruno Sangro.
- 2018.12-2020.09 Senior researcher at University of Modena
- 2020.10 Until now: senior researcher at University Vita e Salute San Raffaele
- 2020.10 Until now: head of hepatobiliary oncology unit at San Raffaele hospital

### *Others Work Experience*

- 2017-present Extensor of hepatocellular Guidelines
- Principal investigator of 59 clinical study (Profit and no-profit); Co-investigator of more of 60 clinical study.

## Representative Publications

1. American Society of Clinical Oncology, gastrointestinal annual conference 2015 (San Francisco); eNOS polymorphisms in relation to outcome in advanced HCC patients receiving sorafenib
2. Associazione Italiana per lo Studio del Fegato 2015 (Rome); eNOS polymorphisms in relation to outcome in advanced HCC patients receiving sorafenib.
3. Second World Conference on Targeting Liver Diseases 2015 (Malta); eNOS polymorphisms in relation to outcome in advanced HCC patients receiving sorafenib.
4. African Organisation for research and training in Cancer 2016 (Marrakech). Exploratory study of histopathological characteristics of hepatocellular carcinoma in african and Caucasian population.
5. Annual conference of the Asian Pacific Association for The Study of the liver 2017: Titolo relazione: Metformin effects on clinical outcome in advanced HCC patients receiving sorafenib: validation study
6. International Liver Cancer Association 2017 Seul: Metformin effects on clinical outcome in advanced HCC patients receiving sorafenib: validation study.
7. International Liver Cancer Association 2018 London: Immune inflammation indicators as predictors of releaps or new HCC in patients treated with direct-acting antiviral (DAA).
8. EASL HCC-summit 2019 Lisboa: Multicentric prospective study of validation of angiogenesisrelated gene polymorphisms in hepatocellular carcinoma patients treated with sorafenib: Results of INNOVATE study.
9. ILCA 2019 Chicago: Multicentric prospective study of validation of angiogenesis-related gene polymorphisms in hepatocellular carcinoma patients treated with sorafenib: Results of INNOVATE study.
10. ESMO GI 2022 : Atezolizumab Plus Bevacizumab Versus Lenvatinib or Sorafenib in Non-Viral Unresectable Hepatocellular Carcinoma: An International Propensity Score Matching Analysis

# Maximizing Early-Stage HCC Outcomes through Neoadjuvant and Adjuvant Strategies

**Andrea Casadei Gardini** *Vita-Salute San Raffaele University, Italy*

**Jin Woo Choi**

*Seoul National University*

## Self Introduction

Dr. Choi serves as a Clinical Associate Professor in the Department of Radiology at the Seoul National University College of Medicine, South Korea. He earned his M.D. from Seoul National University, followed by a residency and fellowship at the Seoul National University Hospital. Further enhancing his academic credentials, Dr. Choi obtained his Ph.D. from the same university in 2022.

Dr. Choi's clinical expertise is centered on vascular and interventional radiology, with a specific emphasis on chemoembolization and radioembolization for liver cancer, interventions related to liver transplantation, and interventions related to portal hypertension. Additionally, Dr. Choi is a pioneering figure in musculoskeletal embolization in Korea.

In the realm of research, Dr. Choi is devoted to the preclinical and clinical advancement of interventional treatments for liver cancer, the development of innovative interventional devices particularly in relation to nanotechnology, and the field of musculoskeletal embolization. His scholarly contributions, including preclinical and clinical studies, have garnered approximately 1,400 citations to date. Presently, Dr. Choi is leading four clinical trials focused on radioembolization and chemoembolization of hepatocellular carcinoma as the principal investigator.

## Research Interests

- Radioembolization of liver cancer
- Chemoembolization of liver cancer
- Musculoskeletal embolization

## Representative Publications

1. Choi JW, Suh M, Paeng JC, Kim JH, Kim HC. Radiation Major Hepatectomy Using Ablative Dose Yttrium-90 Radioembolization in Patients with Large Hepatocellular Carcinoma ≥ 5 cm. J Vasc Interv Radiol 2024; 35:203-212
2. Kim SH, Jung JK, Kim HC, Chung JW, Choi JW. Ideal Size Range for Embolic Agents in Interventional Oncology Experiments Involving Rat Models of Hepatocellular Carcinoma. J Vasc Interv Radiol 2023; 34:23-30
3. Ro DH, Jang M, Koh J, Choi WS, Kim HC, Han HS, Choi JW. Mechanism of action of genicular artery embolization in a rabbit model of knee osteoarthritis. Eur Radiol 2023; 33:125-134
4. Ko G, Choi JW, Shin K, Kim YG, Kang T, Kim D, Lee N, Kim HC, Hyeon T. In Vivo sol-gel Reaction of Tantalum Alkoxide for Endovascular Embolization. Adv Healthc Mater 2022; e2101908.
5. Choi WS, Chang W, Lee M, Hur S, Kim HC, Jae HJ, Chung JW, Choi JW. Spectral CT-Based Iodized Oil Quantification to Predict Tumor Response Following Chemoembolization of Hepatocellular Carcinoma. J Vasc Interv Radiol 2021; 32:16-22.

# Combination of LRT and Systemic Treatments for Intermediate-Stage HCC

**Jin Woo Choi** *Seoul National University*

The combination of locoregional treatments, like transarterial chemoembolization (TACE), with systemic therapies is emerging as a promising approach for managing intermediate-stage hepatocellular carcinoma (HCC). This may be particularly beneficial for patients who do not respond adequately to locoregional treatment (LRT) alone.

Traditionally, intra-arterial treatment has been effective in treating encapsulated simple nodular type HCCs. However, its efficacy significantly diminishes in cases of confluent multinodular, massive, and infiltrative HCCs. These tumor types often show high frequencies of vascular invasion and resistance to intra-arterial treatments. Additionally, repeated intra-arterial treatments, necessary for treating disseminated nodules, can lead to liver function deterioration and worsen patient prognosis.

Lenvatinib has demonstrated significant benefits over TACE alone in TACE-naïve patients with a high tumor burden (beyond the up-to-seven criteria). Immunotherapies have also shown clinical benefits in TACE-unsuitable patients. Atezolizumab combined with bevacizumab has demonstrated superior overall survival (OS), progression-free survival (PFS), and objective response rates (ORR) compared to sorafenib mainly in advanced HCC, suggesting potential benefits for intermediate-stage HCC as well.

Recently, the EMERALD-1 trial presented significant findings: adding durvalumab and bevacizumab to TACE improved PFS in patients with unresectable, embolization-eligible HCC. Adverse events (AEs) were considered manageable and as expected with the individual therapies. This is the first global phase 3 trial to show improved clinical outcomes with a systemic therapy in combination with TACE for HCC patients. Now that the EMERALD-1 trial has provided evidence for combining immunotherapy with TACE, the reshaping of treatment strategies for intermediate-stage HCC will be accelerated.

Future studies, such as the EMERALD-Y90 and EMERALD-3 trials, will further assess the role of checkpoint inhibitors and combination therapies in embolization-eligible HCC. These ongoing advances in anticancer agents and combination strategies are likely to transform the treatment paradigm, potentially making systemic therapy along with radioembolization or TACE the standard approach for intermediate-stage HCC with a high tumor burden.

In conclusion, combining locoregional and systemic treatments offers a comprehensive strategy to address the limitations of TACE alone. This approach may enhance overall treatment efficacy and has the potential to transform the management paradigm for intermediate-stage HCC.

**Sang Min Yoon**

*University of Ulsan*

## Self Introduction

Doctor Sang Min Yoon is currently a professor of Department of Radiation Oncology at Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, having been an associate professor from 2014 to 2020, an assistant professor from 2009 to 2014 and a clinical instructor from 2007 to 2009 at Asan Medical Center, University of Ulsan College of Medicine.

He graduated Kyungpook National University College of Medicine, Daegu, Korea in 1998, and went through the residency courses at Asan Medical Center, University of Ulsan College of Medicine from 2000-2004. He performed clinical fellowship at Asan Medical Center, Samsung Medical Center, and National Cancer Center, Korea from 2004 to 2007. He was also a visiting scholar at the University of California San Diego, Moores Cancer Center in USA from August 2013 to July 2014. He earned his master's degree in 2003 and doctor's degree in 2009 at University of Ulsan.

## Research Interests

His research interest is "Radiation therapy for hepatocellular carcinoma". He has published about 94 international scientific peer review papers in addition to 30 domestic scientific journals.

## Representative Publications

1. Jung J, Joo JH, Kim SY, Kim JH, Choi J, Lee D, Shim JH, Kim KM, Lim YS, Lee HC, Park J, Yoon SM. Radiologic response as a prognostic factor in advanced hepatocellular carcinoma with macroscopic vascular invasion after transarterial chemoembolization and radiotherapy. Liver Cancer 2022;11(2):152-161. (Corresponding author)
2. Jeong Y, Lee KJ, Lee SJ, Shin YM, Kim MJ, Lim YS, Lee HC, Jung J, Park JH, Kim JH, Kim SY, Yoon SM. Radiofrequency ablation versus stereotactic body radiation therapy for small (≤3 cm) hepatocellular carcinoma: A retrospective comparison analysis. J Gastroenterol Hepatol 2021;36(7):1962-1970. (Corresponding author)
3. Yoon SM, Kim SY, Lim YS, Kim KM, Shim JH, Lee D, An J, Jung J, Kim JH, Lee HC. Stereotactic body radiation therapy for small (≤5 cm) hepatocellular carcinoma not amenable to curative treatment: Results of a single-arm, phase II clinical trial. Clin Mol Hepatol 2020;26:506-515. (First author)
4. Park S, Jung J, Cho B, Kim SY, Yun SC, Lim YS, Lee HC, Park J, Park JH, Kim JH, Yoon SM. Clinical outcomes of stereotactic body radiation therapy for small hepatocellular carcinoma. J Gastroenterol Hepatol 2020;35:1953-1959. (Corresponding author)
5. Yoon SM, Ryoo BY, Lee SJ, Kim JH, Shin JH, An JH, Lee HC, Lim YS. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion: a randomized trial. JAMA Oncol 2018;4(5):661-669. (First author)

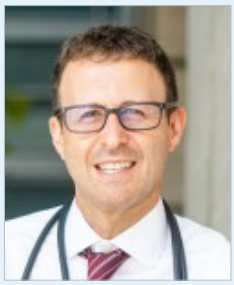
# The Synergistic Role of Radiotherapy in Multimodal HCC Management

**Sang Min Yoon** *University of Ulsan*

External beam radiotherapy (RT) plays a crucial role in the management of hepatocellular carcinoma (HCC). According to the updated 2022 practice guidelines for the management of HCC by the Korean Liver Cancer Association, RT serves not only as an alternative curative treatment for early-stage HCC but also as a treatment to effectively control intrahepatic lesions in locally advanced HCC and improve the quality of life in patients with symptomatic metastatic lesions.

RT can be used alone to achieve therapeutic goals, but it is often combined with other treatments. Efforts are being made to apply RT alongside locoregional treatments such as transarterial chemoembolization to more effectively control intrahepatic lesions and to enhance its efficacy when used with systemic therapies. Recently, there have been ongoing efforts to further improve treatment outcomes by combining RT with immune checkpoint inhibitors, the standard treatment for advanced HCC.

In this presentation, we will explore the combination of RT with various treatments used for HCC, aiming to consider the optimal multidisciplinary approach for the future.



**Richard S. Finn**

*University of California Los Angeles, USA*

## Self Introduction

Dr Finn is a Professor of Clinical Medicine in the Division of Hematology/ Oncology at the UCLA David Geffen School of Medicine and Medical Director of the Clinical Research Unit and Director of the Signal Transduction Program in the Jonsson Comprehensive Cancer Center at UCLA.

He currently splits his time between patient care and laboratory and clinical research. His research interests lie in the development of molecular targeted agents and biomarkers in liver cancer and breast cancer. Dr Finn has served as principal and sub-investigator in trials exploring the use of targeted therapies in breast and hepatobiliary cancers. He has a particular interest in identifying predictive markers of response to novel therapeutics. His work has been published in journals such as the New England Journal of Medicine, The Lancet, Journal of Clinical Oncology, Lancet Oncology, Cancer Research, Clinical Cancer Research, Hepatology, Cancer Cell, Nature Medicine, and elsewhere. Dr Finn has also given oral presentations at major meetings including American Society of Clinical Oncology (ASCO), European Cancer Conference (ECCO/ ESMO), and the American Association of Cancer Research (AACR), International Liver Cancer Association (ILCA), and others. An active cancer researcher, he has been involved in the development of several novel therapeutics in cancer medicine. He has brought several practice changing advances to cancer medicine. He played a lead role in the approval of palbociclib (Ibrance), the first CDK 4/6 inhibitor in cancer medicine, from pre-clinical development to global registration and more recently the combination of atezolizumab and bevacizumab for the treatment of advanced liver cancer.

Dr Finn is a member of ASCO, American Association of Cancer Research (AACR) and the European Society of Medical Oncology (ESMO). He is a past president of the International Liver Cancer Association (ILCA). He is on the editorial board of Clinical Cancer Research, Breast Cancer Research, and Hepatology Communications.

## Representative Publications

1. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150. Atezolizumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020 May 14;382(20):1894- 1905.
2. Finn RS, Ryoo BY, Merle P, Kudo M, Bouattour M, Lim, HY, Breder V, Edeline J, Chao Y, Ogasawara S, Yao T, Garrido M, Chan SL, Knox J, Daniele B, Ebbinghaus SW, Chen E, Zhu AX, Cheng AL. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. J Clin Oncol. 2020 Jan 20;38(3):193-202
3. Finn RS, Ikeda M, Zhu AX, Sung MW, Baron AD, Kudo M, Okusaka T, Kobayashi M, Kumada H, Kaneko S, Pracht M, Mamontov K, Meyer T, Kubota T, Dutcus CE, Saito K, Siegel AB, Dubrovsky L, Mody K, Llovet JM. Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma. J Clin Oncol 2020 Sep 10;38(26):2960-2970.
4. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Lim HY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Ma N, Nicholas A, Wang Y, Li L, Zhu AX, Finn RS. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma
5. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018 Feb 9

# Navigating Future Prospects for Triple Systemic Therapies in HCC

**Richard S. Finn** *University of California Los Angeles, USA*

The landscape of systemic therapies for advanced HCC has rapidly changed in the past few years. Immuno-oncology (IO) doublets have become the front-line standard of care. These include IO-VEGF, IO-IO, and IO-TKI regimens. While there is ongoing debate on which is "best", perhaps the most important question is what is next? Based on these data, median overall survival in front-line advanced HCC is about 24 months with objective response rates of 30% and higher. The challenge moving forward is identifying the next regimen that will push survival further. Approaches include the identification of novel targets for drug development, biomarker selection for patients that benefit most, and the development of combinations that include 3 novel agents. Based on a signal-findings study, the addition of tiragolumab, an anti-TGIT antibody, has shown a signal of efficacy when combined with atezolizumab and bevacizumab and is currently being evaluated in a larg, randomized, Phase 3 study to prove its efficacy in the IMbrave 152 study. We will explore the rational for triplet combinations and the challenges in the development of these including rationale, assessing clinical activity and side effects, and potential impact of economic costs.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THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

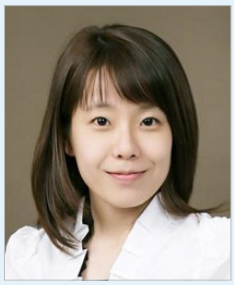
# Special Symposium 2

## The MASH-HCC Nexus: From Epidemiology to Clinical Outcomes

**Chairs:**

**Jung-Hwan Yoon** (Seoul National Univ.)

**Pierce Chow** (National Cancer Centre Singapore, Singapore)



**Jeong-Ju Yoo**

*Soonchunhyang University*

## Self Introduction

### *Education*

Bachelor's Degree of Medicine, 2009, Seoul National University College of Medicine
Master's Degree of Internal Medicine, 2015, Seoul National University College of Medicine
Doctor's Degree of Internal Medicine, 2019, Seoul National University College of Medicine

### *Hospital and Research Appointments*

| | |
|---|---|
| 2009-2010 | Medical Internship, Seoul National University Hospital |
| 2010-2014 | Residency in Internal Medicine, Seoul National University Hospital |
| 2014- 2015 | Research Fellow, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine |
| 2016-2023 | Assistant professor of Internal Medicine, Soonchunhyang University College of Medicine, Department of Hepatology, Soonchunhyang University Bucheon Hospital |
| 2024-present | Associate professor of Internal Medicine, Soonchunhyang University College of Medicine, Department of Hepatology, Soonchunhyang University Bucheon Hospital |

## Research Interests

대한내과학회 정회원, 고시위원
대한소화기학회 정회원, 윤리법제위원
대한간학회 정회원, 보험위원, 연구기획위원, 교육위원, 편집위원
대한간암연구회 정회원, 편집위원, 홍보위원
대한내시경학회 정회원

## Representative Publications

1. Jeong-Ju Yoo, Jeong-Hoon Lee*, Kyung Boon Lee, Jae Moon Koh, Minjong Lee, Young Hoon Choi, and Jung-Hwan Yoon. Pathologically confirmed spontaneous partial regression of hepatocellular carcinoma. Korean J Intern Med. 2014 Feb;86(2):198-203.
2. Jeong-Ju Yoo, Jeong-Hoon Lee*, Sang Hwan Lee, Minjong Lee, Dong Hyeon Lee, Yuri Cho, Yun Bin Lee, Su Jong Yu, Hyo-Cheol Kim, Yoon Jun Kim, Jung-Hwan Yoon, Chung Yong Kim, and Hyo-Suk Lee. Comparison of the Effects of Transarterial Chemoembolization for Advanced Hepatocellular Carcinoma between Patients with and without Extrahepatic Metastases. PLoS One. 2014; 9(11): e113926.
3. Jeong-Ju Yoo, Jeong-Hoon Lee, Jung-Hwan Yoon*, Minjong Lee, Dong Hyeon Lee, Yuri Cho, Eun Sun Jang, Eun Ju Cho, Su Jong Yu, Yoon Jun Kim, and Hyo-Suk Lee. Hepatitis B Virus-Related Glomerulonephritis: Not a Predominant Cause of Proteinuria in Korean Patients with Chronic Hepatitis B. Gastroenterol Res Pract. 2015;2015:126532
4. Jeong-Ju Yoo, Eun Ju Cho, Minjong Lee, Dong Hyeon Lee, Yuri Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon and Yoon Jun Kim*. Efficacy of antiviral prophylaxis in HBsAg-negative, anti-HBc positive patients undergoing hematopoietic stem cell transplantation. Liver Int. 2015 Dec;35(12):2530-6.
5. Yoo JJ, Lee DH, Cho Y, Cho EJ, Lee JH, Yu SJ, Kim YJ, Kim CY, Yoon JH*. Differential sensitivity of hepatocellular carcinoma cells to suppression of hepatocystin transcription under hypoxic conditions. J Bioenerg Biomembr. 2016 Sep 17. [Epub ahead of print]

# Changing HCC Epidemiology: Shifting from Non-MASH to MASH-HCC

**Jeong-Ju Yoo** *Soonchunhyang University*

Hepatocellular carcinoma (HCC) is a major health concern worldwide, particularly in regions with high rates of chronic hepatitis B virus (HBV) infection, such as sub-Saharan Africa and Eastern Asia, where about 80% of HCC cases occur. As the second leading cause of cancer-related deaths in Asia, HCC presents a significant challenge for healthcare systems.

Historically, the primary causes of HCC have been HBV and hepatitis C virus (HCV). However, advancements in vaccination and antiviral treatments have led to a decrease in HBV-related HCC cases. Similarly, the introduction of direct-acting antivirals (DAAs) has significantly reduced the incidence of HCV-related HCC. This shift has resulted in a growing proportion of HCC cases attributed to metabolic-associated steatohepatitis (MASH), a severe form of non-alcoholic fatty liver disease (NAFLD). NAFLD, which encompasses a spectrum of liver conditions from simple fatty liver to non-alcoholic steatohepatitis (NASH), is becoming a leading cause of HCC. This trend is particularly evident in Western countries but is also emerging in Eastern populations. The pathogenesis of NAFLD-related HCC is complex and multifactorial, involving metabolic syndromes such as obesity, diabetes, and dyslipidemia, as well as genetic factors.

The incidence of HCC in patients with NASH varies depending on the presence of cirrhosis. Patients with NASH cirrhosis are at a higher risk of developing HCC compared to those without cirrhosis. The transition from NASH to HCC underscores the importance of early detection and management of metabolic risk factors to prevent the progression of liver disease. Preventive strategies for NAFLD-related HCC include maintaining glycemic control and using medications such as statins, which have been shown to reduce the risk of liver cancer. Additionally, lifestyle modifications, including weight loss and increased physical activity, are crucial in managing NAFLD and reducing the risk of HCC.

Recently, there has been a shift in terminology from NAFLD to MAFLD (metabolic dysfunction-associated fatty liver disease) or MASLD (metabolic-associated steatohepatitis). This change reflects a better understanding of the disease's association with metabolic dysfunction and aims to improve diagnostic criteria and management strategies. The new terminology emphasizes the metabolic risk factors involved in the disease, aligning more closely with its pathophysiology and promoting more targeted therapeutic approaches.

The evolving epidemiology of HCC highlights the need for continuous research and adaptation of clinical practices to address the changing landscape of liver cancer. Understanding the shift from viral hepatitis-related HCC to MASH-related HCC is essential for developing effective prevention, diagnosis, and treatment strategies to combat this global health issue.

**Tim F. Greten**

*National Cancer Institute, USA*

## Self Introduction

Tim F. Greten, M.D., received his medical training at the Christian Albrechts University in Kiel, Germany. He did his internship in Munich followed by a 3-year postdoctoral fellowship at the Johns Hopkins University (Baltimore, Maryland), where he initiated his work in the field of tumor immunology. In 1999, Dr. Greten returned to Hannover Medical School, where he finished his training in Internal Medicine (2003), Medical Oncology (2004) and Gastroenterology (2007). He held an Associate Professor position in the Department of Gastroenterology, Hepatology and Endocrinology in Hannover Medical School. In February 2010, Dr. Greten joined CCR's Medical Oncology Branch as the head of the Gastrointestinal Malignancy Section and was promoted as a tenured Senior Investigator in 2015 and Deputy Branch Chief in 2018 and CCR Deputy Director in 2023.

Dr. Greten has published more than 250 peer-reviewed papers in different journals including Science, Nature, Cell, Cancer Cell, Cancer Discovery and New England Journal of Medicine. In 2023 Dr. Greten was awarded the NCI and CCR Director's Award for Outstanding Mentorship.

## Research Interests

Immunotherapy of Liver Cancer

## Representative Publications

1. Ma, C., et al., NAFLD causes selective CD4(+) T lymphocyte loss and promotes hepatocarcinogenesis. Nature, 2016. 531(7593): p. 253-7.
2. Duffy, A.G., et al., Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. J Hepatol, 2017. 66(3): p. 545-551.
3. Ma, C., et al., Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. Science, 2018. 360(6391): p. eaan5931.
4. Ma, C., et al., Platelets control liver tumor growth through P2Y12-dependent CD40L release in NAFLD. Cancer Cell, 2022. 40(9): p. 986-998 e5.
5. Ruf, B., et al., Tumor-associated macrophages trigger MAIT cell dysfunction at the HCC invasive margin. Cell, 2023. 186(17): p. 3686-3705 e32.

# Immune and Molecular Pathophysiology of MASH-HCC

**Tim F. Greten** *National Cancer Institute, USA*

Metabolic dysfunction-associated steatohepatitis (MASH) is a liver disease that causes inflammation, damage to the liver and finally lead to the development of hepatocellular carcinoma. The incidence of MASH is increasing globally. MASH-HCC has unique molecular and immune traits compared with other aetiologies of HCC. Our group is studying how MASH may affect tumor-specific immune response in preclinical murine MASH/HCC models. In my presentation I will summarize our understanding how MASH affects the function of CD4 and CD8+ T cells and how we can potentially overcome MASH-dependent impairment of T cell responses in the context of immune checkpoint inhibitor therapy.

Based on initial studies demonstrating a specific loss of CD4 T cells in the context of MASH[1] we decided to extend these studies and study CD8 T cell responses in murine models of MASH and liver tumors. We demonstrated how MASH can affect not only CD4 T cell responses, but also CD8 T cell responses and the effect of different types of immunotherapies.[2] In follow-up studies we investigated the underlying mechanism, which was related to T cell mobility and what can be done to overcome MASH related impairment of T cell function. We noticed that metformin treatment was effective and could reverse the negative effects of MASH.[3]

Recently we extended our studies on the effect of MASH and HCC to other immune cells. Platelets, the often-overlooked component of the immune system, have been shown to promote tumor growth. We observed that platelets can inhibit the growth of established HCC in MASH mice. Through pharmacological inhibition and genetic depletion of P2Y12 as well as in vivo transfusion of wild-type (WT) or CD40L(-/-) platelets, we demonstrate that the anti-tumor function of platelets is mediated through P2Y12-dependent CD40L release, which leads to CD8(+) T cell activation by the CD40 receptor.[4]

In summary MASH has been shown to impact immune cell function in the context of HCC and treatment significantly. Future in depth studies are needed to verify whether these effects also apply to patients with MASH and HCC.

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2. Heinrich, B., et al., Steatohepatitis Impairs T-cell-Directed Immunotherapies Against Liver Tumors in Mice. Gastroenterology, 2021. 160(1): p. 331-345 e6.
3. Wabitsch, S., et al., Metformin treatment rescues CD8(+) T-cell response to immune checkpoint inhibitor therapy in mice with NAFLD. J Hepatol, 2022. 77(3): p. 748-760.
4. Ma, C., et al., Platelets control liver tumor growth through P2Y12-dependent CD40L release in NAFLD. Cancer Cell, 2022. 40(9): p. 986-998 e5.


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**Bo Hyun Kim**

*National Cancer Center*

## Self Introduction

### *Education*

| | |
|---|---|
| 1996.03-2002.02 | Medical School, Han Yang University, College of Medicine, Seoul, South Korea |
| 2007.03-2009.02 | Master's degree of Medicine, Seoul National University, College of Medicine, Seoul, South Korea |
| 2009.03-2011.02 | Doctor's degree of Medicine,Seoul National University, College of Medicine, Seoul, South Korea |

### *Profession*

| | |
|---|---|
| 2002.03-2003.02 | Medical Internship, Asan Medical Center, Seoul, South Korea |
| 2003.03-2007.02 | Residency in Internal Medicine, Seoul National University Hospital, Seoul, South Korea |
| 2007.03-2009.02 | Clinical & Research Fellow, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, South Korea |
| 2012.03-2019.01 | Specialist, Center for Liver Cancer, National Cancer Center, Gyeonggi-do, South Korea |
| 2019.02-Present | Specialist, Division of Gastroenterology, Department of Internal Medicine, Center for Liver and Pancreato-biliary Cancer, National Cancer Center, Gyeonggi-do, South Korea |
| 2019.02-Present | Senior Scientist, Division of Clinical Research, National Cancer Center, Gyeonggi-do, South Korea |
| 2024-Present | Adjunct Professor, Department of Cancer Control and Population Health, National Cancer Center Graduate School of Cancer Science and Policy, Gyeonggi-do, South Korea |

## Research Interests

Liver cancer

## Representative Publications

1. Kim BH, Park HC, Kim TH, Koh Y-H, Hong JY, Cho Y, Sinn DH, Park B, Park J-W. Concurrent nivolumab and external beam radiation therapy for hepatocellular carcinoma with macrovascular invasion: a phase II study. JHEP Reports 2024;6: 100991
2. Kim BH, Lee D, Jung KW, Won YJ, Cho H. Cause of death and cause-specific mortality for primary liver cancer in South Korea: A nationwide population-based study in hepatitis B virus-endemic area. Clin Mol Hepatol 2022; 28: 242-253.
3. Kim BH, Cho Y, Park JW. Surveillance for hepatocellular carcinoma: It is time to move forward. Clin Mol Hepatol 2022.
4. Kim BH. Surgical resection versus ablation for early hepatocellular carcinoma: The debate is still open. Clin Mol Hepatol 2022; 28: 174-176.
5. Kim BH, Yu SJ, Kang W, Cho SB, Park SY, Kim SU, Kim DY. Expert consensus on the management of adverse events in patients receiving lenvatinib for hepatocellular carcinoma. J Gastroenterol Hepatol. 2021
6. Kim TH, Koh YH, Kim BH, Kim MJ, Lee JH, Park B, Park JW. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial. J Hepatol. 2021;74(3):603-612.
7. Kim BH, Park J-W. Systemic therapy for advanced hepatocellular carcinoma: consideration for selecting second-line treatment. J Liver Cancer 2021; 21: 124-138.
8. Park JW, Kim YJ, Kim DY, Bae SH, Paik SW, Lee YJ, Kim HY, Lee HC, Han SY, Cheong JY, Kwon OS, Yeon JE, Kim BH, Hwang J. Sorafenib with or without concurrent transarterial chemoembolization in patients with advanced hepatocellular carcinoma: The phase III STAH trial. J Hepatol. 2019;70(4):684-691.

# Strategies for Surveillance and Diagnosis in MASH-HCC

**Bo Hyun Kim** *National Cancer Center*

Most hepatocellular carcinoma (HCC) develops in the setting of cirrhosis from chronic liver disease, with hepatitis B virus (HBV) and hepatitis C virus (HCV) as the predominant risk factor. Current guidelines recommend hepatocellular carcinoma (HCC) surveillance in patients at high risk, such as liver cirrhosis and chronic hepatitis B or C. However, in parallel with the rising prevalence of obesity and metabolic syndrome, metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the leading cause of HCC. The increasing prevalence of metabolic-associated steatohepatitis (MASH) as a precursor HCC necessitates refined strategies for surveillance. Although MASH increases the risk of HCC, targeting the entire MASH patient population for HCC surveillance is not yet considered a cost-effective strategy. Consequently, more specific research is needed to identify which characteristics within the MASH population justify the cost-effectiveness of HCC surveillance.

The traditional surveillance approach involves biannual ultrasound and alpha-fetoprotein (AFP) testing. However, due to the high prevalence of obesity among MASH patients, ultrasound's sensitivity in detecting early HCC is significantly compromised. This challenge necessitates exploring alternative imaging modalities that offer better diagnostic accuracy in this patient group. Novel blood-based biomarkers as non-invasive alternatives could enhance early detection and improve the overall effectiveness of surveillance programs; however, further studies are warranted.

**Yun Bin Lee**

*Seoul National University*

## Self Introduction

Prof. Yun Bin Lee is a Professor at the Department of Internal Medicine, Seoul National University Hospital. Prof. Lee graduated from Seoul National University College of Medicine in 2006 and completed her internship, residency, and fellowship at the Department of Internal Medicine at Seoul National University Hospital, receiving her diploma in Internal Medicine in 2018.

Since 2014, Prof. Lee has been taking a number of roles in the Korean Association of the Study of the Liver and the Korean Liver Cancer Association.

## Research Interests

Prof. Yun Bin Lee is conducting translational research with clinical research, including big data research. In the aspect of clinical research, her research team is working to identify the risk factors for developing liver cancer in patients with chronic liver diseases. In the aspect of translational research, her current research area is regenerative medicine using stem cells. In Prof. Lee's laboratory, research is underway to identify the mechanisms of mitochondrial dysfunction and the efficacy of various mesenchymal stem cells in metabolic dysfunction-associated steatotic liver disease (MASLD).

## Representative Publications

1. A phase 1/2a trial of yttrium-90 radioembolization in combination with durvalumab for locally advanced unresectable hepatocellular carcinoma. Clin Cancer Res. 2023;29(18):3650-3658. (first author)
2. Association between daily aspirin therapy and risk of hepatocellular carcinoma according to metabolic risk factor burden in non-cirrhotic patients with chronic hepatitis B. Aliment Pharmacol Ther. 2023;58(7):704-714. (first & corresponding author)
3. Aspirin Use and Risk of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B With or Without Cirrhosis. Hepatology. 2022;76:492-501. (first & corresponding author)
4. Association of Metabolic Risk Factors With Risks of Cancer and All-Cause Mortality in Patients With Chronic Hepatitis B. Hepatology. 2021;73:2266-2277. (first & corresponding author)
5. Association of Chronic Hepatitis B Infection and Antiviral Treatment with the Development of the Extrahepatic Malignancies: A Nationwide Cohort Study. J Clin Oncol. 2022;40:3394-3405 (contributing author)

# The Future Landscape of Personalized Medicine for Immunotherapies in MASH-HCC

**Yun Bin Lee** *Seoul National University*

Metabolic dysfunction-associated steatotic liver disease (MASLD) and in particular its specific disease stage, metabolic dysfunction–associated steatohepatitis (MASH), represent an increasingly prevalent global healthcare problem tightly associated with metabolic syndrome, including type 2 diabetes and obesity.[1] Being associated with complex metabolic disturbances, MASLD develops through a chronic inflammatory process that is responsible for promoting and maintaining a pro-carcinogenic environment leading to liver cancer. Whereas chronic hepatitis B virus infection remains the most relevant risk factor for HCC globally as of today, MASLD has arisen to be the fastest growing cause of hepatocellular carcinoma (HCC) globally in the last two decades.[2] Chronic inflammation is a critical driver of hepatocyte transformation and carcinogenesis in MASH. The hepatic immune microenvironment in MASH is distinct, characterized by persistent necro-inflammation and immune cell infiltration. Kupffer cells and infiltrating monocytes contribute to the chronic inflammatory milieu that promotes tumorigenesis.[3]

Recent preclinical studies suggest that the efficacy of immunotherapy may be reduced in MASH-related HCC compared to other etiologies like viral hepatitis. This is partly due to the unique immunosuppressive environment in MASH-related HCC, which affects the tumor microenvironment and immune cell function.[4] Overactive CXCR6+ CD8+ T cells in MASH can acquire an autoaggressive phenotype, reducing the effectiveness of immune checkpoint inhibitors (ICIs).[5] In the retrospective study of a small cohort of patients with HCC showed reduced overall survival in patients with NASH-HCC who received anti–programmed cell death protein 1 (PD-1) or anti–programmed cell death ligand 1 (PD-L1) treatment compared with patients with other HCC etiologies.[5]

Identifying and targeting specific immunological pathways in MASH-related HCC is crucial for developing effective personalized therapies. Although the actual therapeutic effects of chemokine CCR2 inhibition in MASH-related HCC necessitate further investigations, inhibitors targeting the CCL2/CCR2 axis can reduce macrophage infiltration and improve anti-tumor immunity.[6] Additionally, strategies that modulate the gut-liver axis and the metabolic milieu, such as anti-CXCR2 therapies combined with ICIs, are being explored to enhance treatment efficacy.[7] N6-methyladenosine (m6A) modifications play a significant role in regulating tumor progression and immune response in MASH-related HCC.[8,9] METTL3, an m6A methyltransferase, has been demonstrated to promote MASH-related HCC by enhancing

SCAP translation, leading to increased cholesterol biosynthesis and immune suppression.[10] Targeting METTL3 with small-molecule inhibitors or nanoparticle-delivered siRNAs, in combination with anti–PD-1, showed synergistic effect on reinvigorating cytotoxic CD8+ T cells and promoting tumor regression in response to immunotherapy.[10] Similarly, silencing the m6A reader YTHDF1 with siRNA enhances the antitumor immune response by modulating m6A-marked mRNAs involved in tumor progression and immune evasion.[11] This strategy improves the effectiveness of existing immunotherapies by restoring immune surveillance and combating tumor-induced immunosuppression.

The integration of advanced diagnostic tools, including liquid biopsies, genomic profiling, and artificial intelligence algorithms, is anticipated to refine patient stratification and optimize therapeutic outcomes. These approaches will enable the identification of high-risk patients and the personalization of immunotherapy regimens, improving prognosis and survival rates for MASH-related HCC patients.

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1. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11-20.
2. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7:6.
3. Tran S, Baba I, Poupel L, Dussaud S, Moreau M, Gelineau A, et al. Impaired Kupffer Cell Self-Renewal Alters the Liver Response to Lipid Overload during Non-alcoholic Steatohepatitis. Immunity 2020;53:627-640 e625.
4. Dudek M, Pfister D, Donakonda S, Filpe P, Schneider A, Laschinger M, et al. Auto-aggressive CXCR6(+) CD8 T cells cause liver immune pathology in NASH. Nature 2021;592:444-449.
5. Pfister D, Nunez NG, Pinyol R, Govaere O, Pinter M, Szydlowska M, et al. NASH limits anti-tumour surveillance in immunotherapy-treated HCC. Nature 2021;592:450-456.
6. Li X, Yao W, Yuan Y, Chen P, Li B, Li J, et al. Targeting of tumour-infiltrating macrophages via CCL2/CCR2 signalling as a therapeutic strategy against hepatocellular carcinoma. Gut 2017;66:157-167.
7. Leslie J, Mackey JBG, Jamieson T, Ramon-Gil E, Drake TM, Fercoq F, et al. CXCR2 inhibition enables NASH-HCC immunotherapy. Gut 2022;71:2093-2106.
8. Chen H, Gao S, Liu W, Wong CC, Wu J, Wu J, et al. RNA N(6)-Methyladenosine Methyltransferase METTL3 Facilitates Colorectal Cancer by Activating the m(6)A-GLUT1-mTORC1 Axis and Is a Therapeutic Target. Gastroenterology 2021;160:1284-1300 e1216.
9. Han D, Liu J, Chen C, Dong L, Liu Y, Chang R, et al. Anti-tumour immunity controlled through mRNA m(6)A methylation and YTHDF1 in dendritic cells. Nature 2019;566:270-274.
10. Pan Y, Chen H, Zhang X, Liu W, Ding Y, Huang D, et al. METTL3 drives NAFLD-related hepatocellular carcinoma and is a therapeutic target for boosting immunotherapy. Cell Rep Med 2023;4:101144.
11. Wang L, Zhu L, Liang C, Huang X, Liu Z, Huo J, et al. Targeting N6-methyladenosine reader YTHDF1 with siRNA boosts antitumor immunity in NASH-HCC by inhibiting EZH2-IL-6 axis. J Hepatol 2023;79:1185-1200.

THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# Special Symposium 3

## Predictive Analytics and Risk Assessment

**Chairs:**

**Won Young Tak** (Kyungpook National Univ.)
**Moon Seok Choi** (Sungkyunkwan Univ.)

**Sangwook Kang**

*Yonsei University*

## Self Introduction

### *Education and Qualifications*

| | |
|---|---|
| 2007 | Ph.D. in Biostatistics Department of Biostatistics, University of North Carolina at Chapel Hill |
| 2001 | B.S. in Statistics Department of Computer Science and Statistics, Seoul National University |

### *Positions*

| | |
|---|---|
| 2023.09- | Department Head, Department of Applied Statistics, College of Commerce and Economics, Yonsei University |
| 2023.03- | Professor, Department of Applied Statistics / Statistics and Data Science, College of Commerce and Economics, Yonsei University |
| 2021.03-2023.02 | Director of Graduate Studies, Department of Statistics and Data Science, College of Commerce and Economics, Yonsei University |
| 2017.03-2023.02 | Associate Professor, Department of Applied Statistics / Statistics and Data Science, College of Commerce and Economics, Yonsei University |
| 2019.08-2020.07 | Visiting Associate Professor, Department of Statistics, College of Liberal Arts and Sciences, University of Connecticut |
| 2013.09-2017.02 | Assistant Professor, Department of Applied Statistics, College of Business and Economics, Yonsei University |
| 2010.08-2013.08 | Assistant Professor, Department of Statistics, College of Arts and Sciences, University of Connecticut |
| 2007.08-2010.08 | Assistant Professor of Biostatistics, Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia |
| 2001/08-2007/08 | Research Assistant, Department of Biostatistics, University of North Carolina at Chapel Hill |

## Representative Publications

1. Choi, D., W. Bae, J. Yan, and S. Kang* (2024). A general model-checking procedure for semiparametric accelerated failure time models. Statistics and Computing 34(3), 117.
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# Statistical Strategies and Common Pitfalls for Risk Calculators

**Sangwook Kang** *Yonsei University*

Risk calculators are pivotal tools in fields like healthcare and finance, offering essential predictions to inform decision-making processes. This presentation delves into the statistical strategies necessary for developing effective risk calculators and identifies common pitfalls that can undermine their accuracy and reliability.

## Introduction

Risk calculators leverage statistical models to forecast the probability of specific outcomes based on input variables. In healthcare, for example, they are instrumental in estimating disease risk or prognosis, which significantly influences patient management and treatment decisions. The efficacy of these calculators hinges on robust statistical methods and an understanding of potential pitfalls that could compromise their validity.

## Statistical Strategies

1. **Data Quality:** Reliable risk calculators are built on high-quality data sets. Critical steps in data preparation include meticulous data collection, handling of missing data and outliers, and data normalization.
2. **Model Selection:** Choosing the right model is crucial. Common models include linear regression, logistic regression, Cox proportional hazards, and machine learning-based models. Factors such as accuracy, interpretability, and computational efficiency should guide model selection.
3. **Validation:** Cross-validation is vital to ensure that models generalize well to new data. Properly utilizing training and testing datasets is necessary to avoid overfitting and underfitting.
4. **Performance Metrics:** Performance is assessed using metrics like Accuracy, Precision, F1 score, ROC-AUC, and C-index. Calibration curves are important for evaluating how well predicted probabilities align with observed outcomes.
5. **Uncertainty Assessment:** Estimating and communicating uncertainty through methods such as con-

fidence intervals is essential for providing stakeholders with a comprehensive understanding of the predictions.

## Common Pitfalls

1. **Overfitting and Underfitting:** Overfitting occurs when a model is too complex and captures noise rather than the underlying pattern, while underfitting happens when a model is too simplistic. Regularization and model complexity adjustments can help mitigate these issues.
2. **Bias and Variability:** Bias can arise from sampling, measurement errors, or data processing. Identifying and correcting bias is crucial for ensuring fair and accurate predictions. Understanding variability aids in interpreting the robustness of model predictions.
3. **Misinterpretation of Results:** Sole reliance on statistical significance can be misleading. It is important to emphasize clinical or real-world significance and appropriately use performance metrics to avoid misinterpretation.
4. **Implementation and Maintenance:** Models require regular updates with new data to remain relevant. Continuous monitoring and re-evaluation are essential for sustained performance and effective integration into decision-making processes.

## Examples and Conclusion

Real-world examples illustrate the practical application of these strategies and the ramifications of common pitfalls. Successful risk calculators, such as the MELD score for liver disease prognosis, underscore the importance of rigorous statistical methods. Adhering to these strategies and being mindful of potential pitfalls can significantly enhance the reliability and utility of risk calculators.

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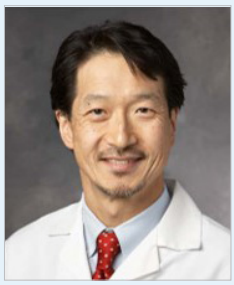

**W. Ray Kim**

*Stanford University, USA*

## Self Introduction

W. Ray Kim, MD is Professor and Chief in the Division of Gastroenterology and Hepatology at Stanford University School of Medicine. Dr. Kim earned his medical diploma at Seoul National University. After moving to the US, he received his GI and hepatology training at Mayo Clinic College of Medicine. He rose through the ranks to be a Professor of Medicine at Mayo. In 2013, he assumed his current position at Stanford.

He is currently serving as President of the American Association for the Study of Liver Disease.

## Research Interests

Dr. Kim's research interest has been in outcomes modeling in chronic liver disease. His research accomplishments include development of the Model for End Stage Liver Disease (MELD) and the Steatosis-Associated Fibrosis Estimator (SAFE) score. His research has produced >250 original publications to date with an h-index of >90.

# The Evolution and Implications of MELD Score: Version 3.0

**W. Ray Kim** *Stanford University, USA*

**Grace L. Su**

*University of Michigan, USA*

## Self Introduction

Undergraduate- Yale University
Medical School- University of Chicago, Pritzker School of Medicine
GI Fellowship- University of Pittsburgh
President-Elect, American Association for the Study of Liver Diseases
Professor of Medicine and Surgery, University of Michigan Medical School
Associate Chief, Medicine Service, VA Ann Arbor Healthcare System
Chief, Gastroenterology and Hepatology, VA Ann Arbor Healthcare System
Director of the Morphomics analysis group, University of Michigan

## Research Interests

- Analytic Morphomics for the diagnosis, treatment, and risk stratification of chronic liver disease.
- Novel methods for delivering subspecialty care and improving access.
- Digital biomarkers in cancer

## Representative Publications

1. Su GL, Zhang P, Belancourt PX, Youles B, Enchakalody B, Perumalswami P, Waljee A, Saini S. Incorporation of quantitative imaging data using artificial intelligence improves risk prediction in veterans with liver disease. Hepatology. 2023 Dec 29. doi: 10.1097/HEP.0000000000000750. Epub ahead of print. PMID: 38156985.
2. Mazumder NR, Enchakalody B, Zhang P, Su GL. Using Artificial Intelligence to Predict Cirrhosis From Computed Tomography Scans. Clin Transl Gastroenterol. 2023 Oct 1;14(10):e00616. doi: 10.14309/ctg.0000000000000616. PubMed PMID: 37436183; PubMed Central PMCID: PMC10584300
3. Horbal SR, Belancourt PX, Zhang P, Holcombe SA, Saini S, Wang SC, Sales AE, Su GL. Independent Associations of Aortic Calcification with Cirrhosis and Liver Related Mortality in Veterans with Chronic Liver Disease. Dig Dis Sci. 2024 Apr 23. doi: 10.1007/s10620-024-08450-5. Epub ahead of print. PMID: 38653948.
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# Analytic Morphomics for Predicting Outcomes of Liver Disease

**Grace L. Su** *University of Michigan, USA*

Analytic morphomics refers to the detailed and quantitative analysis of body morphology (shape and structure) through advanced imaging techniques such computed tomography (CT) scans. This approach aims to provide precise and reproducible measurements of various body tissues and structures to uncover associations with diseases, surgical outcomes, and other health-related factors.[1-3] Morphomics, akin to the field of radiomics, involves the extraction and analysis of large amounts of quantitative features from medical imaging. Where traditional radiomics may focus on disease-specific features such as tumor size or vascularity, analytic morphomics broadens the scope to assess and quantify systemic characteristics such as liver/spleen morphology, skeletal muscle mass, subcutaneous and visceral fat, aortic calcification, and bone density. These measurements can provide insight into a patient's physiological state, including their frailty, nutritional status, and functional reserve.[4-6]

In the context of predicting outcomes in liver disease, morphomic analysis can be particularly insightful. Cross sectional imaging such as CT scans provide an opportunity to quantify the liver's status including steatosis and development of cirrhosis. Assessment of muscle mass which may reflect sarcopenia and are critical determinants of clinical outcome in patients with liver disease.[7] Many morphomics features have been shown to improve prediction of clinical outcomes such as hepatic decompensation and death in patients with liver disease.[8-10] Multimodal models which incorporate morphomics with standard laboratory and clinician reported data significantly refines the accuracy of prognostic models.[1]

With the advent of artificial intelligence, automating the analysis and extraction of morphomics features from clinical CT scans has made clinical implementation more realistic.[11] The wealth of digital data embedded within these scans was historically underutilized due to the complexity of quantitative analysis. However automated processing, these data now be accessible to be used either alone or in conjunction classic electronic health data and provide improved risk prediction in patients with chronic liver disease.

In conclusion, analytic morphomics offers a powerful suite of quantitative instruments that are pivotal in advancing the prognosis and clinical outcome prediction for liver disease patients. Through meticulous analysis of morphological data, healthcare professionals can gain a more complete evaluation of liver health, enabling well-informed decision-making concerning patient treatment plans, operative risk assessments, and vigilant tracking of disease progression or response to treatment protocols. The inte-

grative future envisioned for morphomics in liver disease seeks to marry these imaging biomarkers with clinical and molecular information, paving the way for personalized patient care models grounded in precise, predictive insights.

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**Minjong Lee**

*Ewha Womans University*

## Self Introduction

Prof. Minjong Lee is an Associate Professor of the Department of Internal Medicine, Ewha Womans University College of Medicine.

Prof. Lee graduated from Seoul National University College of Medicine with his medical degree in 2005 and Ph.D. in 2016 and completed his internship, residency, and fellowship at the Department of Internal Medicine at Seoul National University Hospital.

Since 2016, Prof. Lee has participated in the publication committee of the Korean Association of the Study of the Liver (2017-2023) and currently, in the research committee of the Korean Association of the Study of the Liver and the publication committee of the Korean Association of Gastroenterology (2024-).

## Research Interests

Chronic hepatitis B, Hepatocellular carcinoma, MASLD

## Representative Publications

1. PAGE-B incorporating moderate HBV DNA levels predicts risk of HCC among patients entering into HBeAg-positive chronic hepatitis B. Journal of Hepatology. 2024; 80(1):20-30.
2. Identification of patients with favorable prognosis after resection in intermediate-stage-hepatocellular carcinoma. International Journal of Surgery. 2024; 110(2):1008-1018.
3. Risk Stratification for Sarcopenic Obesity in Subjects With Nonalcoholic Fatty Liver Disease. Clinical Gastroenterology and Hepatology. 2023; 21(9):2298-2307.e18.
4. Association of Physical Activity With Risk of Liver Fibrosis, Sarcopenia, and Cardiovascular Disease in Nonalcoholic Fatty Liver Disease. Clinical Gastroenterology and Hepatology. 2023; 21(2):358-369.e12.
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# HCC Prediction Models Specific to Underlying Liver Disease

**Minjong Lee** *Ewha Womans University*

Hepatocellular carcinoma (HCC) is a fatal malignant neoplasm with limited therapeutic options due to aggressive progression and high recurrence rates. Accurate prediction of HCC development can help making decisions on the need for adequate HCC surveillance strategies to patients at high risk for HCC development. Several risk prediction models among cohorts of different populations, particularly various etiologies and cirrhosis rates at baseline, for estimating HCC incidence have been reported recently by using simple, efficient, and easily applicable parameters.

Among various etiologies for chronic liver disease, hepatitis B or C virus still remains a major factor in the development of HCC although the use of oral antiviral agents has significantly improved the prognosis of patients with chronic viral infection and reduced the risk of HCC. Numerous studies have been performed to assess the risk of HCC in patients with chronic viral infection and many models have been proposed to predict the risk of developing HCC. However, as each study has different models for predicting HCC development that can be applied depending on the use of antiviral agents, the type of antiviral agents, and specific situations of each patient such as phase change from immune-tolerant to immune-active phases in chronic hepatitis B or sustained viral response in chronic hepatitis C, it is necessary to properly understand characteristics of each model when using it for the evaluation of HCC in patients with chronic viral infection. In addition, because different variables regarding host factors such as cirrhosis, family history of HCC, or diabetes are used to evaluate the risk of HCC development, it is also necessary to assess the risk by carefully verifying which variables are used. Recently, studies have evaluated the risk of HCC using risk prediction models through genetic polymorphism, transient elastography, and artificial intelligence system. These HCC risk predication models are also noteworthy.

In addition to chronic viral hepatitis B or C, metabolic dysfunction-associated steatotic liver disease (MASLD) is also contributing to HCC development. Genetic predisposition and clinical risk factors for MASLD - related HCC have been identified. Although cirrhosis is also a well - known and major risk factor for MASLD - related HCC, the occurrence of MASLD - related HCC in patients without cirrhosis is increasingly recognized and poses a significant challenge regarding HCC surveillance. It is clinically important to understand optimal risk stratification scores and models to identify subsets of MASLD population at high risk who should be enrolled in surveillance programs.


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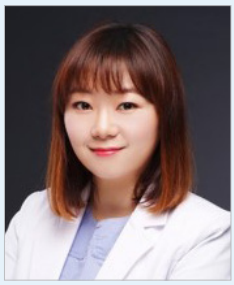
# KAHBPS Symposium 1

## Technical Advances in Minimally Invasive Liver Surgery

**Chairs:**

**Young Seok Han** (Dague Catholic Univ.)
**Hae Won Lee** (Seoul National Univ.)



**Nuri Lee**

*Veterans Health Care Medical Center*

## Self Introduction

Dr. Nuri Lee is working in veterans health service Medical center Seoul, and currently holding a position of Chief of Transplant Center of the VHS medical center.

Dr.Lee graduated from Kosin University College of Medicine with his medical degree in 2009 and completed her residency at the Department of Surgery at Samsung medical Center, receiving her diploma in General Surgery in 2015. Also complete clinical fellow at the Liver and Kidney Transplant Department, and worked at Pusan national hospital as clinical professor in 2019.

- Medical Doctor, Kosin university college of medicin,2009
- Master's Degree, Sungkyunkwan university school of medicine, 2015
- Ph.D. candidate, Sungkyunkwan university school of medicine

## Research Interests

- Liver transplant
- Laparoscopic liver resection
- Solo Robotic liver resection

## Representative Publications

1. Ventilator support in the pretransplant period predisposes early graft failure after deceased donor liver transplantation. Source: Crossref Added: 2023-09-07
2. Careful neurologic examination and treatment for intracranial hemorrhage after liver transplantation in patients with alcoholic cirrhosis: case reports. Source: Crossref Added: 2021-10-27
3. Selected deceased donor liver transplantation in controlled Fournier's gangrene: a case report. Source: Crossref Added: 2021-10-01
4. Case Report of Kidney Paired Donation (KPD) with Desensitization: the Strategy and Experience of 3-Way KPD in Samsung Medical Center. Source: Crossref Added: 2018-01-09
5. Living donor liver transplantation prior to multiple myeloma treatment in a patient with hepatitis B-associated hepatocellular carcinoma and liver cirrhosis: a case report. Source: Nuri Lee Added: 2021-11-15
6. Extracorporeal membrane oxygenation support for refractory septic shock in liver transplantation recipients. Source: Nuri Lee Added: 2021-11-15
7. Application of temporary inflow control of the Glissonean pedicle method provides a safe and easy technique for totally laparoscopic hemihepatectomy by Glissonean approach. Source: Nuri Lee Added: 2021-11-15
8. The possibility of radiotherapy as downstaging to living donor liver transplantation for hepatocellular carcinoma with portal vein tumor thrombus. Source: Nuri Lee Added: 2021-11-15
9. The Impact of Donor-Specific Anti-Human Leukocyte Antigen (HLA) Antibody Rebound on the Risk of Antibody Mediated Rejection in Sensitized Kidney Transplant Recipients. Source: Nuri Lee Added: 2021-11-15
10. Encapsulating peritoneal sclerosis in liver transplant recipients: a report of 2 cases. Source: Nuri Lee Added: 2021-11-15
11. Outcome of living donor liver transplantation using right liver allografts with multiple arterial supply. Source: Nuri Lee Added: 2021-11-15
12. Pre-transplant Predictors for 3-Month Mortality after Living Donor Liver Transplantation. Source: Nuri Lee Added: 2022-05-31

# Considerations and Outcomes in Robotic Hepatectomy for Anatomically Challenging Hepatic Tumors

**Nuri Lee** *Veterans Health Care Medical Center*

## Challenges in Liver Cancer Surgery

The management of hepatocellular carcinoma often involves addressing tumors in challenging segments such as I, VII, VIII, and IVa of the liver. Traditional surgical approaches, including open and laparoscopic techniques, are limited by reduced access and visibility in these areas, complicating the surgical process and potentially impacting the completeness of tumor resection and perioperative safety.

## Advantages of Robotic Systems

Robotic surgical platforms, like the da Vinci Surgical System, offer significant advancements:
- Enhanced Visualization: 3D high-definition views facilitate detailed visualization of complex surgical fields.
- Improved Instrumentation: Robotic arms provide superior articulation, allowing precise maneuvering in restricted spaces.
- Stabilization: Motion scaling and tremor filtration improve surgical precision, essential for meticulous liver resections.

## Evidence Supporting Robotic Approaches

A growing body of evidence supports the use of robotic systems for hepatic resections. Comparative studies have shown that robotic hepatectomy can achieve oncological outcomes similar to those of conventional methods but with added benefits such as reduced blood loss and shorter hospital stays. For example, a systematic review in the 'Journal of Clinical Medicine' detailed these advantages, emphasizing lower perioperative risks and enhanced recovery profiles.

## Illustrative Case Study

Consider a patient with hepatocellular carcinoma located in segment VIII. Using robotic assistance, the surgical team navigated close to major vascular structures with reduced blood loss and without the need for a large surgical incision. This case highlighted the clinical advantages of robotic surgery, in-

cluding enhanced patient safety and quicker postoperative recovery.

## Future Perspectives

The integration of innovations such as intraoperative imaging and artificial intelligence holds promise to further refine robotic hepatectomy. Ongoing research and development are essential to fully leverage the capabilities of robotic technology in complex surgical scenarios.

## Conclusion

Robotic hepatectomy represents a pivotal advancement in the surgical treatment of liver tumors in difficult locations, offering reduced invasiveness and improved clinical outcomes. Continued innovation and research in this field are crucial to maximizing its potential.

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**Wipusit Taesombat**

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## Self Introduction

I am Dr Wipusit Taesombat worked at Hepatobiliary-pancreas surgery and Transplant unit, Department of Surgery, King Chulalongkorn memorial hospital, Chulalongkorn university, Bangkok, Thailand. I have graduated as clinical fellow in advanced laparoscopic surgery from UCSF, USA and fellowship in laparoscopic liver surgery from Samsung medical center, Republic of Korea since 2016. At present my main working involved in minimally invasive surgery for Hepatobiliary and pancreatic disease, particularly laparoscopic liver resection for liver cancer and in liver transplantation.

## Research Interests

Laparosocic Liver Resection
Surgical Treatment for Colorectal Cancer Liver Metastases

## Representative Publications

1. Taesombat W, Kanjanasilp P, Nonthasoot B, Sutherasan M, Vorasittha A, Sirichindakul B. Benefits of simultaneous laparoscopic colorectal surgery and liver resection for colorectal cancer with synchronous liver metastases: Retrospective case-matched study. Ann Med Surg (Lond). 2020;58:120-123.
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4. Taesombat W, Sirichindakul B, Nonthasoot B, Supaphol J, Sutherasan M, Nivatvongs S. Outcomes of hepatic resection for hepatocellular carcinoma with major portal or hepatic vein tumor thrombosis: retrospective cohort study. Asian Biomedicine 2016;10(5).

# Hepatic Vein-Guided Anatomical Liver Resection

**Wipusit Taesombat** *Chulalongkorn University, Thailand*

Laparoscopic liver resection is challenging and technical demanding procedure. Recently, laparoscopic liver resection has become a standard procedure for most types of liver resection. Although previous evidences revealed incongruent details regarding surgical techniques, the basic principle required for liver resection include inflow control, parenchymal transection and outflow control. One of the obstacles of laparoscopic liver resection is transection-direction when performing parenchymal transection, particularly in anatomical liver resection.

Hepatic vein-guided approach is one of techniques that can be used to identify the correct parenchymal transection plane1,2 and also as a landmark for anatomical liver resection. This anatomical plane have lower number of blood vessels and bile ducts. Therefore, it is supposed to have lesser degree of blood loss during parenchymal transection following the course of major hepatic vein especially when performing major hepatectomy2. In addition, hepatic vein-guided approach can be used as a landmark for securely surgical margin when performing liver resection for deep seated tumor or tumor that located close to major hepatic vein.

Several techniques have been employed for identification of major hepatic vein. The first one is ventral approach that required the transection of liver parenchyma to expose major hepatic vein locating deeply in the liver parenchyma3. For cranial approach, this technique is a dissection of the roots of major hepatic vein followed by dissecting along major hepatic vein to caudal side. The last technique is dorsal or Arantius's ligament approach. This technique is used to identify root of middle hepatic vein by dividing Arantius's ligament at its junction to left hepatic vein. This technique is used mostly for laparoscopic left hepatectomy4. The procedures that can facilitate each approach are the followings:

1) Creation of ischemic demarcation line, these need to perform selective inflow control and then perform parenchymal along demarcation line to identify major hepatic vein which is located deep inside the parenchyma.

2) Usage of intraoperative ultrasonography (IOUS), this is technical demanding procedure to identify major hepatic vein during parenchymal transection. These all techniques can be used in combination depend on anatomical variations, tumor location and surgeon preference5.

In conclusion, hepatic vein-guided approach is very useful procedure for laparoscopic liver resection which can provided relatively precise and safe dissection.

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## Self Introduction

### *Education and Training*

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| 2018.03-2021.08 | Doctor of Philosophy, Graduate School of Medicine, Sungkyunkwan University, Seoul, Korea |
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| 2023.03- | Professor, Division of transplantation, Department of Surgery, Samsung Medical Center, Seoul, Korea |

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| | |
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| 2014.02 | Board of Surgery, Republic of Korea (Certificate No: 7213) |

### *Society Memberships*

Korean Medical Association, Member
The Korean Surgical Society, Member
The Korea Society for Transplantation, Member
Korean Association of HBP Surgery, Member
The Korean society of surgical oncology, member
The Korean association for the study of liver, member
The Korean Association of Medical Visualization Artists, board member

# Pre-Reconstructed 3D Images Using AI Model for Liver Resection

**Jinsoo Rhu** *Sungkyunkwan University*

As liver resection is becoming more and more abundantly performed by many liver surgeons around the world, the effort to do it safer is evolving with the innovation of technology. One of the simple but also high-tech measure is to introduce 3D modeling of the liver. Liver is a solid organ with minimal deformity during surgical procedure compared to other soft organs in the abdomen. Furthermore, the functional aspect of liver necessitates proper surgical planning to maintain enough future liver remnant. The 3D model of the liver will help the surgeons plan hepatectomy safer. As the introduction of GPU-based computing and deep learning model for medical images, artificial intelligence is starting to be applied to the field of surgery. Our laboratory has been developing various automated 3D modeling applications for liver surgery. Based on this, we successfully applied the AI model for use in our clinical setting. In this presentation, I am going to introduce some of the examples where AI helps the surgeon plan their surgery.


## Ho Joong Choi

*The Catholic University of Korea*


## Self Introduction

### *Education*

| | |
|---|---|
| 1997-2003 | College of Medicine, The Catholic University, Seoul, Korea |
| 2011-2017 | Ph.D., College of Medicine, The Catholic University, Seoul, Korea |

### *Professional Experience*

| | |
|---|---|
| 2003-2004 | Internship, Catholic Medical Center |
| 2004-2008 | Surgical Residency, Catholic Medical Center |
| 2011-2013 | Fellowship, HBP Division, Department of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |
| 2013-2016 | Clinical Assistant professor of Surgery, Bucheon St. Mary's hospital, The Catholic University of Korea |
| 2016-2017 | Clinical Assistant professor of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |
| 2018-2019 | Clinical Associate professor of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |
| 2019-2023 | Assistant professor of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |
| 2023- | Associate professor of Surgery, Seoul St. Mary's hospital, The Catholic University of Korea |

## Research Interests

- HCC
- LT
- Liver resection
- Minimal invasive liver surgery

## Representative Publications


1. The Clinical Outcomes of Patients with Portal Vein Tumor Thrombi After Living Donor Liver Transplantation. Liver Transplantation 2017.
2. Clinical Course of Hepatic Artery Thrombosis After Living Donor Liver Transplantation Using the Right Lobe. Liver Transplantation 2018.
3. Comparison of the long-term efficacy and safety of generic tacrolimus, Tacrobell, with Prograf in liver transplant recipients. Drug Design, Development and Therapy 2018.
4. Combining Everolimus and Ku0063794 Promotes Apoptosis of Hepatocellular Carcinoma Cells via Reduced Autophagy Resulting from Diminished Expression of miR-4790-3p. International Journal of Molecular Science 2021.
5. Intrahepatic IgA complex induces polarization of cancer-associated fibroblasts to matrix phenotypes in the tumor microenvironment of HCC. Hepatology 2024.

# Overcoming Difficult Anatomical Variations of Minimal Invasive Donor Hepatectomy

**Ho Joong Choi** *The Catholic University of Korea*

Due to a shortage of deceased donor grafts, living donor liver transplantation (LDLT) has increased, gradually. Since living liver donors are healthy adults, the safety of the donors is paramount in LDLT. Next, the recipient's outcome is also important, so both donor safety and graft quality should be considered in LDLT. To date, conventional open donor hepatectomy (ODH) is well established and accepted as the standard treatment option for living donor liver transplantation.

Minimal invasive surgery has the advantage of being less invasive to the patient and faster recovery, so it is widely applied to major hepatectomy. As less invasive techniques have made impressive advances, laparoscopic donor hepatectomy (LDH) has been proposed as an ideal method for donor hepatectomy. LDH can be useful to improve postoperative recovery while meeting the cosmetic needs of young donors. Therefore, minimal invasive donor hepatectomy (MIDH) has emerged as a preferred approach for live liver donation due to its potential benefits in reducing donor morbidity and accelerating postoperative recovery.

However, pure laparoscopic donor right hepatectomy or left hepatectomy is still being performed cautiously because of the need to secure donor safety and high-quality grafts. And for this reason, most MIDH have been performed by experts with sufficient experience in laparoscopic liver resection and donor hepatectomy. To advance from ODH to MIDH, minimizing liver mobilization-related trauma, effectively managing bleeding during transection, and handling of hepatic duct are a few of the hurdles that need to be overcome.

Another hurdle in MIDH is the anatomical variation of the liver. In the beginning, most centers apply strict selection criteria for suitable donors MIDH. The presence of anatomical variations poses unique challenges to the success of MIDH. Anatomy of the liver is well known for its various variations, including vascular and bile duct anomalies. In the context of MIDH, these variations demand meticulous preoperative planning, advanced imaging modalities, and a comprehensive understanding of hepatobiliary anatomy.

Advanced imaging techniques such as three-dimensional reconstructions from computed tomography (CT) or magnetic resonance imaging (MRI) scans play a crucial role in identifying and characterizing

anatomical variations. Surgical planning based on these reconstructions enables surgeons to anticipate challenges and devise customized operative strategies tailored to each donor's unique anatomy.

During the surgical procedure, hilar dissection is an important step for donor hepatectomy. Firstly, identifying the graft inflow structure without endangering the donor side is the main goal of initial stage of hilar dissection. Next, the demarcation line must be confirmed after temporary inflow control. Identifying the exact parenchymal transection line is particularly important in MIDH. It is helpful to use indocyanine green fluorescence when determining the transection line. Recently, most centers performing MIDH depend on an ICG near-infrared fluorescence camera to visualize the exact transection plane of the liver. Another critical step of donor hepatectomy is the precise transection of the bile duct. It is essential for minimizing biliary complications in both donors and recipients. If there is bile duct variation, it is especially important to recognize it through 3D CT or MRCP before surgery, and it may be helpful to use an ICG near-infrared fluorescence camera when transecting the bile duct during surgery.

In conclusion, overcoming difficult anatomical variations in MIDH requires both innovative technologies and meticulous surgical techniques for minimally invasive surgery. By embracing these strategies, surgeons can confidently navigate the complexities of liver anatomy to ensure the safety and success of MIDH.

THE LIVER WEEK 2024

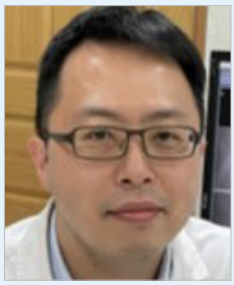
DAY 3: June 29 (Sat)

# KAHBPS Symposium 2

## Biliary Pancreatic Disease in Cirrhotic Patients

**Chairs:**

**Sung Su Yun** (Yeungnam Univ.)
**Hyeyoung Kim** (Soonchunhyang Univ.)



**Shang Yu Wang**

*Chang Gung Memorial Hospital, Taiwan*

## Self Introduction

### *Education*

Medicine Department, Chang Gung University, Taiwan

### *Post-Graduate Education*

PhD, Graduate Institute of Clinical Medical Science, Chang Gung University, Taiwan

### *Employment Record*

- Attending Physician, Trauma & Emergency Surgery, Department of Surgery, Chang Gung Memorial Hospital, Linkou Branch (Sep 2009-Jun 2019)
- Attending Physician, General Surgery, Department of Surgery, Chang Gung Memorial Hospital, Linkou Branch (Jul 2019-present)
- Associate Professor of Surgery, Chang Gung Memorial Hospital, Linkou Branch (Jul 2019-Jun 2023)
- Professor of Surgery, Chang Gung Memorial Hospital, Linkou Branch (Jul 2023-present)

## Research Interests

Biliary Surgery
Pancreatic cancer and surgery
Abdominal wall reconstruction and hernia surgery

## Representative Publications

1. Wang SY, Hung YL, Hsu CC, Hu CH, Huang RY, Sung CM, Li YR, Kou HW, Chen MY, Chang SC, Lee CW, Tsai CY, Liu KH, Hsu JT, Yeh CN*, Yeh TS, Hwang TL, Jan YY, Chen MF. Optimal Perioperative Nutrition Therapy for Patients Undergoing Pancreaticoduodenectomy: A Systematic Review with a Component Network Meta-Analysis. Nutrients. 2021 Nov 12;13
2. Hung YL, Chen HW, Tsai CY, Chen TC, Wang SY*, Sung CM, Hsu JT, Yeh TS, Yeh CN, Jan YY. The optimal timing of interval laparoscopic cholecystectomy following percutaneous cholecystostomy based on pathological findings and the incidence of biliary events. J Hepatobiliary Pancreat Sci. 2021 Sep;28(9):751-759.
3. Chung HY, Hsu CC, Hung YL, Chen HW, Wong MS, Fu CY, Tsai CY, Chen MY, Wang SY*, Hsu JT, Yeh TS, Yeh CN*, Jan YY Alternative application of percutaneous cholecystostomy in patients with biliary obstruction. Abdom Radiol (NY). 2021 Jun;46(6):2891-2899.
4. Wang SY, Yeh CN*, Jan YY, Chen MF. Management of Gallstones and Acute Cholecystitis in Patients with Liver Cirrhosis: What Should We Consider When Performing the Surgery? Gut Liver. 2021 Jul 15;15(4):517-527.
5. Hung YL, Chong SW, Cheng CT, Liao CH, Fu CY, Hsieh CH, Yeh TS, Yeh CN, Jan YY, Wang SY*. Natural Course of Acute Cholecystitis in Patients Treated With Percutaneous Transhepatic Gallbladder Drainage Without Elective Cholecystectomy. J Gastrointest Surg. 2020 Apr;24(4):772-779.

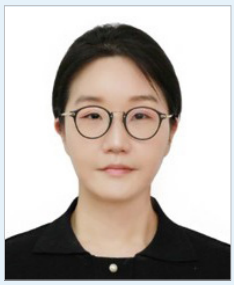
# Management of Acute Cholecystitis

**Shang Yu Wang** *Chang Gung Memorial Hospital, Taiwan*

Acute cholecystitis (AC) is a commonly encountered biliary condition. Over the past few decades, guidelines such as the Tokyo Guidelines (TG) and those from the World Society of Emergency Surgery (WSES) have been developed to improve the management of AC. These guidelines provide diagnostic criteria, severity stratification, and treatment options. Based on these clinical guidelines, practitioners can treat patients with AC using evidence-based approaches.

Cirrhosis is a highly complex condition that induces substantial physiological changes, alters local anatomy, modifies immune status, and introduces various associated risks, all of which impact patient life expectancy. The prevalence of cholelithiasis is approximately 10% to 20%, while symptomatic cholelithiasis occurs in about 20% of individuals with cholelithiasis. Cholelithiasis is more frequent in individuals with cirrhosis compared to the general population, and a longer duration of cirrhosis increases the risk of cholelithiasis. Therefore, clinicians inevitably encounter cirrhotic patients suffering from complicated and symptomatic cholelithiasis, such as AC.

For the treatment of AC, surgical intervention is the definitive approach. However, the timing of surgery depends on the patient's clinical condition, with options being immediate surgery or delayed elective surgery. Additionally, several alternative treatments have been adopted. In the context of cirrhosis, thorough and special considerations should be applied to optimize treatment outcomes.



**Yun Nah Lee**

*Soonchunhyang University*

## Self Introduction

Prof. Yun Nah Lee is an associate professor of the Department of Gastroenterology, SoonChunHyang University School of Medicine. Prof. Lee graduated from SoonChunHyang University School of Medicine with her medical degree in 2006 and completed his internship and residency at the Department of Internal Medicine at SoonChunHyang University Bucheon Hospital, receiving her diploma in Internal Medicine in 2010.

Currently, Prof. Lee is a vice director of general affairs.

## Research Interests

- ERCP
- EUS
- Cholangiosocpy

## Representative Publications

1. Efficacy and safety of direct peroral cholangioscopy using a new multibending ultra-slim endoscope for the management of biliary diseases. J Hepatobiliary Pancreat Sci 2022;29:1292-1299 Lee YN, Moon JH, Lee TH, Yoo HW, Yang JK, Cha SW, Cho YD, Park SH.
2. Prospective randomized trial of a new multibending versus conventional ultra-slim endoscope for peroral cholangioscopy without device or endoscope assistance (with video). Gastrointest Endosc 2020;91:92-101. Lee YN, Moon JH, Choi HJ, Lee TH, Choi HJ, Itoi T, Beyna T, Neuhaus H.
3. The safety of newly developed automatic temperature-controlled endobiliary radiofrequency ablation system for malignant biliary strictures: A prospective multicenter study. J Gastroenterol Hepatol 2019;34:1454-1459 Lee YN, Jeong S, Choi HJ, Cho JH, Cheon YK, Park SW, Kim YS, Lee DH, Moon JH
4. Preliminary study of a modified, nonflared, short, fully covered metal stent for refractory benign pancreatic duct strictures (with videos). Gastrointest Endosc 2020;91:826-33. Lee YN, Moon JH, Choi HJ, JK Park, Cho SJ, Lee TH, Cha SW, Cho YD, Park SH.
5. Tissue acquisition for diagnosis of biliary strictures using peroral cholangioscopy or endoscopic ultrasound-guided fine-needle aspiration. Endoscopy 2019;51:50-59. Lee YN, Moon JH, Choi HJ, Kim HK, Lee HW, Lee TH, Choi MH, Cha SW, Cho YD, Park SH

# Non-Operative Management of Acute Cholecystitis

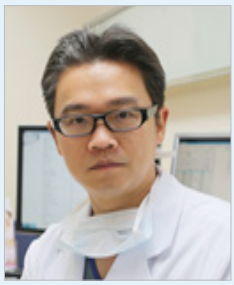
**Yun Nah Lee** *Soonchunhyang University*

Acute cholecystitis is a common medical condition and operative management with laparoscopic or open cholecystectomy is the gold standard treatment. However, the management of acute cholecystitis in the cirrhotic patient remains challenging especially when the patient requires an urgent surgical intervention. Often, cirrhotic patients who are considered unfit candidates for surgery may instead be offered nonoperative management with antibiotics and observation.

Percutaneous transhepatic gallbladder drainage (PTGBD) has demonstrated efficacy in temporary decompression of the gallbladder. However, it is limited by presence of severe coagulopathy, anatomically inaccessible gallbladders, and is associated with adverse events including catheter dislodgment, cellulitis, pneumothorax, bleeding, and infection. In addition, there is a high recurrence rate of cholecystitis if the catheter is removed. Especially, in patients with cirrhosis, PTGBD carry a risk of dislodgement, which may be increased by ascites or hepatic encephalopathy.

Endoscopic gallbladder drainage was developed to supplant the need for PTGBD in treatment of cholecystitis in patients deemed unfit for surgery due to comorbidities or advanced malignancy unable to undergo cholecystectomy. Endoscopic options include endoscopic retrograde cholangiopancreatography (ERCP) with transpapillary placement of a plastic stent into the cystic duct and endoscopic ultrasound-directed gallbladder drainage (EUS-GBD). ERCP and EUS-GBD have demonstrated similar efficacy, however, EUS-GBD has a higher technical success rate, particularly when the gallbladder is distended or the cystic duct is inaccessible due to tortuosity or obstruction. In addition, long-term drainage via cystic duct is a concern due to the narrow diameter of the plastic stent used. Currently, nonsurgical option for management of gallbladder disease has arisen in recent years in the form of EUS-GBD, however, little data exist on its use in patients with cirrhosis. With parallel development in novel endoscopic devices such as fully covered self-expandable metal stents (FCSEMS) and lumen-apposing metal stents (LAMS), substantial technical progress has been made to enable subsequent interventional procedures such as magnifying endoscopy, gallstone removal and polypectomy.

In cirrhotic patients who are not fit for surgery, PTGBD, ERCP with transpapillary stent placement, and EUS-GBD are effective alternative procedures to cholecystectomy. The optimal non-operative treatment modality should be individualized based on patient conditions and the techniques available in the facility.



**Young-Dong Yu**

*Korea University*

## Self Introduction

### *Education*

| | |
|---|---|
| 1994-2000 | Korea University College of Medicine, Seoul, Korea<br>Preliminary Medicine & Doctor of Medicine |
| 2001-2003 | Korea University Graduate School, Seoul, Korea<br>Surgery / Master. |
| 2004-2011 | Korea University Graduate School, Seoul, Korea<br>Surgery / Ph. D. |

### *Residencies/Fellowships*

| | |
|---|---|
| 2000-2001 | Internship: Korea University Medical Center, Seoul, Korea |
| 2001-2005 | Residency: Korea University Medical Center, Department of Surgery, Seoul, Korea |
| 2008-2011 | Clinical Fellowship: Liver Transplantation and Hepatobiliary Surgery, Department of Surgery<br>Asan Medical Center, Seoul, Korea |
| 2018-2019 | Research fellowship: Liver transplantation and HBP Surgery, Department of Surgery<br>New York Presbyterian hospital (Weill Cornell medical center), New York, USA |

## Research Interests

- Circulating tumor cells in HBP surgery and liver transplantation
- Artificial intelligence in HBP surgery and liver transplantation
- Robotic pancreatic surgery

## Representative Publications

1. Usefulness of artificial intelligence for predicting recurrence following surgery for pancreatic cancer: Retrospective cohort study. Lee KS, Jang JY, Yu YD, Heo JS, Han HS, Yoon YS, Kang CM, Hwang HK, Kang S.Int J Surg. 2021 Sep;93:106050. doi: 10.1016/j.ijsu.2021.106050. Epub 2021 Aug 10.
2. Artificial intelligence for predicting survival following deceased donor liver transplantation: Retrospective multi-center study. Yu YD, Lee KS, Man Kim J, Ryu JH, Lee JG, Lee KW, Kim BW, Kim DS; Korean Organ Transplantation Registry Study Group.Int J Surg. 2022 Sep;105:106838. doi: 10.1016/j.ijsu.2022.106838. Epub 2022 Aug 24.PMID: 36028137
3. Whose Liver Is It Anyway? Two Centers Participating in One Living Donor Transplantation. Yu YD, Hwang R, Halazun KJ, Griesemer A, Kato T, Emond J, Samstein B. Liver Transpl. 2019 Nov;25(11):1710-1713. doi: 10.1002/lt.25596. Epub 2019 Aug 21. No abstract available.
4. Should we be reluctant to perform pancreatectomy in patients with chronic liver disease? A single center 10-year experience. Kang WH, Yu YD, Yoon KC, Jo HS, Kim DS.Acta Chir Belg. 2021 Aug 16:1-7. doi: 10.1080/00015458.2021.1963911. Online ahead of print.
5. Single-port robot plus one port (SP + 1) distal pancreatectomy using the new da Vinci SP system. Choi YJ, Jo HS, Kim DS, Yu YD. Langenbecks Arch Surg. 2022 Mar 14. doi: 10.1007/s00423-022-02477-w. Online ahead of print.

# Pancreatic Surgery in Cirrhotic Patients

**Young-Dong Yu** *Korea University*

Cirrhosis has been associated with worse outcomes in patients undergoing general surgical operations. The Child-Pugh score and the model for end stage liver disease (MELD) have been widely applied to predict outcomes in patients with cirrhosis undergoing abdominal surgery. An overall mortality of approximately 20% has been reported, 10% in patients with Child A cirrhosis, 30% in those with Child B cirrhosis, and 80% in those with Child C cirrhosis. Contemporary practice has seen major advances in perioperative care and an improved understanding of liver disease. Nevertheless, contemporary series of patients with cirrhosis undergoing general surgical procedures reveal persistently poor outcomes even in patients undergoing relatively simple operations such as inguinal or ventral hernia repair. As a result, many surgeons have considered major pancreatic surgeries, such as pancreaticoduodenectomy a contraindication if cirrhosis is present. Since there are no formal guidelines and few randomized controlled trials have been performed, the pathophysiological characteristics of LC mean that an individualized approach to the care of the patients is essential. Preoperative optimization after risk stratification is mandatory before surgery. A multidisciplinary team approach involving surgeons, anesthesists, intensivists, and gastroenterologist/hepatologists together with specialized hospital staff with experience in the perioperative management of those patients can improve outcomes.

**Min-Su Park**

*Kyung Hee University*

## Self Introduction

| | |
|---|---|
| Sep 2023-Present | Professor<br>Division of Hepatobiliary Surgery and Organ Transplantation<br>Kyung Hee University Medical Center, Seoul, South Korea |
| Feb, 2013 | Ph.D. degree<br>College of Medicine, Kyung Hee University, Seoul, South Korea |
| Feb, 2008 | M.S. degree<br>College of Medicine, Kyung Hee University, Seoul, South Korea |
| Feb, 2003 | M.D. degree<br>College of Medicine, Kyung Hee University, Seoul, South Korea |

## Research Interests

Liver Transplantation, HBP surgery, MIS, Genetics

## Representative Publications

1. Protective Role of Rapamycin in Fibrotic Liver Ischemia/Reperfusion Injury (C57bl/6 Mouse)
2. Identification of Multiple Hub Genes in Acute Kidney Injury after Kidney Transplantation by Bioinformatics Analysis
3. Living-donor liver transplantation associated with higher incidence of hepatocellular carcinoma recurrence than deceased-donor liver transplantation

# Perihilar Cholangiocarcinoma in Cirrhotic Patients

**Min-Su Park** *Kyung Hee University*

Extrahepatic cholangiocarcinoma (CC) is infrequently reported with a background of liver cirrhosis. Established risk factors for extrahepatic CC include primary sclerosing cholangitis, parasitic infection, choledocholithiasis, and toxins. However, the incidence of extrahepatic CC associated with hepatitis virus-induced cirrhosis is estimated to be 0.3% per year. The relationship between hepatitis virus-induced cirrhosis and CC is still unclear and there are conflicting results in the literature which mandate further studies.

Traditionally, cirrhosis has been considered an absolute contraindication to major abdominal operations. The hospital mortality rates have been reported to be 17-38% in cirrhotic patients undergoing any abdominal operation. Cirrhotic patients have an increased tendency to bleeding, sepsis, hepatic decompensation including hepatic coma. Now, major surgical operations can safely be performed in cirrhotic patients with improvement in preoperative care, surgical techniques with minimal intraoperative bleeding, and improvement in medical management.

No guideline has been issued for the management of resectable hilar cholangiocarcinoma in cirrhotic patients. In the presence of cirrhosis, the management of hilar CC requires careful patient selection, good perioperative care, adequate counseling on operative risk, and good decision on the extent of resection. The tumor extent in the biliary system, radial growth of the tumor, and portal vein infiltration are the main determinants of the extent of resection during surgery for hilar CC. In cirrhosis, the surgeon is concerned with the volume and quality of the remnant liver after resection to avoid post-hepatectomy liver failure.

Hilar CC has a dismal prognosis even after R0 resection with an estimated 5 year survival of about 20%. Prognostic factors that are established to affect survival are negative resection margin, caudate lobe resection, lymph node metastasis, and well-differentiated tumor grade. The presence of cirrhosis is independently associated with reduced long-term survival outcomes with the negative effects of these factors. Cirrhosis is relatively common in patients with advanced CC and is associated with increased chemotherapy-induced toxicity and shorter OS.

About two-thirds of Hilar CC are considered unresectable at the time of diagnosis or exploration. When

resective surgery is deemed unfeasible, liver transplantation (LT) could be an effective alternative. The overall survival rates after LT at 1 and 3 years are 91% and 81%, respectively. The overall five-year survival rate after transplantation is 73.

Patients with concomitant liver cirrhosis and hilar CC should not be precluded from surgical resection. Surgical resection should be limited to patients with well-compensated chronic liver diseases. A thorough and precise pre-operative evaluation is needed to assess tumor resectability before subjecting patients to surgical exploration. The extent of surgical resection is dependent on the balance between radicality and adequate hepatic reserve in cirrhotic patients.

## References

1. K. Nomoto, K. Tsuneyama, C. Cheng, et al., Intrahepatic cholangiocarcinoma arising in cirrhotic liver frequently expressed p63-positive basal/stem-cellphenotype, Pathol. Res. Pract. 202 (2) (2006) 71-76.
2. C.K. Hui, M.F. Yuen, W.K. Tso, I.O. Ng, A.O., et al, Cholangiocarcinoma in liver cirrhosis, J. Gastroenterol. Hepatol. 18 (2003) 337-341.
3. J.J. Kloek, F.J. Ten Kate, O.R.C. Busch, D.J. Gouma, et al Surgery for extrahepatic cholangiocarcinoma: predictors of survival. HPB 10 (2008) 190-195.
4. Abdelwahab M, El Nakeeb A, Salah T, et al. Hilar cholangiocarcinoma in cirrhotic liver: a case-control study. Int J Surg. 12, (2014} 762-767.

THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# KAHBPS Symposium 3

## Surgical Liver Resection of HCC in Various Conditions

**Chairs:**

**Yang-Seok Koh** (Chonnam National Univ.)
**Bong-Wan Kim** (Ajou Univ.)

**Jae Hyun Kwon**

*Hallym University*

## Self Introduction

Prof. Jae Hyun Kwon is an Assistant Professor of the Department of Surgery, Hallym University College of Medicine.

Prof. Kwon graduated from Ewha Womans University College of Medicine with her medical degree in 2010 and completed her internship and residency at the Department of Surgery at Asan Medical Center, receiving his diploma in General Surgery in 2015. She earned her MD from the University of Ulsan College of Medicine in February 2015, followed by a PhD from the same institution in February 2018.

Professionally, she has extensive experience in the field of hepatobiliary surgery, having served as a Clinical Fellow and Clinical Instructor in the Division of Liver Transplantation and Hepatobiliary Surgery at Asan Medical Center. Since March 2020, she has held academic positions at Hallym University Sacred Heart Hospital, progressing from Clinical Assistant Professor to her current role as an Assistant Professor in the Department of Surgery at Hallym University College of Medicine.

## Research Interests

Investigations to improve surgical outcomes of hepatobiliary and pancreatic cancer including hepatocellular carcinoma, liver transplantations and integration of artificial intelligence to improve surgical precision and patient outcome.

## Representative Publications

1. Park S#, Kwon JH#, Kim SY, Kang JH, Chung JI, Jang JK, Jang HY, Shim JH, Lee SS, Kim KW, Song GW. Cutoff Values for Diagnosing Hepatic Steatosis Using Contemporary MRI-Proton Density Fat Fraction Measuring Methods. Korean J Radiol. 2022 Dec;23(12):1260-1268.
2. Kwon JH, Lee JW, Lee JW, Lee YJ. Effects of Anatomical or Non-Anatomical Resection of Hepatocellular Carcinoma on Survival Outcome. J Clin Med. 2022 Mar 2;11(5):1369.
3. Kwon JH, Jung DH, Hwang S, Kim KH, Ahn CS, Moon DB, Ha TY, Song GW, Park GC, Yoon YI, Lee SG. Feasibility of modified endarterectomized aortic allograft for middle hepatic vein reconstruction in living donor liver transplantation: A retrospective cohort study. Int J Surg. 2021 Oct;94:106124.
4. Kwon JH, Song GW, Hwang S, Kim KH, Ahn CS, Moon DB, Ha TY, Jung DH, Park GC, Yoon YI, Shim JH, Kim KW, Lee SG. Surgical Outcomes of Spontaneously Ruptured Hepatocellular Carcinoma. J Gastrointest Surg. 2021 Apr;25(4):941-953.

# Management and Prognosis of Ruptured HCC

**Jae Hyun Kwon** *Hallym University*

## 1. Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths globally, particularly prevalent in regions with high incidences of hepatitis B and C infections and non-alcoholic fatty liver disease (NAFLD). Spontaneous rupture of HCC (srHCC) is a critical and often fatal complication, with mortality rates ranging from 25% to 75% in the acute phase.

## 2. Incidence and Risk Factors

The incidence of srHCC varies significantly by region, being more common in Asia and Africa compared to the West. This discrepancy is likely due to the higher prevalence of hepatitis B and C infections in these regions. Factors contributing to srHCC include large tumor size (>5 cm), obesity, non-cirrhotic liver conditions, hypertension, and high levels of total bilirubin (TB).

## 3. Pathophysiology

Several hypotheses explain the mechanisms behind srHCC:

- Vascular Injury Hypothesis: Tumor growth can cause vascular damage, leading to bleeding.
- Venous Congestion Hypothesis: Obstruction of venous outflow increases pressure within the tumor, causing rupture.
- Small Room Hypothesis: Limited space in the liver parenchyma exacerbates the pressure from tumor growth, particularly in the left lobe.

## 4. Clinical Presentation and Diagnosis

Patients typically present with acute abdominal pain, shock, and signs of hemoperitoneum. Diagnostic tools include computed tomography (CT) scans, ultrasonography, and abdominal paracentesis to detect hemoperitoneum.

## 5. Management Strategies

The management of srHCC requires a multidisciplinary approach focusing on hemostasis and stabilization:

(1) Initial Hemostasis: Transarterial embolization (TAE) is the preferred initial treatment for achieving hemostasis, with success rates of 53-100%.

(2) Surgical Intervention: Options include emergency hepatectomy, staged hepatectomy following initial TAE, or other hemostatic surgical techniques depending on the patient's stability and liver function.

(3) Conservative Management: Reserved for patients not suitable for surgery or TAE, though this approach generally has poor outcomes with high mortality rates.

## 6. Prognosis

The prognosis for patients with srHCC is generally poor compared to non-ruptured HCC. Factors such as large tumor size, hypertension, and poor liver function are associated with worse outcomes. Long-term survival rates for patients undergoing hepatectomy after srHCC are lower than those for non-ruptured HCC, with significant differences in overall survival (OS) but not disease-free survival (DFS).

- Immediate Survival: The acute phase post-rupture has high mortality rates, but with timely and effective intervention, survival rates can improve.
- Long-term Survival: Patients who undergo successful hepatectomy may achieve favorable long-term outcomes, although these are still inferior to those for non-ruptured cases. Median overall survival after resection in ruptured cases ranges significantly based on the presence of complications and liver function.

## 7. Conclusion

The management of srHCC is challenging due to its acute presentation and the critical nature of the condition. A combination of early detection, appropriate use of TAE, and timely surgical intervention can improve outcomes. Continuous efforts in HCC surveillance, especially among non-cirrhotic patients with metabolic risk factors, are essential to prevent srHCC and improve overall prognosis.

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1. Xia F, Ndhlovu E, Zhang M, Chen X, Zhang B, Zhu P. Ruptured Hepatocellular Carcinoma: Current Status of Research. Front Oncol. 2022;12:848903.
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3. Lv TR, Liu F, Jin YW, Hu HJ, Ma WJ, Li FY. Meta-analysis of Prognostic Factors for Overall Survival Among Resected Patients with Spontaneous Ruptured Hepatocellular Carcinoma. J Gastrointest Surg. 2023;27(12):2983-3000.
4. Xu X, Chen C, Liu Q, Huang X. A Meta-analysis of TAE/TACE Versus Emergency Surgery in the Treatment of Ruptured HCC. Cardiovasc Intervent Radiol. 2020;43(9):1263-76.
5. Goh MJ, Sinn DH, Kim JM, Lee MW, Hyun DH, Yu JI, et al. Clinical practice guideline and real-life practice in hepatocellular carcinoma: A Korean perspective. Clin Mol Hepatol. 2023;29(2):197-205.

**Alfred Kow**

*National University of Singapore, Singapore*

## Self Introduction

### *Current Positions*

- Head & Senior Consultant, Division of Hepatobiliary & Pancreatic Surgery, Department of Surgery, University Surgical Cluster, National University Health System, NUS
- Senior Consultant, Liver Transplantation Program, National University Center for Organ Transplantation (NUCOT), NUHS
- Vice Chairman of Medical Board (Education), National University Hospital Singapore
- Assistant Dean (Education), Yong Loo Lin School of Medicine, NUS
- Associate Professor, Department of Surgery, Yong Loo Lin School of Medicine, NUS

### *Academic Qualifications*

- Bachelor of Medicine and Bachelor of Surgery (Singapore), NUS (2002)
- Member of Royal College of Surgeons MRCS (Edinburgh), RCS(Ed) (2005)
- Member of Royal College of Surgeons MRCS (Ireland), RCS(Ire) (2005)
- Masters in Medicine (Surgery) (NUS) (2006)
- Fellow of Royal College of Surgeons of Edinburgh (Gen Surg), RCS(Ed) (2009)
- Fellow of Academy of Medicine Singapore (2010)
- Fellow of American College of Surgeons (2016)

## Representative Publications

1. An international multicentre study of protocols for liver transplantation during a pandemic: A case for quadripartite equipoise. Chew CA, Iyer SG, Kow AWC, Madhavan KK, Bonney GK et al. Journal of Hepatology May 2020: 73(4): 873-881.
2. Optimization of Outpatient Transplantation Services During the COVID-19 Pandemic: A South-East Asian Tertiary Organ Transplant Center Experience. Letter to Editor. Tan JKH, Pang NQ, Bonney GK, Kow AWC, Vathsala A, Ganpathy IS. Accepted for publication in British Journal of Surgery July 2020.
3. Onco-fetal Reprogramming of Endothelial Cells Drives Immunosuppressive Macrophages in Hepatocellular Carcinoma. Ankur Sharma, Justine Jia Wen Seow, Charles-Antoine Duterte, Rhea Pai…..Alfred Kow Wei Chieh….Ramanuj DasGupta. Cell 183, October 15, 2020: 1-18.
4. Intratumoral immune heterogeneity as a hallmark of tumour evolution and progression in hepatocellular carcinoma. Phuong Nguyen, Siming Ma, Cheryl Phua, Neslihan Kaya, Hannah Lai, Chun Jye Lim, Jia Qi Lim, Martin Wasser, Liyun Lai, Wai Leong Tam……Shridhar Iyer, Alfred Kow, Yock Young Dan, Alexander Chung…Pierce Kah-Hoe Chow, Weiwei Zhai, Valerie Chew. Nature Communication Nov 2020: 12(1): 1-13.
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6. Jeon AJ, Teo YY, Sekar K, Chong SL, Wu L, Chew SC, Chen J….Kow AWC….Chow P. Multi-region sampling with paired sample sequencing analyses reveals sub-groups of patients with novel patient-specific dysregulation in hepatocellular Carcinoma. BMC Cancer 2023; 23(1): 118. Doi: 10.1186/s12885-022-10444-3. PMID: 36737737.

# Overcoming Small Estimated Future Remnant Liver Volume

**Alfred Kow** *National University of Singapore, Singapore*

Liver resection is the mainstay of potentially curative treatment options for patients with liver malignancies as well as benign liver lesion. In addition, it is also an essential component of living donor liver transplant where a healthy donor's liver is partially resected to serve as a graft to be implanted into a potential recipient.

All this is made possible due to the unique nature of the liver, whereby it is a large solid organ that has regenerative function. In addition, although the liver is one large solid organ, the anatomical structures within it, namely the hepatic artery, portal vein, hepatic vein and bile ducts can be further divided into independently functioning segments (based on the Couinaud's anatomical segments). Each segment of the liver is served by a set of porta-hepatic structures, wrapped in the glisson's sheath with the HA, PV and BD going to that segment, and a corresponding hepatic vein outflows. All these allow precise resection of a portion of the liver and maintain minimal FLR that is essential for the liver to function and undergo regeneration.

While liver resections have become very safe in recent decades due to the improvement in surgical techniques and peri-operative management, the risk of liver failure post-liver resection remains the chief concerns of the liver surgeons. This may be directly related to the small FLR of the liver after resection. Oftentime, a small FLR is the main reason for declaring irresectability of the liver lesion. However, many strategies have been explored to try to overcome small estimated FLR volume in liver resection. These strategies can be divided into pre-operative, intra-operative and post-operative settings.

In this talk, I shall attempt to highlight some of the strategies that have been used to overcome the small FLR issue in liver surgeries.

**Sang Jin Kim**

*Korea University*

## Self Introduction

Prof. Sang Jin Kim graduated from Sungkyunkwan University of Medicine in 2010 and finished his internship and residency at the Department of Surgery at Samsung Medical Center. Also, he finished the fellowship in the Transplantation division in Samsung Medical Center.

Since 2021, Prof. Sang Jin Kim work as a professor of the Department of Surgery, Korea University Ansan Hospital. He performs lots of laparoscopic and robotic liver resection with Liver and Kidney transplantation.

## Research Interests

Hepatocellular carcinoma, Liver resection, Liver transplantation

## Representative Publications

1. Detecting Donor-Derived DNA by Real-Time PCR in Recipients Suspected of Graft-Versus-Host-Diseases After Liver Transplantation: A Case Series and Literature Review. Ann Transplant 2023.
2. The clinical impact of donor against recipient HLA one way mismatch on the occurrence of graft versus host disease in liver transplantation. Sci Rep 2022.
3. Prediction models of hepatocellular carcinoma recurrence after liver transplantation: A comprehensive review. Clin Mol Hepatol 2022.

# Large HCC in Surgical Resection Era

**Sang Jin Kim** *Korea University*

Hepatocellular carcinoma (HCC) is the sixth most common cancer and ranks third in mortality worldwide. The Barcelona Clinic Liver Cancer (BCLC) staging and classification system stratifies treatment methods according to tumor size, number, and liver function.[1] Western guidelines, such as those from the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer (EASL-EORTC), typically recommend liver resection (LR) only for patients with 2–3 nodules within 3 cm or a single nodule of any size without vascular invasion.[2] In contrast, Asian guidelines from Japan, China, and Korea provide more flexibility for LR.[3,4]

Liver resection continues to play a significant role even in cases of large HCC (≥ 10 cm), with numerous studies showing a 5-year survival rate of 30-40%.[5,6] However, survival and outcomes vary depending on specific factors. Some studies indicate that tumors with vascular invasion, underlying liver cirrhosis, satellite nodules, capsular infiltration, or an AFP level ≥ 100 ng/ml worsen outcomes after LR. Additionally, downstaging procedures such as pre-operative trans-arterial chemoembolization (TACE), trans-arterial radioembolization (TARE), or radiation therapy (RT) can support LR and lead to favorable outcomes. One review article reported that 2,477 TACE-pretreated patients with large HCC had higher disease-free survival (DFS) than 1,513 patients treated with LR alone.[7] A recent study showed favorable DFS in patients with large HCC and portal vein tumor thrombosis (PVTT) who were treated with TARE followed by liver resection[8] When the tumor achieved complete remission after TARE, the DFS was nearly 100% for 4 years post-LR.

Also, recent advances in surgical techniques have reduced the complication risk after LR. Minimally invasive surgeries, such as laparoscopic or robotic LR, have shown comparable tumor-related outcomes with lower blood loss and shorter post-operative stays, even in large or huge HCC cases.[9-11]

In this session, we introduce and review published studies on LR for large and huge HCC, as well as some cases treated at our hospital.

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3. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clinical and molecular hepatology. 2022;28(4):583-705.
4. Hasegawa K, Takemura N, Yamashita T, Watadani T, Kaibori M, Kubo S, et al. Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2021 version (5th JSH-HCC Guidelines). Hepatology research : the official journal of the Japan Society of Hepatology. 2023;53(5):383-90.
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**Boram Lee**

*Seoul National University*

## Self Introduction

### *Education*

2010.03-2014.02 M.D., Gyeongsang National University College of Medicine, Jinju-si, Korea

### *Professional Experience*

**Residency**

2015.03-2019.02 Department of surgery, Seoul National University Bundang Hospital, Gyeonggi-do, Korea

**Fellowship**

2019.03-2021.02 Department of surgery, Seoul National University Bundang Hospital, Gyeonggi-do, Korea

2021.03-2022.03 Clinical Instructor, Department of surgery, Seoul National University Bundang Hospital, Gyeonggi-do, Korea

**Assistant Professor**

03/2022- Department of surgery, Seoul National University Bundang Hospital, Gyeonggi-do, Korea

**Associate Professor**

09/2023 – Present. Department of surgery, Seoul National University Bundang Hospital, Gyeonggi-do, Korea

## Representative Publications

1. Lee B, Lee YT, Park YS, Ahn SH, Park DJ, Kim HH. Learning Curve of Pure Single-Port Laparoscopic Distal Gastrectomy for Gastric Cancer. J Gastric Cancer. 2018 Jun;18(2):182-188.
2. Lee, Boram & Ahn, Soomin & Kim, Haeryoung & Han, Ho-Seong & Yoon, Yoo-Seok & Cho, Jai & Choi, YoungRok. (2019). Donor Specific Antibody Negative Antibody-Mediated Rejection after ABO Incompatible Liver Transplantation Case Report. The Journal of the Korean Society for Transplantation. 32. 10.4285/jkstn.2018.32.4.108.
3. Lee B, Cho JY, Choi Y, Yoon YS, Han HS. Laparoscopic liver resection in segment 7: Hepatic vein first approach with special reference to sufficient resection margin. Surg Oncol. 2019 Sep;30:87-89.
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5. Lee B, Choi Y, Han HS, Yoon YS, Cho JY, Jeong SH, Kim JW, Jang ES, Ahn S. ABO-incompatible liver transplantation using only rituximab for patients with low anti-ABO antibody titer. Ann Hepatobiliary Pancreat Surg. 2019 Aug;23(3):211-218.
6. Lee B, Suh SW, Choi Y, Han HS, Yoon YS, Cho JY, Kim KH, Hyun IG, Han SJ. Solo single incision laparoscopic cholecystectomy using the parallel method; Surgical technique reducing a steep learning curve. Ann Hepatobiliary Pancreat Surg. 2019 Nov;23(4):344-352.
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# Liver Resection in Elderly HCC Patients

**Boram Lee** *Seoul National University*

Hepatocellular carcinoma (HCC) presents a significant clinical challenge, particularly in elderly patients who often have comorbid conditions and reduced physiological reserves. This lecture, titled "Liver Resection in Elderly HCC Patients," aims to explore the complexities and considerations involved in the surgical management of HCC in this demographic.

We will begin by discussing the epidemiology of HCC in elderly populations, highlighting the increasing incidence due to aging demographics and improved surveillance. The lecture will then delve into the preoperative assessment, emphasizing the importance of a comprehensive evaluation of liver function, comorbidities, and overall frailty. Advanced imaging techniques and liver function tests critical for surgical planning will be reviewed.

A significant portion of the talk will focus on the surgical techniques tailored to elderly patients, including the selection criteria for resection versus other therapeutic modalities such as ablation or transplantation. We will discuss the nuances of perioperative management, addressing strategies to mitigate the risks of surgery in older patients, such as enhanced recovery after surgery (ERAS) protocols and careful anesthetic management.

Outcomes of liver resection in the elderly will be analyzed through recent studies and meta-analyses, comparing morbidity, mortality, and long-term survival with younger cohorts. Special attention will be given to postoperative complications and their management, emphasizing the importance of a multidisciplinary approach in the postoperative care of elderly patients.

Lastly, the lecture will cover emerging trends and future directions in the field, including minimally invasive surgical techniques and advancements in prehabilitation and postoperative care. Attendees will gain a comprehensive understanding of the unique challenges and best practices in performing liver resections in elderly HCC patients, ultimately aiming to improve patient outcomes through evidence-based strategies.


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THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# KASL Branch EMW 5 [Daegu-Gyeongbuk]

**Chair:**

**Byoung Kuk Jang** (Keimyung Univ.)

**Jeong Eun Song**

*Daegu Catholic University*

## Self Introduction

Prof. Hong graduated from Daegu Catholic University School of Medicine with his medical degree in 2009 and completed his internship at Seoul Asan Medical Center and residency at the Department of Internal Medicine at Daegu Catholic University Medical Center, receiving his diploma in Internal Medicine in 2015.

Prof. Jeong Eun Song is a Professor of the Department of Internal Medicine, Daegu Catholic University School of Medicine.

Since 2019, Professor Song has been active as a committee member in various organizations such as the Korean Association for the Study of the Liver, the Korean Liver Cancer Association, and the Korean Society of Clinical Ultrasound.

## Research Interests

Viral hepatitis, Autoimmune liver disease, Hepatocellular carcinoma

## Representative Publications

1. Jeong Eun Song, Chang Hyeong Lee, Byung Seok Kim. Efficacy of long-term tenofovir disoproxil fumarate therapy in chronic hepatitis B patients with partial virologic response in real practice. Koran J Intern Med. 2019;34:802-810.
2. Jeong Eun Song, Min Kyu Kang, Yu Rim Lee, et al. Multicenter analysis of clinical features and prognosis of COVID-19 patients with hepatic impairment. Gut Liver. 2021;15:606-615.
3. Min Kyu Kang, Yu Rim Lee, Se Young Jang, Won Young Tak, Young Oh Kweon, Jeong Eun Song, Rohit Loomba, Soo Young Park, Jung Gil Park. Impact of metabolic factors on risk of cardiovascular disease in nondiabetic metabolic dysfunction-associated fatty liver disease. Hepatol Int. 2023 Jun;17(3):626-635.
4. Ah Young Yang, Kiryeong Kim, Hyun Hee Kwon, Jaechan Leem, Jeong Eun Song. 6-Shogaol Ameliorates Liver Inflammation and Fibrosis in Mice on a Methionine- and Choline-Deficient Diet by Inhibiting Oxidative Stress, Cell Death, and Endoplasmic Reticulum Stress. Molecules. 2024 Jan 15;29(2):419.
5. Min Kyu Kang, Jeong Eun Song, Se Young Jang, et al. The Clinical Significance of Myosteatosis in Survival Outcomes in Patients with Hepatocellular Carcinoma Treated with Sorafenib. Cancers (Basel). 2024 Jan 20;16(2):454.

# Is There a Complete Biochemical Response Indicative of Histological Remission in Autoimmune Hepatitis?

**Jeong Eun Song** *Daegu Catholic University*

Autoimmune hepatitis (AIH) is a chronic liver disease characterized by inflammation that typically responds well to immunosuppressive therapy. Without treatment, AIH can progress to cirrhosis, ultimately leading to death due to liver failure. Controlled trials from the 1970s have shown that therapies combining prednisolone with or without azathioprine can enhance survival rates.[1] The aim of treatment in AIH is to suppress liver inflammation, thereby preventing progression to cirrhosis and liver failure.

Elevated serum transaminases are indicative of the intensity of inflammation. Observational studies have linked persistently mild elevations in serum transaminases (1-2 times the upper limit of normal) to poor clinical outcomes,[2] thereby establishing the importance of fully normalizing transaminases as a treatment objective. Additionally, elevated levels of $\gamma$-globulin or immunoglobulin G (IgG) may signal continuing inflammatory processes.[3] Thus, a complete biochemical response (CBR), defined as the normalization of serum transaminases along with $\gamma$-globulin or IgG, is now recognized as the most reliable biochemical indicator of histological remission.[4] While CBR is a valuable non-invasive marker for predicting histological remission in AIH treatment, research indicates that only 55-70% of patients achieve histological remission following a CBR.[3, 5] Furthermore, despite normal biochemical markers, some patients with AIH continue to exhibit histological activity, which poses a significant risk for diminished long-term survival without the need for a transplant.[6, 7] Notably, a long-term study suggested that even moderate histological activity could contribute to AIH progression in patients whose transaminases and globulin levels are normal.[6] Another study highlighted that in AIH patients with cirrhosis, normal transaminases and IgG levels might not reliably reflect histological remission, underscoring the limitations of standard biochemical markers in accurately forecasting disease activity.[8]

While follow-up liver biopsies are the most reliable tests for confirming histological remission, considering the potential complications associated with liver biopsies, it is crucial to explore additional non-invasive markers. Recent studies have reported that transient elastography could be useful for monitoring disease activity and progression in patients with autoimmune hepatitis (AIH). Further research on this is necessary.

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2. Miyake Y, Iwasaki Y, Terada R, Takagi S, Okamaoto R, Ikeda H, Sakai N, et al. Persistent normalization of serum alanine aminotransferase levels improves the prognosis of type 1 autoimmune hepatitis. Journal of hepatology 2005;43:951-957.
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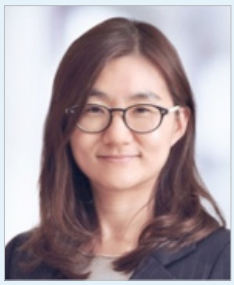
# Pathology Seminar

## Bridging Pathology and Clinical Practice in Liver Disease

**Chairs:**

**Young Nyun Park** (Yonsei Univ.)

**Xiong Ma** (Shanghai Jiao Tong Univ., China)



**Haeryoung Kim**

*Seoul National University*

## Self Introduction

Prof. Haeryoung Kim is a Professor at the Department of Pathology, at Seoul National University College of Medicine. She graduated from Yonsei University College of Medicine in 2000, and completed her internship and residency at Severance Hospital, receiving her diploma in Pathology in 2005.

She has numerous roles in various societies, including Director of Publication of the Korean Liver Cancer Association, Director of Education of the Korean Society of Cytopathology, Director of International Cooperation of the Korean Society of Pathologists. She is currently Editor-in-Chief of the Journal of Liver Cancer, and associated editor for the Journal of Pathology and Translational Medicine and Clinical and Molecular Hepatology.

## Research Interests

Histo-molecular classification of primary liver carcinomas and pancreaticobiliary tumors; medical liver biopsy interpretation; pancreaticobiliary cytology; transplantation pathology

## Representative Publications

1. Ahn S, Jeong SH, Cho EJ, Lee K, Kim G, Kim H. Comparison of four histological scoring systems for autoimmune hepatitis to improve diagnostic sensitivity. Clin Mol Hepatol. 2024;30(1):37-48. (Corresponding author)
2. Hwang YJ, Bae JS, Lee Y, Hur BY, Lee DH, Kim H. Classification of microvascular invasion of hepatocellular carcinoma: correlation with prognosis and magnetic resonance imaging. Clin Mol Hepatol. 2023;29(3):733-746. (Corresponding author)
3. Oh MY, Kim H, Yi NJ, Hong S, Lee JM, Lee S, Hong SK, Choi Y, Lee KW, Suh KS. The fate of donor-type ABO blood group antigen expression in liver grafts in ABO-incompatible adult living donor liver transplantation. J Hepatobiliary Pancreat Sci. 2023;30(7):871-881. (Corresponding author)
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5. Calderaro J, Ghaffari Laleh N, Zeng Q, et al. Deep learning-based phenotyping reclassifies combined hepatocellular-cholangiocarcinoma. Nat Commun. 2023;14(1):8290.
6. Calderaro J, Di Tommaso L, Maillé P, et al. Nestin as a diagnostic and prognostic marker for combined hepatocellular-cholangiocarcinoma. J Hepatol. 2022 Dec;77(6):1586-1597. doi: 10.1016/j.jhep.2022.07.019. Epub 2022 Aug 18.

# Challenges in the Diagnosis and Care of AIH, DILI, and DI-ALH: A Pathologist's Perspective

**Haeryoung Kim** *Seoul National University*

The histopathological diagnosis of autoimmune hepatitis (AIH) poses challenges. Although we may be fortunate enough to encounter cases that perfectly fit the clinicopathological picture of AIH, including the typical histology of plasma cell-rich portal infiltrates and interface activity, the histology is often not as straightforward as in the textbooks. An important example is AIH with acute presentation (including aggravation), because the classical features of AIH are not always seen in such cases. Moreover, the degree of lobular necroinflammation may significantly outweigh that of interface hepatitis or portal lymphoplasmacytic infiltration, potentially leading to a completely different histopathological interpretation.

Scoring systems for research purposes and clinical practice have been devised and developed by the International Autoimmune Hepatitis Group (IAIHG), and these include the revised IAIHG scoring system of 1999 and the 2008 simplified scoring system. For pathologists, important features of AIH that are emphasized in the 1999 revised scoring system consist of interface hepatitis, lymphoplasmacytic infiltration, hepatocyte rosette formation and the absence of biliary changes or other features suggesting alternative etiologies. Interestingly, according to the simplified criteria of 2008, the histology is graded into three categories: (1) "typical histology for AIH", which requires the presence of interface hepatitis, emperipolesis and hepatocyte rosette formation; (2) "histology compatible with AIH", described as a chronic hepatitis pattern of injury with lymphocytic infiltration, but lacking some of the features considered "typical"; and (3) "atypical histology for AIH", in which features suggestive of other etiologies are present. From the pathologist's perspective, emphasizing the presence of emperipolesis and hepatocyte rosette formation in this system may be problematic, as there may be inter/intraobserver variability in interpretation and the sensitivity is modest at best. Moreover, hepatocyte rosettes and emperipolesis are not specific for AIH. With this background, recent studies have proposed modified histological criteria that may be more applicable to daily practice. Most notably, the International AIH Pathology Group proposed a scoring system that accommodates cases with acute lobular hepatitis patterns, resulting in increased sensitivity for the diagnosis of AIH. However, this may be at the expense of a decrease in specificity, and further validation studies with various types of liver injury as control groups would be necessary to improve the specificity of the newer systems.

An important and challenging question for pathologists is the differential diagnosis between AIH and drug-induced liver injury (DILI), especially drug-induced liver injury with AIH-like features (DI-AIH). The histological differences between AIH and DI-AIH remain poorly characterized. Higher degrees of portal and interface inflammation and more prominent plasma cell infiltration have been noted in AIH compared to DI-AIH, and fibrosis has been shown to be more common in AIH compared with DI-AIH. However, it should be noted that fibrosis may not be as prominent in acute AIH cases, and these observations originate from small studies – thus further validation is necessary.

Finally, clinicopathological correlation and active communication between the pathologist and hepatologist are crucial in optimizing the histological diagnosis of AIH. The current IAIHG systems include histology scores, suggesting that histology is pivotal in making a clinical diagnosis of AIH. For the pathologist, having access to the clinical information, including laboratory findings and medication history, facilitates the histopathological interpretation of liver biopsies in this context.


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## Kyung-Ah Kim

*Inje University*


## Self Introduction

### *Education*

| | |
|---|---|
| 1995 | M.D., College of Medicine, Seoul National University, Seoul, Korea |
| 2000 | M.Sc. in Internal Medicine, Graduate School, Seoul National University, Seoul National University, Seoul, Korea |
| 2002 | Ph.D. in Internal Medicine, Graduate School, Seoul National University, Seoul, Korea |

### *Professional Experience*

| | |
|---|---|
| 2002.03-present | Professor, Internal medicine in Ilsan Paik Hospital Inje University |
| 2006.04-2007.05 | Fellowship, Visiting Scholar, MGH, Harvard medical school |
| 2000.03-2002.02 | Hepatology in Seoul National University Hospital |
| 1996.03-2000.02 | Residency, Internal Medicine in Seoul National University Hospital |
| 1995.03-1996.02 | Internship, Seoul National University Hospital |

### *Academic Activities*

| | |
|---|---|
| 2022 | Chairperson of Clinical Practice Guidelines Committee of KASL for the Management of Autoimmune Hepatitis |

## Research Interests

Autoimmune liver disease, Viral hepatitis

## Representative Publications


1. Kim KA, Choi HY, Ki M, Jang ES, Jeong SH.Epidemiological trends and outcomes of primary biliary cholangitis in South Korea between 2009 and 2019. J Gastroenterol. 2023;58(7):682-692.
2. Kim KA, Lee S, Park HJ, et al. Next-generation sequencing analysis of hepatitis C virus resistance-associated substitutions in direct-acting antiviral failure in South Korea. Clin Mol Hepatol 2023;29 (3):779-793
3. Kim HL, Kim KA, Choi GH, Jang ES, Ki M, Choi HY, Jeong SH. A cost-effectiveness study of universal screening for hepatitis C virus infection in South Korea: A societal perspective.Prevalence. Clin Mol Hepatol 2022;28(1):91-104.
4. Kim KA, Kim YS, Park SH, Chung WJ, Choi DH, Jang ES, Jeong SH. Environmental risk factors and comorbidities of primary biliary cholangitis in Korea: a case-control study. Korean J Intern Med. 2021 Mar;36(2):313-321.
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# Challenges in the Diagnosis and Care of AIH, DILI, and DI-ALH: A Clinician's Perspective

**Kyung-Ah Kim** *Inje University*

Drug-induced liver injury (DILI) refers to liver injury caused by drugs, herbals, dietary supplements which has diverse patterns including acute hepatitis, cholestatitic hepatitis or chronic hepatitis. The pathogenesis of idiopathic DILI was not clear but immune response to drug is one of the mechanisms. Drug-induced autoimmune hepatitis (DI-AIH), also called as drug-induced autoimmune-like hepatitis (DI-ALH) is one of the phenotypes of DILI, which is characterized by histological features highly overlapping with classical AIH and often associated with the presence of serum liver autoantibodies and elevated IgG levels.

Differentiating DI-ALH from AIH is challenging, since there is no differentiating biomarker between the two entities. Recent study has proposed criteria to define DI-ALH: (1) drug as a potential trigger of liver injury with autoimmune features and histological findings compatible with AIH, (2) no or incomplete recovery or worsening of liver tests after discontinuation of the drug, (3) corticosteroids requirement or spontaneous recovery, (4) follow - up without immunosuppression and no relapse of AIH at least 6 months after discontinuation of immunosuppression.

ANA and other autoantibodies are frequently associated with DI-ALH. However, ANA and ASMA positivity is common in the general population, particularly in older individuals. Considering autoantibodies are frequently present in DILI regardless of the causative drugs, the presence of ANA might, at least in some patients, represent an epiphenomenon of the acute DILI episode, rather than constituting a specific disease entity or DILI phenotype.

Liver biopsy is useful for confirmation of AIH-like histology and exclusion of other potential diagnoses (e.g., steatohepatitis). DI-ALH mimics the morphological pattern of AIH, including the prominent lympho-plasmocytic infiltrates in portal spaces and interface hepatitis. Histological characteristics do not seem to enable distinction between these entities. Whilst a greater degree of fibrosis has been reported in AIH, this may be a reflection of disease chronicity rather than reflective of etiology.

Autoantibody profiling is being explored to differentiate DI-ALH from AIH. According to Lammert et al, AIH is associated with both IgG and IgM autoantibodies, while DI-ALH is characterized only by IgM. A study by Taubert et al. used protein microarrays to identify elevated polyreactive IgG in AIH, suggesting

it could be a new marker with higher specificity and accuracy than traditional autoantibodies (ANA, SMA, anti-LKM) for diagnosing AIH.

Corticosteroid responsiveness was similar in both the DI-ALH and AIH groups. Discontinuation of immunosuppression was successful in all DI-ALH cases, whereas 65% of patients with AIH had a relapse after withdrawal of immunosuppression. Differentiating DI-ALH from AIH is crucial since most published studies suggest that DI-ALH often resolves spontaneously after withdrawal of the causative drug and affected patients rarely require long-term immunosuppression.


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**Sung Hak Lee**

*The Catholic University of Korea*

## Self Introduction

Prof. Sung Hak Lee currently works as a professor at the department of hospital pathology at Seoul St. Mary's hospital (2022-present)

Prof. Lee received his Doctor of Medicine from The Catholic University of Korea in 2002. He received his Ph.D. from The Catholic University of Korea in 2013. Dr. Lee completed his residency in pathology at the Catholic Medical Center.

After the program, he was an assistant professor, department of hospital pathology at Seoul St. Mary's hospital (2014-2018). Then he was an associate professor in the same institute (2018-2021). Prior to his professorship, he worked as a visiting scholar at Center for biomedical informatics and biostatistics (CB2), University of Arizona and Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic (2017-2018).

## Research Interests

- GI & Hepatobiliary tract pathology
- Artificial intelligence in computational pathology
- Bioinformatics analysis in molecular pathology

## Representative Publications

1. Deep Learning for the Pathologic Diagnosis of Hepatocellular Carcinoma, Cholangiocarcinoma, and Metastatic Colorectal Cancer. Cancers (Basel). 2023 Nov 13;15(22):5389.
2. Deep learning captures selective features for discrimination of microsatellite instability from pathologic tissue slides of gastric cancer. Int J Cancer. 2023 Jan 15;152(2):298-307.
3. Deep learning-based prediction of molecular cancer biomarkers from tissue slides: A new tool for precision oncology. Clin Mol Hepatol. 2022 Oct;28(4):754-772.
4. Spatially Distinct Reprogramming of the Tumor Microenvironment Based On Tumor Invasion in Diffuse-Type Gastric Cancers. Clin Cancer Res. 2021 Dec 1;27(23):6529-6542.
5. Feasibility of deep learning-based fully automated classification of microsatellite instability in tissue slides of colorectal cancer. Int J Cancer. 2021 Aug 1;149(3):728-740.

# Computational Pathology in Liver Diseases

**Sung Hak Lee** *The Catholic University of Korea*

Pathology has a critical role in managing patients with liver tumors and disease. It allows for a definitive diagnosis, provides prognostic information, and enables several histologic scores to be routinely performed to guide therapeutic strategies. Recently, pathology is undergoing a significant transformation because it is possible to transform conventional glass slides into digital files that can be viewed with a computer or screen. The implementation of digital pathology (DP) will revolutionize current practice by providing pathologists with additional tools and algorithms to improve workflow. Furthermore, DP will open up opportunities for development of artificial intelligence (AI)-based tools for more precise and reproducible diagnosis through computational pathology. In research studies, AI methods have been shown to have an astounding ability to predict genetic alterations and identify prognostic and predictive biomarkers directly from routine tissue slides.

This review provides a comprehensive overview of DP/AI tools in development for neoplastic and non-neoplastic diseases, highlights key regulatory considerations, and discusses how these advances may impact the future of liver diseases management.

The applications of AI tools can be considered as a paradigm shift that will change pathology fields in the era of precision medicine. Thus, the traditional role of pathologists in delivering accurate diagnoses or assessing biomarkers for companion diagnostics may be enhanced by AI-powered analysis tools.


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THE LIVER WEEK 2024

# KASL Branch EMW 6 [Jeonbuk]

**Chair:**

**Eun Young Cho** (Wonkwang Univ.)


## Chang Hun Lee

*Jeonbuk National University*


## Self Introduction

### *Education*

| | |
|---|---|
| 2008 | Doctor of Medicine, Jeonbuk National University Medical School |
| 2018 | Master of Science in Internal Medicine, Jeonbuk National University Graduate School |
| 2020 | Doctor of Science in Internal Medicine, Jeonbuk National University Graduate Schoo |
| 2018.05 | Clinical professor – The division of Gastroenterology and Hepatology, Department of Internal Medicine, Jeonbuk National University Hospital |
| 2022.03 | Endowed assistant professor – The division of Gastroenterology and Hepatology, Department of Internal Medicine, Jeonbuk National University Medical School |
| 2023.09 | Assistant professor – The division of Gastroenterology and Hepatology, Department of Internal Medicine, Jeonbuk National University Medical School |
| 2024-2025 | Member, Publication Committee, KASL |
| 2024-2025 | Member, Medical Policy Committee, KASL |

## Research Interests

Hepatology
- Alcoholic liver disease
- Nonalcoholic fatty liver disease
- Viral hepatitis

## Representative Publications


1. Kang MG, Lee CH, Shen C, Kim JS, Park JH. Longitudinal changes in fatty liver index are associated with risk of hepatocellular carcinoma: A nationwide cohort study in Korea. J Hepatol. 2024 May;80(5):e216-e218.
2. Lee CH, Choi GH, Choi HY, Han S, Jang ES, Chon YE, Chang Y, Kim KA, Kim DY, Yim HJ, Kim HL, Jeong SH, Kim IH. Core indicators related to the elimination of hepatitis B and C virus infection in South Korea: A nationwide study. Clin Mol Hepatol. 2023 Jul;29(3):779-793.
3. Lee CH, Kang HJ, Yu SY, Seo SY, Kim SH, Kim SW, Lee SO, Lee ST, Kim IH. Initial treatment response and short-term mortality of spontaneous bacterial peritonitis in cirrhotic patients with hepatocellular carcinoma. Sci Rep. 2023 Apr 13;13(1):6067.
4. Lee CH, Jo HG, Cho EY, Song JS, Jung GM, Cho YK, Seo SY, Kim SH, Kim SW, Lee SO, Lee ST, Kim IH. Maximal diameter of liver abscess independently predicts prolonged hospitalization and poor prognosis in patients with pyogenic liver abscess. BMC Infect Dis. 2021 Feb 11;21(1):171.
5. Lee CH, Choi Y, Seo SY, Kim SH, Kim IH, Kim SW, Lee ST, Lee SO. Addition of probiotics to antibiotics improves the clinical course of pneumonia in young people without comorbidities: a randomized controlled trial. Sci Rep. 2021 Jan 13;11(1):926.
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# Noninvasive Assessment of MASLD and Liver Fibrosis: Clinical Perspectives and Case Reviews

**Chang Hun Lee** *Jeonbuk National University*

Metabolic Associated Steatohepatitis Liver Disease (MASLD), formerly known as Non-Alcoholic Fatty Liver Disease, affects approximately 30% of the global population and is increasingly prevalent worldwide. While liver biopsy has been the gold standard for diagnosing and assessing the disease, there is a growing demand for non-invasive diagnostic methods due to its invasiveness and low patient acceptance. Moreover, there is a rising emphasis on accurate and repeatable non-invasive testing methods with advancements in the treatment of hepatic steatosis and fibrosis. Several non-invasive methods have been introduced and are used for diagnosis and prognostic prediction, as reflected in clinical guidelines. These approaches help overcome the limitations of traditional tissue biopsy, providing patients with safer and more convenient alternatives. They are expected to play a crucial role in effectively identifying and monitoring high-risk patients. Herein, we aim to summarize methods for non-invasive evaluation of MASLD and liver fibrosis, discussing their clinical application through case reviews.

CASE 1.

CASE 2.


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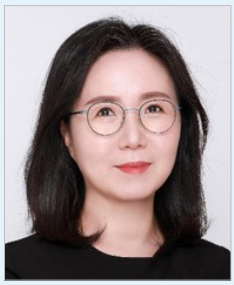
DAY 3: June 29 (Sat)

# Basic Research 2

## Molecular and Cellular Dynamics in Liver Fibrosis and Cancer

**Chairs:**

**Kyun-Hwan Kim** (Sungkyunkwan Univ.)
**Kang Mo Kim** (Univ. of Ulsan)



**Haeng Ran Seo**

*Institut Pasteur Korea*

## Self Introduction

Dr. Haeng Ran Seo is a Team Head of Advanced Biomedical Research Laboratory, Institut Pasteur Korea and is currently holding a representative Professor of the Department of advanced drug discovery & development, UST-IPK University simultaneously.

Dr. Seo graduated from Korea University College of Science with her Ph.D. degree in 2008 and completed his Post-Doctorate at Korea Institute of Radiological and Medical Sciences, Korea (2008-2010), Institut Pasteur Korea (2010-2012).

Dr. Seo has been taking a number of roles, including organizing chairperson of the Korean Society for Biochemistry and Molecular Biology (2022-2024), Women's Bioscience Forum (2023), and Society for Free Radical Research (2023-2024).

## Research Interests

Dr. Seo has tried to establish an efficient and physiologically relevant assay system based on 3D culture techniques (such as organoids and multicellular tumor spheroids) for drug discovery across various fields, including metabolic and inflammatory diseases, cancer, and infectious diseases. In particular, her intensive research areas include the identification of novel therapeutic targets and hits for liver-related diseases, including hepatocellular carcinoma (HCC), nonalcoholic steatohepatitis (NASH)/hepatic fibrosis, and 3D culture-based infectious disease therapy.

## Representative Publications

1. Silva ESS, Kim Y, Kim TH, Kim M, Seo D, Shoi J, Seo HR, Song Y, Shoi GS, Jung YK, Lee KG, Jeong J, Shin JH, Choi D.. Human chemically-derived hepatic progenitors (hCdHs) as a source of liver organoid generation: Application in regenerative medicine, disease modeling, and toxicology testing. Biomaterials 303(2023)122360
2. Lee SY, Kim S, Choi I, Song Y, Kim N, Ryu HC, Lim JW, Kang HJ, Kim J, Seo HR. Inhibition of 11 $\beta$-hydroxysteroid dehydrogenase 1 relieves fibrosis through depolarizing of hepatic stellate cell in NASH. Cell Death Dis. 2022 Nov 29;13(11):1011.
3. Lee SY, Kim S, Song Y, Kim N, No J, Kim KM, Seo HR. Sorbitol dehydrogenase induction of cancer cell necroptosis and macrophage polarization in the HCC microenvironment suppresses tumor progression. Cancer Lett. 2022 Oct 14;551:215960.
4. Song Y, Kim S, Heo J, Shum D, Lee SY, Lee M, Kim AR, Seo HR. Identification of hepatic fibrosis inhibitors through morphometry analysis of a hepatic multicellular spheroids model. Sci Rep. 2021 May 25;11(1):10931.
5. Kim S, Lee M, Song Y, Lee SY, Choi I, Park IS, Kim J, Kim JS, Kim KM, Seo HR. Argininosuccinate synthase 1 suppresses tumor progression through activation of PERK/eIF2 $\alpha$/ATF4/CHOP axis in hepatocellular carcinoma. J Exp Clin Cancer Res.. 2021 Apr 10;40(1):127.

# Drug Discovery for Liver Fibrosis through Employing Functional Morphometry in Multicellular Hepatic Spheroid (MCHS)

**Haeng Ran Seo** *Institut Pasteur Korea*

Hepatic fibrosis results as a consequence of a pattern of severe inflammation that leads to the excessive accumulation of extracellular matrix (ECM) proteins. Advanced liver fibrosis results in cirrhosis and is directly related to the high mortality of cirrhosis. Because liver transplantation is currently the only treatment option for patients with advanced liver fibrosis and cirrhosis, there is an urgent need for the development of effective anti-fibrotic agents for the treatment of hepatic fibrosis.

As an alternative to target-based approaches, there is growing interest in developing phenotypic assays for screening drugs. To overcome liver fibrosis, multicellular hepatocyte spheroid (MCHS) models can be used for high-throughput screening (HTS) to identify anti-fibrotic drugs. The phenotype-based MCHS model, which addresses the problems associated with 2D cultures, reflects the in vivo microenvironment of fibrosis.

We constructed, characterized, and tested an MCHS model that mimics the in vivo microenvironment of liver fibrosis, and we used it to screen for drugs that could treat liver fibrosis effectively. In antifibrotic drug development, the MCHS model provides HTS using phenotypes to discover novel targets and drugs. After MCHS-based screening, the efficacy of epithelial-mesenchymal transition (EMT) and endothelial-mesenchymal transition (EndMT) inhibition is verified through 2D assays, and candidate drugs can be confirmed using an animal model of the disease.

In addition, we found that anti-fibrotic drugs are not only effective in the treatment of liver fibrosis but can also enhance the anti-cancer activity of other therapeutics by increasing tissue permeability, allowing drug delivery to cancer cells of interest.

Collectively, these findings support the potential utility of morphometric analyses of hepatic multicellular spheroid models in the development of new drugs with novel mechanisms for the treatment of hepatic fibrosis and hepatocellular carcinomas.

**Chang-Woo Lee**

*Sungkyunkwan University*

## Self Introduction

Prof. Chang-Woo Lee is a Professor of the Department of Molecular Cellular Biology, Syungkwan University School of Medicine and is currently also a Professore of the Department of Molecular Medicine, Samsung Advanced Institute of Sciences and Technology simultaneously.

Prof. Lee graduated from University of Glasgow, UK (British Embassy Scholarship and Oversea Research Studentship), with his Ph.D. degree in 1998 and did postdoctoral study at the Department of Cell Biology at Harvard Medical School, USA.

After return to Korea, Prof. Lee joined National Cancer Center as independent researcher focusing on the physiological study of cell cycle checkpoint defects in human cancer. In 2006, Prof. Lee has been appointed as Professor at Sungkyunkwan University School of Medicine.

Prof. Lee has been invited to give more than 150 seminars and lectures, including Mayo Clinic, Harvard Medical School and Oxford Univ. Prof. Lee has been taking roles as the member of editorial board of journals, including Mol Cells, IJST, PFM and MCB, and also actively participating as the member of society, including AACR, KASL, KCA, KSMBM, KSMCB, KCB, KSI, KSSCR, and etc.

## Research Interests

Our laboratory is interested in understanding the mechanisms that cancers have evolved to suppress the generation of tumor antigen-specific immune responses and how this knowledge can be exploited for the development of novel and more effective immunotherapy strategies. In particular, we are developing model systems to investigate on how T cells are anergic and/or exhausted during the development of tumor.

In addition, we are currently examining the gain-of-function and loss-of-function physiology from the conditional transgenic, -inducible transgenic, -conventional knockout and conditional knockout mice of Pellino1 ubiquitin ligase and Ssu72 protein phosphatase genes, and further implications of human disease pathogenesis and therapeutics.

## Representative Publications

1. Park EJ*, Kim HS*, Kim SM, Lee DH, Lee JK, Jeon Y, Lim KH, Lee H, and Lee CW. 2023. Ssu72 phosphatase is essential for thermogenic adaptation by regulating cytosolic translation. Nature Communications 14(1097): 1-16 (2023).
2. Park J, Lee SY, Jeon Y, Kim KM, Lee JK, Go J, Park EJ, Yoon JS, Lee H, Shin SJ, Go H, and Lee CW. Pellino1-PKC$\theta$ signaling axis is an essential target for improving anti-tumor CD8+ T lymphocyte function. Cancer Immunology Research 10: 327-342 (2022)
3. Lee JK, Koo SY, Nam HM, Lee JB, Ko J, Kim KM, Park EJ, Kim TJ, Lee H, Go H, and Lee CW. Ssu72 is a T cell receptor-responsive modifier that is indispensable for regulatory T cells. Cellular & Molecular Immunology 18: 1395-1411 (2021).
4. Kim SH, Jeon Y, Kim HS, Lee JK, Lim HJ, Kang DR, Cho HS, Park CK, Lee H, and Lee CW. Hepatocyte homeostasis for chromosome ploidization and liver function is regulated by Ssu72 protein phosphatase. Hepatology 63: 247-259 (2016).
5. Park HY, Go HJ, Song HR, Kim SH, Ha GH, Jeon YK, Kim JE, Lee Ho, Cho HS, Kang HC, Chung HY, Kim CW, Chung DH, and Lee CW. Pellino 1 promotes lymphomagenesis by deregulating BCL6 polyubiquitination. Journal of Clinical Investigation 124: 4976-4988 (2014).
6. Shin HJ, Baek KH, Jeon AH, Chung DH, Lee SJ, Lee HS, Sung YC, McKeon F, and Lee CW. Dual roles of human BubR1, a mitotic checkpoint kinase, in the monitoring of chromosomal instability. Cancer Cell 4: 483-497 (2004).

# Role of Protein Phosphatase in the Development and Treatment of HCC

**Chang-Woo Lee** *Sungkyunkwan University*

Ssu72 is a dual-specific protein phosphatase and is expressed in a tissue-specific manner. Ssu72 was activated by various receptor signaling, such as IL-2R, T cell receptor, PMA and ionomycin, and Toll-like receptor, and localizes at cytoplasmic membrane in many cells. It thus highly possible that Ssu72 acts as a critical modifier in orchestrating the various tissue-specific homeostatic functions as a receptor signal-responsive phosphatase. We initially found that hepatic Ssu72 depletion led to the high incidence of MASLD and MASH development in mice, even without metabolic syndrome-inducing conditions. Moreover, hepatic Ssu72-depleted mice showed the rapid development of MASH with severe fibrosis by additional metabolic syndrome-induction such as western and fructose diet or methionine-choline deficient diet.

To examine whether hepatic Ssu72 might be associated with HCC development, we employed the various chemical- and metabolic syndrome-induced HCC models. In these models, we found that loss of Ssu72 leads to marked susceptibility to HCC development. Importantly, we found the marked increment of the hepatic progenitor pool and the induction of mature hepatocyte-to hepatic progenitor cell conversion in Ssu72-deleted liver in response to liver damage. Significantly, Ssu72 expression was decreased in MASH and HCC patients. The level of Ssu72 was much lower in MASH-associated HCC patients than in non-MASH-associated HCC patients.

Can HCC be treated by introducing Ssu72 because HCC was caused by loss of Ssu72? It would be highly reasonable to say that this would not happen mostly. However, if the Ssu72 plays a substantial role at the upstream signaling of HCC development and is a highly common target in the development of HCC, the introduction of Ssu72 can be a potential approach to treat HCC. In this talk, we will introduce a novel strategy to attenuate HCC using various mouse models and delivery vehicle expressing Ssu72.

**Soon Sun Kim**

*Ajou University*

## Self Introduction

Soon Sun Kim is an Associate Professor at the Department of Gastroenterology, Ajou University School of Medicine. Currently, she serves in this position since March 2020. Previously, she held several roles at the same institution, including Assistant Professor (2016-2020), Clinical Assistant Professor (2012-2016), and Clinical Fellow (2010-2012). She completed her residency and internship in Internal Medicine at Ajou University Hospital. Prof. Kim earned her Ph.D. in Medicine from Ajou University School of Medicine in 2013 and holds a Master's degree and Doctor of Medicine from the same institution.

## Research Interests

- Hepatocellular carcinoma
- Biomarkers
- Non-Alcoholic Fatty Liver Disease (NAFLD)
- Big data
- Microbiome

## Representative Publications

1. Son JA, Weon JH, Baek GO, Ahn HR, Choi JY, Yoon MG, et al. Circulating small extracellular vesicle-derived splicing factor 3b subunit 4 as a non-invasive diagnostic biomarker of early hepatocellular carcinoma. J Exp Clin Cancer Res. 2023;42:288.
2. Kim SS, Lee JY, Park SJ, Choi HJ. Early detection of hepatocellular carcinoma via liquid biopsy: Panel of small extracellular vesicle-derived long noncoding RNAs identified as markers. Mol Oncol. 2021;15:2715-2731.
3. Ahn HR, Baek GO, Yoon MG, et al. Hypomethylation-mediated upregulation of the WASF2 promoter region correlates with poor clinical outcomes in hepatocellular carcinoma. J Exp Clin Cancer Res. 2022;41(1):158.
4. Kim SS, Cho HJ, Lee JH, Park SY. Serum small extracellular vesicle-derived LINC00853 as a novel diagnostic marker for early hepatocellular carcinoma. Mol Oncol. 2020;14:2646-2659.
5. Kim SS, Eun JW, Cho HJ, Song DS, Kim CW, Kim YS, Lee SW, Kim YK, Yang J, Choi J, Yim HJ, Cheong JY. Microbiome as a potential diagnostic and predictive biomarker in severe alcoholic hepatitis. Aliment Pharmacol Ther. 2021;53(4):540-551.

# Circulating Extracellular Vesicles as a Promising Source of Biomarkers of HCC

**Soon Sun Kim** *Ajou University*

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and ranks as the third leading cause of cancer-related deaths worldwide. Early detection of HCC is challenging due to its asymptomatic nature in early stages and the lack of highly sensitive and specific biomarkers. Consequently, many patients are diagnosed at advanced stages when treatment options are limited and prognosis is poor. Extracellular vesicles (EVs) are heterogeneous, membrane-bound particles released by cells into the extracellular environment and are involved in various physiological and pathological processes, including cell-cell communication, immune response modulation, and the transfer of bioactive molecules such as proteins, lipids, and nucleic acids (DNA, mRNA, miRNA, and lncRNA). This makes them valuable for understanding disease mechanisms and as potential biomarkers for various conditions. In this presentation, I will discuss the potential of EVs as biomarkers for HCC based on my research experience.

Firstly, miR-4661-5p has been identified as a promising marker. Serum exo-miR-4661-5p demonstrated high diagnostic accuracy for HCC at all stages (AUROC = 0.917), including early-stage HCC (AUROC = 0.923). When used in combination with exo-miR-4746-5p, it formed the most accurate biomarker panel for early-stage HCC (AUROC = 0.947, 95% confidence interval = 0.889-0.980, sensitivity = 81.8%, and specificity = 91.7%). Secondly, SF3B4 showed significant diagnostic potential. Serum EV-SF3B4 displayed superior diagnostic power compared to alpha-fetoprotein (AFP) for all stages of HCC (AUC = 0.968 vs. 0.816), including early-stage HCC (AUC = 0.960 vs. 0.842), a finding consistent across external cohorts. Thirdly, well-known oncogenic lncRNAs were evaluated. Serum small EVs containing MALAT1, DLEU2, HOTTIP, and SNHG1 were identified as promising diagnostic markers for very early-stage HCC. The panel combining EV-MALAT1 and EV-SNHG1 achieved the highest area under the curve (AUC; 0.899, 95% CI = 0.816-0.982) for very early HCC, while a panel with EV-DLEU2 and AFP showed the highest positivity (96%) for very early HCC. Lastly, a novel lncRNA, LINC00853, demonstrated excellent diagnostic capability. EV-LINC00853 had an AUC of 0.934 (95% confidence interval = 0.887-0.966) for all-stage HCC diagnosis. EV-LINC00853 showed a positivity of 97% and 67% in AFP-negative and AFP-positive early HCC, respectively. Serum EV-derived LINC00853 may be a novel potential diagnostic biomarker for early HCC, particularly for AFP-negative cases.

These findings collectively underscore the potential of EV-derived biomarkers in improving the early

diagnosis and management of HCC, offering new avenues for non-invasive detection and personalized treatment strategies. Despite these promising findings, several challenges remain. There is a need for standardized protocols for EV isolation and characterization to ensure reproducibility and reliability of results. Extensive clinical trials are required to validate the diagnostic and prognostic value of EV-based biomarkers in diverse patient populations. Addressing these challenges will be crucial for translating EV-based biomarkers into clinical practice and improving outcomes for HCC patients.

## References


1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Théry C, Witwer KW, Aikawa E, Alcaraz MJ, Anderson JD, Andriantsitohaina R, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): A position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. J Extracell Vesicles 2018;7:1535750.
3. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science 2020;367.
4. Son JA, Weon JH, Baek GO, Ahn HR, Choi JY, Yoon MG, et al. Circulating small extracellular vesicle-derived splicing factor 3b subunit 4 as a non-invasive diagnostic biomarker of early hepatocellular carcinoma. J Exp Clin Cancer Res 2023;42:288.
5. Kim SS, Lee JY, Park SJ, Choi HJ. Early detection of hepatocellular carcinoma via liquid biopsy: Panel of small extracellular vesicle-derived long noncoding RNAs identified as markers. Mol Oncol 2021;15:2715-2731.
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7. Kim SS, Cho HJ, Lee JH, Park SY. Serum small extracellular vesicle-derived LINC00853 as a novel diagnostic marker for early hepatocellular carcinoma. Mol Oncol 2020;14:2646-2659.

THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# Special Interest Group 2

## Advancing and Discovering Cures for Rare Liver Disease

**Chairs:**

**Sook-Hyang Jeong** (Seoul National Univ.)
**Ja Kyung Kim** (Yonsei Univ.)

**Beom Hee Lee**

*University of Ulsan*

## Self Introduction

### *Education*

Prof. Beom Hee Lee is a Professor at the Department of Pediatrics and Medical Genetics Center at Asan Medical Center, Seoul Korea.

He was a graduate of the Seoul National University and proceeded to do a Ph.D. in molecular genetics. In 2013-15, Dr. Lee did a post-doctoral fellowship at the Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai New York with Dr. Robert J. Desnick's Lab.

Dr Lee is an active member of the Korean Society of Medicines, Pediatrics, Medical Genetics, Society of Inherited Metabolic Disease and the Korean Society of Pediatric Nephrology

## Research Interests

His work has been widely published with more than 160 publications, and his research has been focused on the molecular diagnostic and mechanistic studies and development of new therapeutic strategies in diverse genetic diseases including Wilson disease, lysosomal storage disease, Lesch-Nyhan syndrome and neurofibromatosis.

## Representative Publications

1. Seo GH, Kim YM, Oh SH, Chung SJ, Choi IH, Kim GH, Yum MS, Choi JH, Kim KM, Ko TS, Lee BH, Yoo HW. Biochemical and molecular characterisation of neurological Wilson disease. J Med Genet. 2018 Sep;55(9):587-593.
2. Lee BH, Kim JH, Kim JM, Heo SH, Kang M, Kim GH, Choi JH, Yoo HW. The early molecular processes underlying the neurological manifestations of an animal model of Wilson's disease. Metallomics. 2013 May;5(5):532-40.
3. Lee BH, Kim JM, Heo SH, Mun JH, Kim J, Kim JH, Jin HY, Kim GH, Choi JH, Yoo HW. Proteomic analysis of the hepatic tissue of Long-Evans Cinnamon (LEC) rats according to the natural course of Wilson disease. Proteomics. 2011 Sep;11(18):3698-705.
4. Lee BH, Kim JH, Lee SY, Jin HY, Kim KJ, Lee JJ, Park JY, Kim GH, Choi JH, Kim KM, Yoo HW. Distinct clinical courses according to presenting phenotypes and their correlations to ATP7B mutations in a large Wilson's disease cohort. Liver Int. 2011 Jul;31(6):831-9. Erratum in: Liver Int. 2011 Sep;31(8):1242. PMID: 21645214.
5. Park JY, Mun JH, Lee BH, Heo SH, Kim GH, Yoo HW. Proteomic analysis of seraof asymptomatic, early-stage patients with Wilson's disease. Proteomics Clin Appl. 2009 Oct;3(10):1185-1190.

# Emerging Diagnostic and Therapeutic Approaches for Wilson's Disease

**Beom Hee Lee** *University of Ulsan*

Wilson disease (WD; OMIM 277900) is a disorder of copper metabolism, caused by the recessive *ATP7B* mutations. The natural course of WD has been described by a progressive pathological process that starts from the liver and involves the extrahepatic tissues, including the brain, kidney and cornea. In Korean population, hepatic manifestations are observed in 60% of patients, whereas neurological and presymptomatic manifestations in 24% and 16% of patients, respectively.

The diagnosis of WD is mainly based on the biochemical findings representing liver dysfunction, low ceruloplasmin, low serum copper, and increased urine copper excretion. Single gene testing for the *ATP7B* gene is recommended for the confirmative diagnosis. With the rapid development of genetic diagnostic technologies, genome sequencing (panel, exome, or whole genome) can be recommended for the suspicious cases. These genetic methods are being considered for the screening of WD.

The first-line therapy of Wilson disease is copper chelating agents (D-penicillamine and trientine). Zinc salts (which interfere with absorption of copper from the gastrointestinal tract) are usually used as a maintenance therapy after a chelating agent, but can be suggested as the first-line medication in some patients; Especially, in patients with neurological manifestations, copper chelating agents may aggravate neurological manifestions. Cytopenia, skin allergic reaction, and proteinuria are the major serious adverse reaction that should be monitored in patients on D-penicillamine, whereas gastrointestinal symptoms are the most common adverse reactions of trientine and Zinc salts. In particular, trientine should be stored in the refrigerator and recently, an alternative formulation, triethylene tetramine tetrahydrochloride, which can be stored in room temperature, has shown similar efficacy. For those who fail to respond to medical therapy, present with fulminant acute liver failure, or decompensated liver cirrhosis, orthotopic liver transplantation is recommended. Supportive management is warranted for those with neurological manifestations. Currently, clinical trials are ongoing for a new copper-protein-binding molecule, bis-choline tetrathiomolybdate to reduce toxicity of free (non-ceruloplasmin bound) copper and gene therapy using AAV vectors.


## Xiong Ma

*Shanghai Jiao Tong University, China*


## Self Introduction

Xiong Ma, MD, PhD earned his under-graduated degree from Zhenjiang Medical College in 1991 and received his doctorate degree from Shanghai Jiao Tong University School of Medicine in 2001. Since then, Dr Ma has worked at Shanghai Renji Hospital, Shanghai Institute of Digestive Disease as attending physician, associate professor and researcher. From 2005 to 2006, he was trained as postdoctoral fellow at the Johns Hopkins University School of Medicine. Director, Department of Gastroenterology and Hepatology, Renji Hospital,

Vice-Director, Shanghai Institute of Digestive Disease;

Member, Globe PBC Study Group, International Autoimmune Hepatitis Group (IAIHG), Chinese Society of Hepatology

## Research Interests

Dr Ma's research interests are mainly focused on autoimmune liver diseases and nonalcoholic fatty liver disease. He has received 10 grants from the National Natural Science Foundation of China, and the National Distinguished Young Scholarship in 2013. Dr Ma has more than 60 peer-reviewed papers in English published in international journals including Gastroenterology, Journal of Hepatology, Gut, Hepatology, Nature Communications and Journal of Autoimmunity.

## Representative Publications


1. Wang R, Lin Q, Lu Z, Wen H, Hu F, You J, He Y, Fang Y, Bian Z, Hou Q, Ju Z, Wang Y, Lian M, Xiao X, Sheng L, Guo C, Hua J, Tang R, You Z, Chen X, Gershwin ME, Huang Z, Wang Q, Miao Q, Ma X. Immunosuppression induces regression of fibrosis in primary biliary cholangitis with moderate-to-severe interface hepatitis. J Autoimmun 2024 Feb:143:103163.
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3. Jun Zhang, Zhuwan Lyu, Bo Li, Zhengrui You, Nana Cui , You Li , Yikang Li , Bingyuan Huang, Ruiling Chen, Yong Chen, Yanshen Peng, Jingyuan Fang, Qixia Wang, Qi Miao, Ruqi Tang, M Eric Gershwin, Min Lian, Xiao Xiao, Xiong Ma. P4HA2 induces hepatic ductular reaction and biliary fibrosis in chronic cholestatic liver diseases. Hepatology 2023 Feb 20. doi: 10.1097/HEP.0000000000000317.
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# Overlap Syndrome: The Difference between Autoimmune Hepatitis and Primary Biliary Cholangitis

**Xiong Ma** *Shanghai Jiao Tong University, China*

**Atsumasa Komori**

*Nagasaki University, Japan*

## Self Introduction

Atsumasa Komori is the director of Department of Treatment for Intractable Disease in Clinical Research Center, and a senior staff member of Hepatology division, National Hospital Organization NHO Nagasaki Medical Center (NHO-NMC), Japan. After graduation of Kyushu University School of Medicine, followed by the training in the field of cancer research at National Cancer Center/Saitama Cancer Center in Japan and of basic immunology at Weill Medical School of Cornell University in USA, I joined in NHO-NMC to study clinical hepatology in 2003. Since 2020, to promote clinical and translational research in primary biliary cirrhosis (PBC), I have been organizing the nationwide multicenter observational studies, as well as the nationwide PBC surveys in Japan, as the head of PBC division in the Intractable Hepato-Biliary Diseases Study Group for Research on Measures for Intractable Disease, which is supported by Health Labor Science Research Grants in Japan. I am also the chief of Division of International Medical Cooperation in Nagasaki Medical Center, whose continuing clinical mentorship in the Republic of Kazakhstan was awarded as an honorary professor of Kazakhstan National Medical University in 2015. I am a board certified hepatologist and member of the board of trustees of the Japan Society of Hepatology.

## Research Interests

Autoimmune liver disease; Cholestatic liver disease; Steatotic liver disease; Viral hepatitis; Hepatocarcinogenesis

## Representative Publications

1. Yamashita Y, Umemura T, Kimura T, Joshita S, Hirohara J, Nakano T, Komori A, Tanaka A. Prognostic utility of albumin-bilirubin grade in Japanese patients with primary biliary cholangitis. JHEP Reports 2023; 5: 100662
2. Matsumoto K, Ohfuji S, Abe M, Komori A, et al. Environmental factors, medical and family history, and comorbidities associated with primary biliary cholangitis in Japan: a multicenter case-control study. J Gastroenterol 2022; 57:19-29.
3. Komori A. Recent updates on the management of autoimmune hepatitis. Clin Mol Hepatol 2020; 27:58-69.
4. Yagi M, Matsumoto K, Komori A et al. A validation study of the Ursodeoxycholic Acid Response Score in Japanese patients with primary biliary cholangitis. Liver Int. 2020; 40: 926-933.
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# Second-Line Pharmacotherapies for Hard-to-Treat Autoimmune Hepatitis and Primary Biliary Cholangitis

**Atsumasa Komori** *Nagasaki University, Japan*

## Introduction

The aim of the treatment of autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC), autoimmune liver diseases of non-self-limiting clinical course, is not a cure, but a prevention of disease progression from liver-related outcomes, ensuring healthy quality-of life. To this end, it is necessary to monitor treatment response to pharmacotherapies using surrogate endpoints. For AIH, the International Autoimmune Hepatitis Group (IAIHG) presented response criteria and endpoints: Complete biochemical response defined as normalization of serum transaminases and IgG below the upper limit normal at 6 months after the initiation of 1st line treatment (with predniso(lo)ne or budesonide, coupled with azathioprine, that is, standard of care: SOC).[1] On the other hand for PBC, biochemical treatment response was evaluated usually at 1 year after the initiation of ursodeoxycholic acid (UDCA) by the criteria (e.g., Barcelona, Paris) which were endorsed in several clinical guidelines.[2] In either disease, treatment failure, insufficient response, and intolerance to treatment are the indication of second-line pharmacotherapies.

## Second-Line therapy for hard-to-treat AIH[3]

Though azathioprine (AZA) is a key drug in SOC, widely-varying metabolizing activity for AZA to 6-thioguanine nucleotides (6-TGN), that contain main active drug metabolites, and non-adherence to AZA are the main reason for insufficient response and for intolerance to SOC, respectively. Patients in insufficient response, even after dose-optimization of AZA with the aid of measurement of 6-TGN, and those in AZA/ 6-mercaptopurine (6-MP, the first metabolite of AZA) double-intolerance, are then changed to 2nd-line therapy either with mycophenolate mofetil (MMF) or with calcineurin inhibitors (tacrolimus [TAC]>cyclosporin A). Comparative effectiveness study of MMF verses TAC with high-quality is warranted in the future.

## Second-Line therapy for hard-to-treat PBC

2nd-line drugs are introduced as "add-on" to patients with insufficient response to UDCA. In western countries, obeticholic acid (OCA), a farnesoid X receptor agonist, was licensed for such usage in 2016,

but the treatment-associated pruritus has been a significant concern. On the other hand, de facto 2nd-line in Japan, non-selective peroxisome proliferator activator receptor (PPAR) agonist bezafibrate (BZF), has a decade-longer history of usage than OCA, as add-on to UDCA. The propensity-matched cohort study within Japanese nation-wide registry of PBC revealed that patients in add-on with BZF to UDCA was associated with the better outcome, compared with those in UDCA alone.[4] BZF is embraced as the prototype 2nd-line drug, as it was also proved its efficacy for biochemical response by RCT.[2] Recent RCTs using seladelpar and elafibranor, both of which are novel selective PPAR agonists, demonstrated their efficacy as add-on drugs to UDCA,[5] expanding choice of 2nd-line pharmacotherapies to hard-to-treat PBC and cementing the role of PPAR agonists as the preferred 2nd-line drug.

## Conclusion

While PBC goes ahead of AIH in the clinical development of 2nd-line pharmacotherapies to hard-to-treat patients, we are also expecting success in ongoing clinical trials of novel immunotherapeutics as 2nd-line to AIH.

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# KASL Branch EMW 7 [Busan-Ulsan-Gyeongnam]

**Chairs:**

**Jeong Heo** (Pusan National Univ.)
**Nae-Yun Heo** (Inje Univ.)

**Yeowool Kang**

*Dong-A University*

## Self Introduction

Yeo-wool Kang is an assistant Professor of the Department of Hepatology, Dong-A University College of Medicine.

Dr. Kang graduated from Dong-A University College of Medicine and completed her internship and residency at the Department of Gastroenterology & Hepatology at Dong-A university Hospital.

Since 2022, Dr. Kang has been taking a role in member of the Korean Association of the Study of the Liver.

## Research Interests

- Viral Hepatitis, such as chronic hepatitis B &C
- Nonalcoholic Fatty Liver Disease
- Hepatocellular carcinoma

## Representative Publications

1. Kang, Y.W.; Baek, Y.H.; Lee, J.H.; Roh, Y.H.; Kwon, H.J.; Moon, S.Y.; Son, M.K.; Jeong, J.S. Assessing the Utility of Acoustic Radiation Force Impulse in the Evaluation of Non-Alcoholic Fatty Liver Disease with Severe Obesity or Steatosis. Diagnostics 2024, 14, 1083. https://doi.org/10.3390/diagnostics14111083
2. Kang YW, Baek YH, Lee SW, Park SJ, Yoon JS, Yoon KT, Hong Y, Heo NY, Seo KI, Lee SS, Cho HC, Shin JW. Real-world Effectiveness and Safety of Direct-acting Antiviral Agents in Patients with Chronic Hepatitis C Genotype 2 Infection: Korean Multicenter Study. J Korean Med Sci. 2021 May;36(21):e142. https://doi.org/10.3346/jkms.2021.36.e142

**Kiyoun Yi**

*Pusan National University*

## Self Introduction

Prof. Kiyoun Yi is a clinical assistant professor of the Department of Gastroenterology, Pusan National University Hospital.

Prof. Yi graduated from Pusan National University College of Medicine with her medical degree in 2017 and completed her internship and residency at the Department of Internal medicine at Pusan National University Hospital, receiving her board of Internal medicine in 2021 and board of Gastroenterology in 2023.

Prof. Yi is a member of the Korean Medical Association, the Korean Society of Gastroenterology, the Korean Association of the Study of the Liver, and etc.

## Research Interests

Gastroenterology and Hepatology

## Representative Publications

1. Hwang, S. Y., Woo, H. Y., Heo, J., Kim, H. J., Park, Y. J., Yi, K. Y., ... & Tak, W. Y. (2024). Outcome of Atezolizumab Plus Bevacizumab Combination Therapy in High-Risk Patients with Advanced Hepatocellular Carcinoma. Cancers, 16(4), 838.
2. Yi, K., Lee, J., & Kim, D. U. (2023). Metastatic pancreatic solitary fibrous tumor: A case report. World Journal of Clinical Cases, 11(35), 8416.
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# Is the Early Treatment of CHB reasonable? : Pro & Cons

**Yeowool Kang, Kiyoun Yi** *Dong-A University, Pusan National University*

In the era of nucleos(t)ide analogue, we have been able to reduce viral load, prevent hepatic necro-inflammation, and even reverse hepatic fibrosis in the patients with chronic hepatitis B (CHB). Owing to these accomplishments, many lives have been saved from liver failure and its catastrophic complications. Several studies have shown that populations treated with long-term antiviral agent have a lower risk of hepatocellular carcinoma (HCC) compared to untreated controls. However, the crude incidence of HCC has plateaued in South Korea, which is an HBV-endemic area.

Currently, antiviral treatment for hepatitis B virus (HBV) is focused on the immune-active (IA) or immune-escape phase, as these phases are considered periods of progression from chronic liver disease to cirrhosis or HCC. To overcome the limitations of the current treatment strategy for HCC control, some investigators argue that it is necessary to actively treat patients in the immune-tolerant (IT) phase or indeterminate phase (so-called gray zone). Several studies have suggested that early antiviral treatment could induce promising results in long-term survival. However, there are still concerns about expanding the indications for antiviral treatment.

For decades, the IT phase has been considered a period of no progression of liver disease, characterized by high viral load at a young age in the natural course of CHB. However, a significant proportion of patients in the IT phase, who present with normal ALT and high serum HBV DNA levels, have been found to have significant hepatic fibrosis upon liver biopsy. Additionally, a study by Kim et al. in 2018 reported a higher risk of HCC and death in untreated CHB patients in the IT phase compared to those in the IA phase treated with nucleos(t)ide analogues (NUCs). These findings suggest that some patients in the IA phase might be misclassified as those in the IT phase in clinical settings, and they could take advantage of antiviral treatment.

Emerging data suggest that hepatic carcinogenesis, such as HBV DNA integration into the host genome and clonal hepatocyte expansion, may start during the IT phase of CHB. Moreover, HBV-specific T cells in IT patients can still proliferate and secrete T cell cytokines, similar to those in IA patients, challenging the classic definition of immune tolerance. Therefore, patients currently ineligible for antiviral treatment may have liver damage and remain at risk for disease progression and HCC. Based on this, some

avant-garde investigators propose that it is time to consider adapting expanded treatment strategies to reduce these risks.

On the other hand, concerns remain about early antiviral treatment in CHB patients, including limited antiviral efficacy, compliance with long-term therapy, the occurrence of drug-resistant HBV, and costs. A clinical trial by Chan et al. in 2014 reported limited effects of TDF in HBeAg-positive patients with normal ALT levels and high HBV DNA levels, with HBeAg seroconversion occurring in 5% and a complete virologic response in 55% over four years of treatment. Consequently, conservative investigators suggest that antiviral treatment during the IT-phase could be applied to high-risk groups for HCC, such as older individuals (over 30 or 40 years) and those with a family history of HCC.

In anticipation of the introduction of HBV cure medication, early antiviral treatment with NUCs among CHB patients might serve as a bridge strategy to reduce the risk of HCC. However, to include this suggestion in clinical guidelines, more explanation is necessary to address related issues.

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2. Kim GA, Lim YS, Han S, et al. High risk of hepatocellular carcinoma and death in patients with immune tolerant-phase chronic hepatitis B. Gut 2018;67:945-952.
3. Jeng WJ, Wong GL. The truth of the matter: will immune-tolerant chronic hepatitis B patients benefit from antiviral treatment? Hepatol Commun 2023;7:e0060. doi: 10.1097/HC9.0000000000000060
4. Chan HL, Chan CK, Hui AJ, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA.


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# Clinical Hepatology

**Chairs:**

**Joon Hyeok Lee** (Sungkyunkwan Univ.)
**Chang Hyeong Lee** (Daegu Catholic Univ.)

**Tae Hyung Kim**

*Hallym University*

## Self Introduction

Prof. TaeHyung Kim is a Professor of the Department of Gastroenterology and Hepatology, Hallym University College of Medicine.

Prof. Kim graduated from Korea University College of Medicine with his medical degree in 2006 and completed his internship and residency at the Department of Internal Medicine at Korea University Hospital, receiving his diploma in Internal Medicine in 2011.

Since 2022, Prof. Kim has been taking a number of roles, including board members of the Korean Association of the Study of the Liver (2022-2023), Korean Liver Cancer Association(2022-2024), and Korean association of Gastroenterology (2023-2024).

## Research Interests

Viral hepatitis; Liver cirrhosis; MASLD, Liver cancer

## Representative Publications

1. Kim TH, Kim JH, Yim HJ, et al. Noninferiority Outcomes of Besifovir Compared to Tenofovir Alafenamide in Treatment-Naïve Patients with Chronic Hepatitis B. Gut Liver. 2024;18(2):305-315.
2. Kim TH, Yim HJ, Jung YK,et al. Korean Acute-on-Chronic Liver Failure (KACLiF) Study Group. New prognostic model for hospitalized patients with alcoholic cirrhosis and Maddrey's discriminant function <32. Hepatol Int. 2024;18(2):500-508.
3. Yim HJ, Kim TH, Suh SJ, et al. Response-Guided Therapy With Cefotaxime, Ceftriaxone, or Ciprofloxacin for Spontaneous Bacterial Peritonitis: A Randomized Trial: A Validation Study of 2021 AASLD Practice Guidance for SBP. Am J Gastroenterol. 2023;118(4):654-663.
4. Kim TH, Jung YK, Yim HJ,et al. Impacts of muscle mass dynamics on prognosis of outpatients with cirrhosis. Clin Mol Hepatol. 2022;28(4):876-889.

# Sarcopenia, Malnutrition, and Frailty in Patients with Liver Cirrhosis

**Tae Hyung Kim** *Hallym University*

Liver cirrhosis is a disease that is not limited to the liver but affects the entire body system. Therefore, it forms a correlation axis with various organs such as the Liver-Gut axis. It also forms the Liver-Muscle axis with skeletal muscle, which are the main components of physical performance. In other words, it significantly affects human activities, including intake, and these activities conversely affect the clinical course of cirrhosis. I would look into these interactions by dividing them into sarcopenia, frailty, and malnutrition.

## Sarcopenia: A Silent Threat

Sarcopenia, the progressive loss of skeletal muscle mass and strength, is common (30-70%) in patients with cirrhosis. As liver function deteriorates, the prevalence of sarcopenia increases. It contributes to decreased physical function, increased decompensation, and mortality in the patients with cirrhosis.

The liver plays a vital role in protein metabolism, and cirrhosis disrupts this delicate balance. As a result, serum branched-chain amino acids (BCAAs) are reduced, leading to muscle wasting. Impaired hepatic ammonia clearance and increased portosystemic shunts increase the serum ammonia concentration. Ammonia has toxic effects on muscle through increasing autophagy, proteolysis, and mitochondrial oxidative dysfunction in the muscle.

Early detection and intervention are essential to prevent further decline in muscle mass and function. There are many tools for evaluation of the sarcopenia. For the muscle mass, skeletal muscle index (SMI) and psoas muscle index have been commonly calculated using CT imaging, dual-energy X- ray absorptiometry (DEXA), and bioelectrical impedance analysis (BIA).

## Frailty: Beyond Muscle Loss

Frailty reflects decreased physiologic reserve and increased vulnerability to health stressors. It originated from the geriatrics, and is essentially associated sarcopenia. In patients with cirrhosis, frailty is an independent factor for adverse outcomes, including falls, hospitalizations, and mortality. Factors contributing to frailty include malnutrition, sarcopenia, chronic inflammation, and comorbidities. Identifying

frailty early allows targeted interventions to improve patient resilience. For assessing, liver frailty index (LFI) has been commonly used and is composed of several activities such as hand grip strength and gait speed.

## Malnutrition in Cirrhosis

Malnutrition is a clinical syndrome that results from deficiencies or excesses of nutrients. Excluding metabolic dysfunction-associated steatotic liver disease, nutrients deficiencies (undernutrition) are common in patients with cirrhosis, due to various factors, including reduced dietary intake, altered nutrient absorption, and increased energy expenditure. It leads to catabolism of protein rather than synthesis. Micronutrient deficiencies, such as folate, thiamine, zinc, selenium, vitamin D, and vitamin E, have been reported in patients with cirrhosis. These influence on developments of frailty, sarcopenia and encephalopathy. Addressing malnutrition is crucial for optimizing liver function and preventing complications.

## Managements

First, the nutritional optimization should be required through Individualized dietary plans and oral supplements. For sarcopenia, resistance training and aerobic exercises improve muscle strength and function. However, these exercise programs must be carefully applied according to individual frailty and liver function. Multidisciplinary collaboration involving hepatologists, dietitians, physical therapists, and social workers is essential.

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4. Tantai X, Liu Y, Yeo YH, et al. Effect of sarcopenia on survival in patients with cirrhosis: A meta-analysis. J Hepatol. 2022;76(3):588-599.


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**Sung-Eun Kim**

*Hallym University*

## Self Introduction

### *Education*

1996-3.2002 M.D., Hallym University, College of Medicine, Korea
2005-2.2007 Master degree, Hallym University, Graduate School of Medicine, Korea
2008-2010 Ph.D. Ulsan University Graduate School of Medicine, Korea

### *Postdoctoral Training*

2003-2.2007 Resident/Internal Medicine, Kangdong Sacred Heart Hospital, Hallym University Medical Center, Korea
2007-2.2010 Fellow, Gastroenterology& Hepatology, Asan Medical Center, Korea

### *Professional Activities*

2013-2018 Assistant professor, Division of Gastroenterology and Hepatology, Hallym Sacred Heart Hospital, Hallym University College of Medicine
2019-present Associate professor, Division of Gastroenterology and Hepatology, Hallym Sacred Heart Hospital, Hallym University College of Medicine
2019-2020 University of California San Diego

## Research Interests

Alcoholic liver disease/Nonalcoholic Fatty liver disease; Cirrhosis; Acute decompensation of cirrhosis

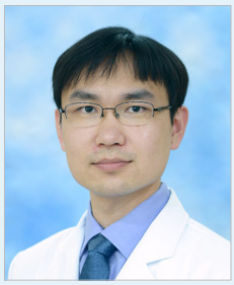
## Representative Publications

| | | | | | | |
|---|---|---|---|---|---|---|
| 1 | The Clinical Courses and Prognosis of Cirrhotic Patients after First Acute Decompensation: Prospective Cohort Study | 41명 | Diagnostics | 2024.01 | 교신 | 3.6 |
| 2 | Expression of peptidyl arginine deiminase 2 is closely associated with recurrence in patients with hepatocellular carcinoma | 14명 | Diagnostics | 2023.02 | 교신 | 3.6 |
| 3 | New prognostic model for hospitalized pateints with alcoholic cirrhosis and Mandrey's discriminant function <32 | 23명 | Hepatology International | 2023.10 | 공동 | 6.6 |
| 4 | The diagnostic significance of hepatitis C virus antibody levels for chronic hepatitis C virus infection | 11명 | Korean J Intern Med | 2023.05 | 공동 | 2.4 |
| 5 | Effectiveness and complication rates of percutaneous transhepatic fluoroscopy-guided management of common bile duct stones: a single-arm meta-analysis | 7명 | Eur Radiol | 2023.11 | 공동 | 5.9 |
| 6 | Prognosis of Patients with Chronic Hepatitis C Genotype 1b Infection Treated Using Daclatasvir/Asunaprevir after Sustained Virologic Response: A 6-Year Multicenter Prospective Observational Study | 9명 | Medicina | 2023.08 | 공동제1저자 | 2.948 |

# Management of Liver Disease in Pregnancy and Pregnancy-Associated Liver Disease

**Sung-Eun Kim** *Hallym University*

The spectrum of liver diseases that can occur during pregnancy, emphasizing the importance of prompt diagnosis and management to minimize risks to both the mother and fetus. Pregnancy-associated liver diseases include conditions such as hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, and preeclampsia-associated hepatic impairment, specifically HELLP syndrome. This lecture discusses the pathophysiology, clinical presentation, diagnostic criteria, and treatment strategies for each condition, drawing on the latest research and clinical practice guidelines. It underscores the need for a multidisciplinary approach involving obstetricians, hepatologists, maternal-fetal medicine specialists, anesthesiologists, and neonatologists to ensure comprehensive care. This also highlights trends in maternal mortality related to liver diseases and provides recommendations for postpartum evaluation and long-term management of women with persistent liver abnormalities. Through case studies and epidemiological data, the lecture provides a detailed understanding of how to effectively manage liver diseases in pregnant women to improve maternal and fetal outcomes.



**Jung Hwan Yu**

*Inha University*

## Self Introduction

### *Education*

| | |
|---|---|
| 2006 | Bachelor of Medicine, Yonsei University Wonju College of Medicine |
| 2011 | Master of Medicine, Yonsei University Graduate School |
| 2016 | Doctor of Medicine, Yonsei University Graduate School |

### *Professional Experience*

| | |
|---|---|
| 2018.3-2019.2 | Clinical Assistant Professor, Inha University Hospital |
| 2019.3-2023.2 | Assistant Professor, Inha University Hospital |
| 2023.3- | Associate Professor, Inha University Hospital |

### *Society Activities*

Current research committee member of Korean Association for the study of the Liver.
Current educational committee member of Korean Association for the study of the Liver.

## Research Interests

MASLD, Viral Hepatitis

## Representative Publications

1. linical outcomes of transarterial chemoembolization in Child-Turcotte Pugh class A patients with a single small (</=3 cm) hepatocellular carcinoma. J Gastroenterol Hepatol 2024.
2. Recurrence of hepatocellular carcinoma in noncirrhotic patients with nonalcoholic fatty liver disease versus hepatitis B infection. Eur J Gastroenterol Hepatol 2023;35:431-439.
3. Noninvasive imaging biomarkers for liver fibrosis in nonalcoholic fatty liver disease: current and future. Clin Mol Hepatol 2023;29:S136-S149.
4. The best predictive model for hepatocellular carcinoma in patients with chronic hepatitis B infection. Clin Mol Hepatol 2022;28:351-361.
5. Association between telomere length and hepatic fibrosis in non-alcoholic fatty liver disease. Sci Rep 2021;11:18004.

# Guidance for Managing the Long-Term Side Effects of Chronic Hepatitis B Antivirals

**Jung Hwan Yu** *Inha University*

Oral antiviral therapy is currently the backbone of chronic hepatitis B (CHB) infection treatment. They are usually well-tolerated by CHB patients and safe to use. To date, a significant number of patients have been treated with oral nucleoside/nucleotide analogues (NAs). Safety data has accumulated over the years. All NAs have a favorable safety profile. However, undesired extrahepatic adverse events may occur during the treatment of CHB infection. The most common extrahepatic adverse events are renal dysfunction, decreased bone mineral density and some neurological findings. Some studies suggest that extrahepatic adverse events may result from mitochondrial toxic effect of NAs.

Antiviral therapy in CHB suppress viral replication by the inhibition of the HBV polymerase enzyme. As NAs structures were similar to natural nucleosides, some of these agents can also inhibit human mitochondrial polymerase-$\gamma$ and cause mitochondrial toxicity. Because NAs lead to a minimal mitochondrial polymerase-$\gamma$ inhibition, All NAs carry a warning of mitochondrial toxicity as part of their prescribing information. The clinical manifestations of mitochondrial toxicity include hematologic disorders, peripheral neuropathy, skeletal and cardiac myopathy, pancreatitis, hepatic failure and lactic acidosis. The most remarkable examples of mitochondrial toxicity were reported with clevudine therapy, but it is known to occur with other NAs as well. It is also thought to be a cause of side effects that occur during long-term use of NAs.

Entecavir (ETV) is a highly selective guanosine nucleoside analogue, approved by the FDA at a dose 0.5 mg in treatment naive and 1 mg/d in lamivudine-resistant CHB patients in 2005. ETV is a well-tolerated antiviral agent in CHB patients, with rates of adverse events similar to placebo or lamivudine therapy. Entecavir is the relatively innocent antiviral agent leading to mitochondrial toxicity among the effective therapies in CHB treatments. However, it was suggested that a high Model for End-Stage Liver Disease (MELD) score that is used to detect highly impaired liver function can be associated with lactic acidosis in patients receiving entecavir. Therefore, the patients should be monitored cautiously for the risk of lactic acidosis during the treatment and entecavir should be suspended in the case of suspected lactic acidosis.

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir that has been approved as a nucleotide

analogue by the United States FDA for use in HIV infection in 2001 and in CHB infection in 2008. It inhibits potentially HBV DNA polymerase and reverse transcriptase. It is also a highly potent inhibitor of HBV DNA replication and recommended as a first-line treatment choice in CHB by the current clinical guidelines due to the absence of resistance to the drug. In phase Ⅲ studies of TDF, the adverse event profiles were similar to those in the comparative arm of adefovir. The most frequent adverse events were headache, nasopharyngitis, back pain and nausea. A 3-year, prospective real-world study reported 68 adverse events in 41 (9.3%) patients among a total of 440 patients receiving tenofovir. Adverse events occurring in more than one patient were renal disorders (n = 11), abdominal pain (n = 8), asthenia (n = 7), nausea (n = 6), vomiting (n = 5) and diarrhea (n = 5). Osteomalacia can occur during long-term TDF treatment. In randomized clinical trials, a great loss of bone mineral density had been well-described in patients with HIV infection treated with tenofovir. TDF can be preferred and used safely in CHB patients in the long-term. Nevertheless, BMD should be periodically performed in patients with CHB infection treated with TDF. Osteoporotic patients, especially with advanced age and smoking history, should be monitored more closely and, if required, consulted with a physical rehabilitation specialist.

The adverse effect of NAs on renal function is an important issue that should be carefully evaluated, since HBV infection alone carries an increased risk of renal impairment. All NAs are excreted through kidneys in unchanged forms and some of them are associated with dose-dependent nephrotoxicity. Nephrotoxicity results from proximal tubular damage and presents with elevated serum creatinine, proteinuria, nephrogenic diabetes insipidus, hypophosphatemia or the more severe form, Fanconi syndrome. All NAs are cleared by kidneys and their dosage should be adjusted in patients with creatinine clearance below 50 mL/min. To minimize the risk of nephrotoxicity, simultaneous administration of the other nephrotoxic drugs should be avoided. Secondly, all patients with CHB infection who are treated with adefovir or tenofovir should be regularly monitored for serum creatinine and phosphate levels and drug dose should be modified if creatinine increases by more than 0.5 mg/dL above baseline or phosphate level decreases below 2.0 mg/dL, to the needed dose.

To date, a complete cure for CHB is difficult and is likely to require long-term treatment. Therefore, when treating these patients with antiviral drugs for a long period of time, it is necessary to carefully consider the side effects that may occur during long-term use and conduct appropriate tests. Additionally, if side effects are discovered, appropriate treatment should be administered for the side effects and switching to another antiviral agents should be considered.

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3. Kayaaslan B, Guner R. Adverse effects of oral antiviral therapy in chronic hepatitis B. World J Hepatol 2017;9:227-241.
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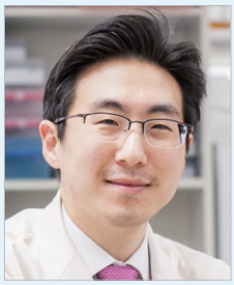

**Wonseok Kang**

*Sungkyunkwan University*

## Self Introduction

Prof. Wonseok Kang is Associate Professor of Medicine at Sungkyunkwan University School of Medicine and Samsung Medical Center.

He graduated from Yonsei University with his medical degree in 2004 and completed his residency at the Department of Internal Medicine in Severance Hospital in 2009. After completing his clinical training, he pursued his Ph.D. in Medical Science and Engineering at Korea Advanced Institute of Science and Technology (KAIST) in 2013.

Recently, he has spent a year at The Jackson Laboratory for Genomic Medicine and at Yale School of Medicine in Connecticut, USA, as a Visiting Research Scholar. After returning from his sabbatical year, he is currently focusing on translational research in the field of hepatology with regards to his clinical practice.

## Research Interests

Translational research in liver diseases including hepatocellular carcinoma, metabolic dysfunction-associated steatotic liver disease, and rare liver diseases.

## Representative Publications

1. Pretransplant Functional Status Predicts Postoperative Morbidity and Mortality after Liver Transplantation in Patients with Cirrhosis. Gut Liver 2023
2. Hepatocellular carcinoma patients with high circulating cytotoxic T cells and intra-tumoral immune signature benefit from pembrolizumab: results from a single-arm phase 2 trial. Genome Med 2022
3. Increased risk of pancreatic cancer in individuals with non-alcoholic fatty liver disease. Sci Rep 2022
4. Association between non-alcoholic fatty liver disease and the risk of biliary tract cancers: A South Korean nationwide cohort study, Eur J Cancer 2021
5. Characterization of Gut Microbiome in Korean Patients with Metabolic Associated Fatty Liver Disease, Nutrients 2021
6. Efficacy and Safety of Lenvatinib Therapy for Unresectable Hepatocellular Carcinoma in a Real-World Practice in Korea, Liver Cancer 2021

# Management and Rechallenge after Immune-Related Adverse Events of Immune Checkpoint Inhibitors

**Wonseok Kang** *Sungkyunkwan University*

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and a major cause of cancer-related mortality worldwide. The systemic treatment landscape for HCC has evolved rapidly in recent years, with several immune checkpoint inhibitors (ICIs) being added to the treatment armamentarium. The combination of atezolizumab and bevacizumab was the first ICI-based regimen to achieve its primary survival endpoints compared to sorafenib in a phase III trial (IMbrave-150), establishing it as the new standard for frontline systemic treatment. More recently, the combination of durvalumab and tremelimumab demonstrated superior overall survival compared to sorafenib in a phase III trial (HIMALAYA), resulting in its inclusion as an additional first-line option.

ICIs have revolutionized cancer therapy for patients with unresectable HCC, yet immune-related adverse events (irAEs) can occur with all ICIs, potentially affecting any organ system. Pre-treatment evaluations are essential to assess the likelihood and risk of AEs and to educate patients about irAEs. Additionally, cirrhosis-related conditions should be considered during the diagnostic evaluation of irAEs in these patients. Most irAEs can be managed with corticosteroids, whereas discontinuation of ICI therapy is recommended for severe AEs.

Rechallenge after irAEs presents a clinical challenge, particularly in patients with severe irAEs. Approximately one-third of patients experience irAEs upon ICI rechallenge, with many encountering a recurrence of the same event. Conditions such as colitis, hepatitis, and pneumonitis are notably associated with higher recurrence risks. Interestingly, the occurrence of irAEs may correlate with treatment response, including longer overall survival, progression-free survival, and increased objective response rates.

The decision to rechallenge with ICIs should be made carefully, considering the severity and location of irAEs, the patient's response to initial immunotherapy, and the availability of alternative treatments.


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THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# Special Interest Group 3

## Navigating the Path to Hepatitis B Virus Eradication: Targets and Trials

**Chairs:**

**Jin-Wook Kim** (Seoul National Univ.)

**Tatsuya Kanto** (National Center for Global Health and Medicine, Japan)

**Wenhui Li**

*Tsinghua University, China*

## Self Introduction

Dr. Wenhui Li is an investigator of the National Institute of Biological Sciences (NIBS),Beijing and a professor of the Tsinghua Institute of Multidisciplinary Biomedical Research. He got his PhD from Peking Union Medical College & Chinese Academy of Medical Sciences in 2001. He worked as a postdoctoral fellow then an instructor at Harvard Medical School from 2001 to 2007. Dr.Li identified ACE2 as the cellular receptor for SARS-CoV in Michael Farzan lab in 2003 (Li et al., Nature, 2003). Dr. Li's team at NIBS discovered sodium taurocholate cotransporting polypeptide (NTCP) as a functional receptor for HBV and HDV in 2012 (Yan et al., eLife,2012). Currently his team studies molecular mechanisms of HBV and HDV infection, and develops antivirals against the infections. Dr. Wenhui Li was awarded Baruch S. Blumberg Prize for HBV research (2021), and Future Science Prize in Life Sciences (2022).

## Research Interests

We combine virology, biochemistry, chemical biology, immunology, and animal models to investigate molecular mechanisms of infection of Hepatitis B virus (HBV). HBV infection remains a public health problem worldwide. About 240 million people are affected by HBV. Chronic HBV infection is a major cause of cirrhosis and hepatocellular carcinoma. Hepatitis D virus (HDV), a satellite of HBV, infects 15 million people among those infected by HBV. We identified sodium taurocholate cotransporting polypeptide (NTCP), a liver bile acid transporter, as a crucial receptor for viral infection of HBV and HDV. This finding has significantly advanced our understanding on the tissue tropism, species specificity and infection mechanisms of HBV and HDV. The finding also provides a candidate intervention target, and has helped establish new HBV/HDV infection platforms for studying HBV biology, as well as developing new treatments against related diseases. Our long-term goal is to elucidate the pathogenesis of HBV and HDV and to develop new drugs for the treatment of the infection and associated diseases.

## Representative Publications

1. Yao Q, Peng B, Li C, Li X, Chen M, Zhou Z, Tang D, He J, Wu Y, Sun Y, Li W*. SLF2 Interacts with the SMC5/6 Complex to Direct Hepatitis B Virus Episomal DNA to Promyelocytic Leukemia Bodies for Transcriptional Repression. J Virol. 2023, 97(7): e0032823.
2. Zhou Z, Li C, Tan Z, Sun G, Peng B, Ren T, He J, Wang Y, Sun Y, Wang F, Li W*. A spatiotemporally controlled recombinant cccDNA mouse model for studying HBV and developing drugs against the virus. Antiviral Res. 2023,doi: 10.1016/j.antiviral.2023.105642.
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# Experimental in Vitro and in Vivo Models for Hepatitis B Virus Cure Research

**Wenhui Li** *Tsinghua University, China*


## Sang Hoon Ahn

*Yonsei University*


## Self Introduction

### *President Position*

Professor, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

2024 Chief, Department of Gastroenterology and Hepatology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

2024 Director, Yonsei Gastroenterology Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

2019-2023 Director, Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

2021-2024 Director, Human Resources Headquaters, Yonsei University Health System, Seoul, Republic of Korea

2020-2021 Director, Administration of Yonsei University Health System, Seoul, Republic of Korea

2018-2020 Director, Planning and Management Headquarter, Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea

### *Overseas Working Experiences*

2001-2003 Postdoctoral Fellowship, Liver Research Center, Brown Medical School, Providence, RI, USA.

2008-2009 Visiting Professor, WHO Collaborating Centres for Virus Reference and Research, Victorian Infectious Diseases Reference Laboratory (VIDRL), Melbourne Health, North Melbourne, Australia

### *Key Academic Society Activities*

- Trustee, Journal of Gastroenterology and Hepatology Foundation (JGHF) (2024-)
- Executive Council Member, the Asian Pacific Association of the Study of the Liver (APASL) (2023-current)
- Secretary-General, the Korean Association of the Study of the Liver (KASL) (2022-current)
- Secretary General: The Korean Association of the Study of Liver (KASL, 2022-Present)
- Chairman of Academic Committee: The Korean Liver Cancer Association (2010-2011)
- Chairman of Academic Committee: The Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE, 2013)
- Chairman of Academic Committee: The Korean Association of the Study of Liver (KASL, 2018-2019)
- Chairman of Academic Committee: The Asia Pacific Association of the Study of Liver (APASL, 2022)

### *Government Advisory Activities*

- Consultant for health authority organizations in KOREA: The Ministry of Health and Welfare; the Ministry of Food and Drug Safety (FDA); Centers for Disease Control and Prevention (CDC), National Evidence-based healthcare Collaborating Agency (NECA)
- Global: BMS, Gilead Sciences, Janssen, AbbVie, Roche, Assembly Biosciences, Arbutus, Brii, Vaccitech, GSK, Inovio, Aligos, Vir Biotechnology
- Domestic: SL Vaxigen, GeneOne Life Science, GreenCross, Yuhan, Samil and Ildong, etc

## Research Interests

- Viral hepatitis B and C: Molecular biology, Clinical trials for new drugs
- Liver fibrosis and liver cancer: Pathogenesis and treatment

# Treatment Endpoints and Study Design to Cure Hepatitis B Virus

**Sang Hoon Ahn** *Yonsei University*

Hepatitis B Virus (HBV) remains a major global health challenge, with chronic infection leading to severe liver disease and cancer. Effective therapeutic interventions are crucial for managing and potentially curing HBV. This lecture will delve into the critical aspects of treatment endpoints and study design essential for the development of effective therapies aimed at curing HBV. The presentation will begin by exploring the current landscape of HBV treatment endpoints, emphasizing the need for well-defined and clinically meaningful markers to assess treatment efficacy accurately.

Key issues such as the selection of appropriate patient populations, the implications of novel biomarkers for monitoring disease progression and treatment response are examined. Additionally, we explore trial designs, including the choice of control groups and variables to be considered, to ensure that the studies are powered to detect clinically meaningful outcomes.

In conclusion, this lecture aims to provide a comprehensive overview of the pivotal role of treatment endpoints and study design in the quest to cure HBV infection. By fostering a deeper understanding of these fundamental principles, clinicians, researchers, and policymakers will be better equipped to navigate the complex landscape of HBV therapeutics and advance towards the goal of HBV eradication.


## Man-Fung Yuen

*The University of Hong Kong, Hong Kong*


## Self Introduction

Professor Yuen is now the Chair Professor of The University of Hong Kong and Li Shu Fan Medical Foundation Professor in Medicine, and the Chief of the Division of Gastroenterology and Hepatology, Queen Mary Hospital, Hong Kong. He obtained his first bachelor's degree of medicine in 1992. He further pursued his academic excellence through the achievement of obtaining three doctoral degrees including Doctor of Medicine with Sir Patrick Manson Gold Medal in 2001, Doctor of Philosophy in 2005 and Doctor of Science in 2017.

He is now one of the top internationally renowned researchers in the field of hepatitis B disease. He has now published more than 570 papers in world-renowned medical journals including New England Journal of Medicine, Lancet, Nature Medicine, Lancet Infectious Diseases and Lancet Oncology. According to Expertscape academic online platform which analyses 25,130 publications during the period between 2013 and 2023, he is ranked the top 1 researcher under the category of "hepatitis B" (https://www.expertscape.com/ex/hepatitis+b). According to another academic performance metric, the AD Scientific Index 2024 (https://www.adscientificindex.com/scientist_print.php?id=409287), he is ranked the 16th world scientist in field of Gastroenterology and the 1,178th out of 148,666 in all subjects of Medical and Health Sciences. Up till now, he has delivered more than 330 lectures all over the world.

## Research Interests

Natural history, Virology, and Treatment of chronic hepatitis B infection

## Representative Publications


1. Yuen MF, Asselah T, Jacobson IM…. on behalf of the REEF-1 Study Group. Efficacy and safety of the siRNA JNJ-73763989 and/or the capsid assembly modulator JNJ-56136379 (Bersacapavir) with nucleos(t)ide analogues for the treatment of chronic hepatitis B virus infection: results from the phase 2b randomised REEF-1 study. Lancet Gastroenterol Hepatol 2023;8(9):790-802.
2. Gane E, Lim YS, Kim JB…Hebner CM, Pang PS, Yuen MF. Evaluation of RNAi therapeutics VIR-2218 and ALN-HBV for chronic hepatitis B: results from randomized clinical trials. J Hepatol 2023;79(4):924-932.
3. Yuen MF, Balabanska R, Cottreel E, Chen E, Duan D, Qiudi Jiang Q, et al. TLR7 agonist RO7020531 versus placebo in healthy volunteers and patients with chronic hepatitis B infection: a randomised, observer-blind, placebo-controlled phase 1 trial. Lancet Infect Dis 2023;23(4):496-507.
4. Yuen MF, Lim SG, Plesniak R, Tsuji K, Janssen HLA, Pojoga C, et al. Efficacy and safety of bepirovirsen in chronic hepatitis B infection. N Engl J Med 2022;387(21):1957-1968.
5. Yuen MF, Locarnini S, Lim TH, Strasser SI, Sievert W, Cheng W, et al. Combination treatments including the small-interfering RNA JNJ-3989 induce rapid and sometimes prolonged viral responses in patients with CHB. J Hepatol 2022;77(5):1287-1298.

# Promising Results for Curing Hepatitis B Virus: Viral and Immune Targets

**Man-Fung Yuen** *The University of Hong Kong, Hong Kong*

Existing treatment for chronic hepatitis B virus (HBV) infection includes nucleos(t)ide analogues and pegylated interferon (Peg-IFN). Functional cure defined as HBV DNA undetectability and loss of HBsAg sustained after treatment cessation is seldomly achieved by these two classes of agents. Hence, many novel direct antiviral agents and immunomodulators have been actively tested in clinical trials. Small interfering RNAs (siRNA) or anti-sense oligonucleotides (ASO) knock down mRNA transcriptional and pre-genomic activities. Profound and sustained suppression of HBsAg, HBeAg, HBcrAg levels as well as HBV DNA, HBV RNA levels have been observed in patients receiving different regimens of these two new agents. For example, HBsAg seroclearance is observed in 9-10% patients receiving ASO. According to several siRNA clinical trials, absolute HBsAg level reductions down to less than 100 IU/mL was achieved in around 60 to 80% of patients. This response is generally sustained up to 1 year after the treatment cessation. Recent phase II studies have shown that combination of siRNA with Peg-IFN were associated with 16 – 33% of HBsAg seroclearance at 24 weeks post treatment.

Another class of novel antiviral agent which has been extensively tested is the core protein allosteric modulators (CpAM)/ core inhibitors. These compounds primarily inhibit HBV pregenomic RNA encapsidation resulting in decreased viral replication and secondarily affect capsid disassembly resulting in depletion of cccDNA replenishment. Recently, treatment of the most potent CpAM in HBeAg-positive patients was found to have promising effect on continuous reduction of HBsAg, in addition to the HBV DNA and HBV RNA reduction up to 72 weeks of treatment.

Another new immunomodulator is monoclonal antibody which inhibits viral entry to hepatocytes, enhance virus presentation to T cell (vaccinal effect) and delivery to dendritic cells. Its use is associated with a rapid and profound HBsAg reduction. Using anti-PDL1 treatment has been shown to be associated with HBsAg reduction and HBsAg seroclearance in patients with low baseline HBsAg levels < 100 IU/mL. Therapeutic vaccine combined with anti-PDL1 also showed initial promising results in term of more patients with baseline HBsAg < 200 IU/mL achieving HBsAg seroclearance. Thyroid dysfunction is the most common immune-related adverse event which occurred in 9 – 10% of patients. Liver selective/ targeting anti-PDL1 is expected to have higher benefit to risk ratio for CHB disease.

In conclusion, many new agents have completed phase II studies and shown promising HBsAg reducing effects through different modes of action against HBV. Many combination treatment regimens using direct antiviral agents and immunomodulators are being studied. Future challenge remains to be the design of treatment strategy using these new agents once their medium-term efficacy and safety have been established.

THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# Plenary Presentation 1

**Chairs:**

**Kyung Sik Kim** (Yonsei Univ.)
**Han Chu Lee** (Univ. of Ulsan)
**Kwang-Woong Lee** (Seoul National Univ.)

## PP 1-1

### Transarterial Radioembolization versus Atezolizumab plus Bevacizumab in Hepatocellular Carcinoma with Portal Vein Thrombosis

Youngsu Park[1,*], Yuri Cho[2,*], Seung Up Kim[3,*], Aryoung Kim[4,*], Hyunjae Shin[1,2], Yunmi Ko[1], Moon Haeng Hur[1], Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Jung-Hwan Yoon[1], Dong Hyun Sinn[2], Yoon Jun Kim[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [2]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Korea; [3]Department of Internal Medicine and Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [4]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

**Aims:** Transarterial radioembolization (TARE) has become promising therapy in patients with hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT), while the combination of atezolizumab plus bevacizumab is a recently highlighted systemic therapy for HCC. It has not yet been determined which treatment method is the best treatment for HCC with PVTT. We compared the outcomes of TARE and atezolizumab plus bevacizumab in HCC patients with PVTT and without extrahepatic metastasis.

**Methods:** This multicenter study included 213 patients treated with TARE (n=125) or atezolizumab plus bevacizumab (the Ate-Bev group, n=88) between 2016 and 2023. The primary outcome was overall survival (OS) and the secondary outcomes included progression-free survival (PFS) and objective response rate (ORR). The comparison of the two groups was also conducted by balancing baseline characteristics through propensity score matching (PSM).

**Results:** The median OS of the TARE and TACE-RT groups were 27.5 and 8.6 months, respectively ($P$<0.001). The TARE group showed significantly longer OS compared to the Ate-Bev group before PSM (hazard ratio [HR]=0.38, 95% confidence interval [CI]=0.25–0.58, $P$<0.001) and after PSM (HR=0.40, 95% CI=0.22-0.74, $P$=0.004). The TARE group exhibited comparable PFS to the Ate-Bev group. The ORR of the TARE group in the matched cohorts was 30.9%, which was comparable to that of the Ate-Bev group, also at 30.9%.

**Conclusions:** For HCC patients with PVTT and no extrahepatic metastasis, TARE may offer a better OS outcome, compared to the combination of atezolizumab plus bevacizumab.

**Keywords:** Hepatocellular carcinoma, Portal vein tumor thrombosis, Radioembolization, Immune checkpoint inhibitor

**Table 1. TARE vs Atezolizumab+Bevacizumab : Outcomes**

| Characteristics | Unmatched Cohort: TARE (n=125) | Unmatched Cohort: Atezolizumab+Bevacizumab (n=88) | Unmatched Cohort: P value | After PSM: TARE (n=55) | After PSM: Atezolizumab+Bevacizumab (n=55) | After PSM: P value |
|---|---|---|---|---|---|---|
| OS, months | 27.5 [18.1–na] | 8.6 [7.1–12.5] | <0.001 | na [17.5–na] | 9.5 [7.1–14.9] | 0.004 |
| Tumor progression, n(%) | 72 (57.60) | 45 (51.1) | 0.427 | 32 (58.2) | 33 (60.0) | 1.000 |
| PFS, months | 5.8 [3.5–11.2] | 9.9 [6.4–21.6] | 0.188 | 5.8 [2.8–15.4] | 8.4 [4.3–14.9] | 0.348 |
| Hepatic progression, n(%) | 68 (54.8) | 45 (51.1) | 0.654 | 31 (57.4) | 30 (54.5) | 0.94 |
| HPFS, months | 2.9 [2.4–3.6] | 4.0 [2.8–6.5] | 0.164 | 2.7 [2.1–4.9] | 3.5 [2.7–7.3] | 0.198 |
| Best response, n(%) | | | 0.241 | | | 0.313 |
| CR | 10 (8.0) | 2 (2.3) | | 4 (7.3) | 1 (1.8) | |
| PR | 33 (26.4) | 21 (23.9) | | 13 (23.6) | 16 (29.1) | |
| SD | 56 (44.8) | 38 (43.1) | | 26 (47.2) | 19 (34.5) | |
| PD | 26 (20.8) | 27 (30.7) | | 12 (21.8) | 19 (34.5) | |
| PVTT response, n(%) | | | 0.092 | | | 0.308 |
| CR | 13 (10.5) | 3 (3.4) | | 6 (10.9) | 2 (3.6) | |
| PR | 28 (22.6) | 21 (23.9) | | 8 (14.5) | 13 (23.6) | |
| SD | 63 (50.8) | 40 (45.5) | | 31 (56.3) | 25 (45.4) | |
| PD | 20 (16.1) | 24 (27.2) | | 10 (18.2) | 15 (27.3) | |
| Rescue treatment, n(%) | 67 (75.0) | 28 (36.4) | <0.001 | 36 (72.0) | 19 (38.0) | 0.001 |

**Figure 1. TARE vs Atezolizumab+Bevacizumab : Overall survival**

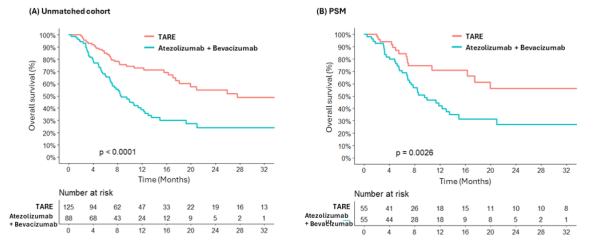
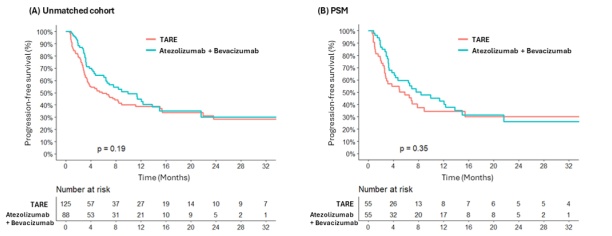



**Figure 2. TARE vs Atezolizumab+Bevacizumab : Progression-free survival**




## PP 1-2

### LI-RADS Imaging Diagnosis of Hepatocellular Carcinoma in Noncirrhotic Patients with Chronic Hepatitis C: A Multicenter Development and Validation Cohort

Ha Il Kim[1], Rohee Park[2], Seong Kyun Na[3,4], Euichang Kim[5], In-Hye Song[6,7], Young Seo Cho[8], Ji Hun Kang[8], Han Chu Lee[5,7], Seungbong Han[9], Jihyun An[1†], Sang Hyun Choi[2,7†], Ju Hyun Shim[5,7]

[1]Department of Gastroenterology and Hepatology, Hanyang University College of Medicine, Guri, Republic of Korea; [2]Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea; [3]Department of Internal Medicine, Jeju National University School of Medicine, Jeju, Korea; [4]Department of Gastroenterology, Inje University Sanggye Paik Hospital, Seoul, Republic of Korea; [5]Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea; [6]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [7]Asan Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [8]Department of Radiology, Hanyang University College of Medicine, Guri, Republic of Korea; [9]Department of Biostatistics, Korea University College of Medicine, Seoul, Republic of Korea

**Aims:** Although the LI-RADS criteria indicate a risk of hepatocellular carcinoma (HCC) beyond chance, they have not been validated for non-cirrhotic patients with chronic hepatitis C

(CHC). This study aims to evaluate the diagnostic performance of LR-5 observations for HCC in non-cirrhotic patients compared to their cirrhotic counterparts.

**Methods:** This retrospective study included CHC patients from two university hospitals who had focal hepatic nodules ≥ 1 cm on dynamic CT or MRI scans and subsequently underwent pathologic confirmation. This group served as the development cohort. The primary outcome was the diagnostic performance of LR-5 for HCC. To translate the findings into clinical practice, we validated the results using CHC cohorts from two additional hospitals based on the clinical composite reference standard.

**Results:** The development cohort comprised 512 lesions from 458 patients: 235 from 219 non-cirrhotic patients and 277 from 239 cirrhotic patients. The pathologies included 434 HCCs, 52 other malignant masses, and 26 benign lesions. For non-cirrhotic livers, the LR-5 criteria achieved the following diagnostic metrics: AUC, accuracy, sensitivity, specificity, PPV, and NPV of 0.90, 85.1%, 82.4%, 97.6%, 99.4%, and 54.7%, respectively. The LR-5 criteria's diagnostic performance for HCC was also excellent in noncirrhotics of the validation cohort, which included 155 lesions from 103 patients. The AUC, accuracy, sensitivity, specificity, PPV, and NPV in the validation cohort were 0.91, 96.1%, 82.9%, 100%, 100%, and 95.2%, respectively.

**Conclusions:** This multicenter study suggests LR-5 diagnosis for HCC may suffice in non-cirrhotic CHC patients. Prospective studies are warranted to confirm our findings.

**Keywords:** Chronic hepatitis C virus infection, LI-RADS, Non-cirrhosis, Hepaocellular carcinoma

## PP 1-3

### Anatomical Risk Factors for Portal Vein Complications Following Right Hepatectomy in Living Donors: Analysis of Results from 4720 Cases

Young-In Yoon, Dong-Hwan Jung, Shin Hwang, Ki-Hun Kim, Tae-Yong Ha, Gi-Won Song, Gil-Chun Park, Chul-Soo Ahn, Duk-Bog Moon, Sung-Gyu Lee

Division of Hepatobiliary Surgery And Liver Transplantation, Asan Medical Center, Republic of Korea

**Aims:** Although various complications after donor hepatectomy have been reported, there have been no large studies on postoperative portal vein (PV) complication. This study evaluated the incidence, risk factors, and clinical outcomes of PV complication after right lobe donor hepatectomy (RLDH).

**Methods:** Single-center retrospective analysis of 4720 consecutive donors who underwent RLDH, between July 1997 and 2020 December. Computed tomographic angiographies of the donor were 2-dimensionally reconstructed, and the portal vein was classified according to angle between main and left PV.

**Results:** The incidence of PV complication after RLDH was 1.9 % (n=88), including PV thrombosis (n=9) and PV stenosis (n=79). Donors with PV complication had had a significantly higher peak Alanine Aminotransferase ($P$=0.023) than donors without PV complication, but had similar peak total bilirubin ($P$=0.055), peak INR ($P$=0.395) and hospital stay ($P$=0.117). Multivariate analysis identified angle between main and left PV less than 60 degrees as a significant independent risk factor for PV complication (odds ratio 6.250; $P$<0.001). In addition, variant PV, No fixation of falciform ligament, and BMI > 30 were independent risk factor for PV complication ($P$<0.001, $P$<0.001, and $P$=0.002, respectively).

**Conclusions:** Acute angulation between main and left PV or variant PV has a higher tendency to occur PV complication after RLDH. For those donors require meticulous surgical techniques during operation and periodic image studies after operation.

**Keywords:** Living donor

## PP 1-4

### Persistent Systemic Inflammation Is Important Driver of Acute-on-Chronic Liver Failure and Organ Failure Development

Do Seon Song[1], Hee Yeon Kim[2], Young Kul Jung[3], Eileen Yoon[4], Ki Tae Suk[5], Sang Gyune Kim[6], Moon Young Kim[7], Soung Won Jeong[8], Jae Young Jang[8], Sung Eun Kim[5], Jung Gil Park[9], Won Kim[10], U Im Chang[1]

[1]Department of Internal Medicine, St. Vincent's Hospital, The Catholic University of Korea, [2]Department of Internal Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of Korea, [3]Department of Internal Medicine, Korea University Ansan Hospital, [4]Department of Internal Medicine, Hanyang University College of Medicine, [5]Department of Internal Medicine, Hallym University College of Medicine, [6]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, [7]Department of Internal Medicine, Yonsei University Wonju College of Medicine, [8]Department of Internal Medicine, Soonchunhyang University College of Medicine, [9]Department of Internal Medicine, Yeungnam University College of Medicine, [10]Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center

**Aims:** We aimed to investigate the association between acute-on-chronic liver failure (ACLF) development and systemic inflammatory markers in acutely decompensated chronic liver disease patients.

**Methods:** We enrolled 1,249 patients without ACLF at baseline in Korean ACLF cohort. Organ failure and ACLF were defined by European Association for the Study of the Liver-Chronic liver failure (EASL-CLIF) criteria. Primary outcome was ACLF development and new organ failure development within 1 year.

**Results:** Patients with high C-reactive protein (CRP) (≥ 1.0 mg/dL), white blood cell count (WBC) (≥ 10.0x10$^9$/mm$^3$), procalcitonin level (≥ 1.0 mg/dL) showed significantly higher 1-year

ACLF development rate than patients with low CRP ($P$<0.001), WBC ($P$=0.004) and procalcitonin ($P$=0.014), respectively. Those with systemic inflammatory response syndrome (SIRS) also had significantly higher ACLF development rate than those without SIRS ($P$=0.045). Cox proportional hazard regression model showed that bilirubin (Hazard ratio (HR) 2.266, $P$=0.012), INR (HR 6.047, $P$<0.001). CRP (HR 2.242, $P$=0.011), and procalcitonin (HR=2.437, $P$=0.011) level were independent factors for ACLF development. Those with high CRP level had significantly higher renal ($P$<0.001), coagulation ($P$<0.001), cerebral ($P$=0.013), circulatory ($P$=0.009) failure development ($P$=0.001) than those with low CRP, and those with high procalcitonin had significantly higher renal failure development rate ($P$=0.032). The ACLF development rate of the patients with low CRP at baseline but high CRP at 7$^{th}$ day was significantly higher than that of the patients with high CRP at baseline but low CRP at 7$^{th}$ day ($P$=0.01) and similar to that of the patients with persistently high CRP ($P$=0.629). The change of the SIRS also showed similar results to the CRP change.

**Conclusions:** Persistent or worsening systemic inflammation is a main driver for development of organ failure and ACLF. The resolution of inflammation could reduce the ACLF development. Reducing systemic inflammation can be a treatment target to prevent disease progression.

**Keywords:** Cirrhosis, Organ failure, Acute-on-chronic failure, Inflammation

THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# Plenary Presentation 2

**Chairs:**

**Jinsub Choi** (Yonsei Univ.)
**Hee Chul Yu** (Jeonbuk National Univ.)
**Hyung Joon Yim** (Korea Univ.)

## PP 2-1

### Merlin-TAZ Pathway by miR-4449 Regulates Fibrosis Progression in MASH

Young-Sun Lee, Eunho Choi, Seong Hee Kang, Sun Young Yim, Yang Jae Yoo, Young Kul Jung, Ji Hoon Kim, Yeon Seok Seo, Hyung Joon Yim, Jong Eun Yeon

Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea

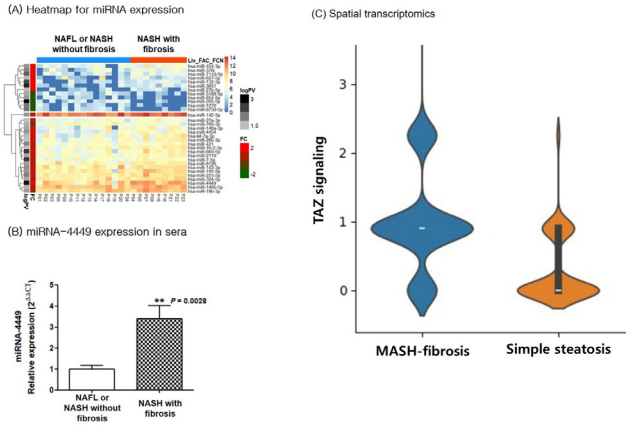
**Aims:** Although most metabolic dysfunction-associated steatotic liver disease (MASLD) patients show benign clinical courses, metabolic dysfunction-associated steatohepatitis (MASH) patients with hepatic fibrosis have poor prognoses compared to patients with simple steatosis or MASH without hepatic fibrosis. In this study, we aimed to analyze the role of miR-4449 in the progression of MASH-fibrosis.

**Methods:** Liver tissue and sera were collected from MASLD patients who received liver biopsies in Korea University Guro hospital. MicroRNA sequencing, using sera, and mRNA sequencing, using liver tissue, were performed in patients with biopsy-confirmed MASLD. To induce *in vitro* lipotoxicity in mice hepatocytes, HepG2 and Huh7 cells were treated with palmitic acids (PA). We transfected miR-4449 mimic or inhibitor into hepatocytes to explore the effect of miR-4449 during lipotoxicity. Spatial transcriptomics was done to analyse gene expression profile in formalin-fixed, paraffin-embedded (FFPE) from patients with biopsy-confirmed MASLD.

**Results:** In total, 24 MASLD patients were recruited, 15 patients had simple steatosis or MASH without fibrosis, whereas nine patients had MASH with fibrosis. In miRNA sequencing analysis, 31 miRNA sequences showed significant differences in expression levels between the two groups, with the expression of miR-4449 most prominently seen among miRNAs that showed higher expression levels in MASH-fibrosis compared to the simple steatosis or MASH without fibrosis group. PA treatment increased the expression level of miR-4449 in both supernatant and hepatocytes. On the other hand, the expression of merlin, which could be the target of miR-4449, decreased in PA-treated hepatocytes compared with vehicle-treated hepatocytes. In addition, merlin expression levels significantly decreased in MASH patients with fibrosis compared to simple steatosis and MASH patients without fibrosis. Hepatocytes with miR-4449 transfection mimic decreased merlin expression but exhibit increased phosphorylated TAZ expression, whereas hepatocytes transfected with miR-4449 inhibitor demonstrate increased merlin expression but decreased phosphorylated TAZ expression. In spatial transcriptomic analysis, TAZ signaling was significantly increased in MASH-fibrosis group comparing with simple steatosis or MASH without fibrosis group.

**Conclusions:** Patients with MASH-fibrosis showed increased miR-4449 expression. miR-4449 regulates merlin expression and TAZ phosphorylation in hepatocytes during lipotoxicity. miR-4449 may be a novel therapeutic target in MASH-fibrosis.

**Keywords:** Mash, Taz, Merlin, Fiborsis




## PP 2-2

### Cardiovascular Risk from Metabolic Dysfunction-Associated Steatotic Liver Disease, Cardiometabolic Risk Factor Count, and Their Longitudinal Changes

Hyeok-Hee Lee[1,2], Han Ah Lee[3], Eun-Jin Kim[1,2], Hwi Young Kim[4], Hyeon Chang Kim[1,2], Sang Hoon Ahn[5,6], Hokyou Lee[1,2], Seung Up Kim[5,6]

[1]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Korea; [2]Institute for Innovation in Digital Healthcare, Yonsei University, Seoul, Korea; [3]Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea; [4]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea; [5]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [6]Yonsei Liver Center, Severance Hospital, Seoul, Korea

**Aims:** Cardiovascular disease (CVD) risk could vary across and within individuals with metabolic dysfunction-associated steatotic liver disease (MASLD). We investigated the cardiovascular implications of MASLD, cardiometabolic risk factor count, and their longitudinal changes.

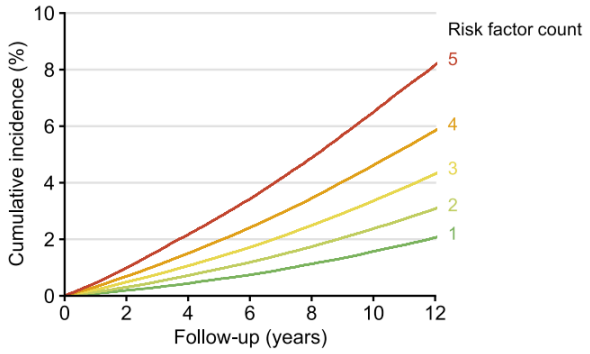
**Methods:** From nationwide health screening data, we included adults aged 20-79 who underwent baseline examinations in 2009 (N=7,292,497). Participants were classified according to MASLD status; those with MASLD were further categorized based on their count of qualifying cardiometabolic risk factors (1-5). The subgroup of participants who underwent follow-up examinations in 2011 (N=4,198,672) were additionally classified according to their baseline and follow-up MASLD status; those with persistent MASLD were further categorized based on the combination of baseline and follow-up cardiometabolic risk factor counts. CVD risk was assessed using multivariable-adjusted Cox model.

**Results:** Over a median follow-up of 12.3 years, 220,088 CVD

events occurred. The presence of MASLD was associated with higher CVD risk. Among participants with MASLD, the CVD risk increased gradually with higher cardiometabolic risk factor count (per 1-higher; HR, 1.18 [95% CI, 1.18-1.19]). The development of MASLD during follow-up was associated with higher CVD risk than its sustained absence (HR, 1.28 [95% CI, 1.25-1.31]), whereas the regression of MASLD was associated with lower CVD risk than its sustained presence (HR, 0.84 [95% CI, 0.82-0.86]). Among individuals with persistent MASLD, gaining and losing cardiometabolic risk factor counts during follow-up were associated with elevated and reduced CVD risk, respectively.

**Conclusions:** MASLD status, cardiometabolic risk factor count, and their changes were all associated with CVD risk.

**Keywords:** Metabolic dysfunction-associated steatotic liver disease, Cardiovascular risk factor, Change, Cardiovascular disease




## PP 2-3

### AI-Assisted Intraoperative Navigation for Safe Right Liver Mobilization during Pure Laparoscopic Donor Right Hepatectomy

Namkee Oh[1], Manuel Lim[2], Chan Woo Cho[3], Jongmin Shin[4], Gyu-Seong Choi[1]

[1]Department of Surgery, Samsung Medical Center, Republic of Korea, [2]Department of Surgery, MyongJi Hospital, Republic of Korea, [3]Department of Surgery, Yeungnam University Medical Center, Republic of Korea, [4]Research Institution for Future Medicine, Samsung Medical Center, Republic of Korea

**Aims:** This study was designed to explore the potential of artificial intelligence (AI) to assist in performing minimally invasive liver surgery by providing intraoperative navigation through real-time segmentation of the avascular plane.

**Methods:** A total of 48 videos of pure laparoscopic donor right hepatectomy (PLDRH) were collected from three institutions: Samsung Medical Center (n=40), Myong-Ji Hospital (n=5), and Yeungnam University Medical Center (n=3). From these videos, frames were extracted every 10 seconds during the right liver mobilization process, resulting in a total of 2,740 frames included in the study. Three surgical professionals annotated the avascular plane and vessels (inferior vena cava, inferior hepatic vein, short hepatic vein and diaphragm vein) in these frames. Subsequently, a 5-fold cross-validation using DeepLabV3+ and SegFormer models was performed on the SMC video dataset, followed by external validation on the MJH and YUMC data. The segmentation outcomes were evaluated using the Dice Similarity Coefficient (DSC).

**Results:** In the internal validation using 5-fold cross-validation, DeepLabV3+ showed DSC values of 61.21±1.73 for the avascular plane and 59.66±6.54 for veins. In external validation, the DSC values were 61.95 for the avascular plane and 62.58 for veins. SegFormer demonstrated DSC values of 61.97±1.14 for the avascular plane and 60.20±5.31 for veins in internal validation. The external validation showed DSC values of 62.4 for the avascular plane and 66.54 for veins.

**Conclusions:** This study showed that AI-guided guided right liver mobilization is a feasible approach during pure laparoscopic donor hepatectomy. Further study is required to prove its clinical benefits and practical application is MILS.

**Keywords:** Artificial intelligence, Deep learning, Laparoscopic liver resection

## PP 2-4

### EMERALD-1: A Phase 3, Randomized, Placebo-Controlled Study of Transarterial Chemoembolization (TACE) Combined with Durvalumab (D) with or without Bevacizumab (B) in Participants with Unresectable Hepatocellular Carcinoma (uHCC) Eligible for Embolization

Jeong Heo[1*], Riccardo Lencioni[2], Masatoshi Kudo[3], Joseph Erinjeri[4], Shukui Qin[5], Zhenggang Ren[5,6], Stephen L. Chan[7], Yasuaki Arai[8], Anh Mai[9], Jose Escobar[10], Yamil Alonso Lopez Chuken[11], Jung-Hwan Yoon[12], Won Young Tak[13], Tanita Suttichaimongkol[14], Mohamed Bouattour[15], Shi-Ming Lin[16], Magdalena Żotkiewicz[17], Stephanie Udoye[18], Gordon J. Cohen[18], Bruno Sangro[19]

[1]Department of Internal Medicine, College of Medicine, Pusan National University and Biomedical Research Institute, Pusan National University Hospital, Busan, Republic of Korea, [2]Department of Diagnostic and Interventional Radiology, University of Pisa School of Medicine, Pisa, Italy, [3]Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan, [4]Interventional Radiology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [5]Cancer Center of Nanjing, Jinling Hospital, Nanjing, China, [6]Department of Hepatic Oncology, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China, [7]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Sir Yue-Kong Pao Center for Cancer, The Chinese University of Hong Kong, Hong Kong SAR, China, [8]Department of Diagnostic Radiology, National Cancer Center, Chuo-ku, Tokyo, Japan, [9]General Surgery Department, Nhan

Dan Gia Dinh Hospital, Ho Chi Minh City, Vietnam, [10]Hospital San Lucas Cardiológica del Sureste, Chiapas, Mexico, [11]I Can Oncology Center, New León, Mexico, [12]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea, [13]Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea, [14]Division of Gastroenterology and Hepatology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, [15]Medical Oncology, AP-HP Hôpital Beaujon, Paris, France, [16]Department of Internal Medicine, Chang Gung Memorial Hospital, Linkou Medical Center Taoyuan, Taiwan, [17]Oncology Biometrics, Late Oncology Statistics, AstraZeneca, Warsaw, Poland, [18]Global Medicines Development, AstraZeneca, Gaithersburg, MD, USA, [19]Liver Unit and HPB Oncology Area, Clínica Universidad de Navarra and CIBEREHD, Pamplona, Spain

**Aims:** For > 20 years, TACE has been a standard of care for embolization-eligible uHCC; however, most people with uHCC treated with TACE progress within 1 year. Embolization creates a proinflammatory tumor microenvironment and increases VEGF signals; clinical studies have established the role of immune checkpoint inhibitors (ICIs; e.g. D) and VEGF inhibitors (e.g. B) in advanced HCC.

**Methods:** In EMERALD-1 (NCT03778957; double-blind, global, Phase 3 study), participants (pts) with embolization-eligible uHCC, Child-Pugh A to B7 liver function, Eastern Cooperative Oncology Group performance status 0–1, and no evidence of extrahepatic disease were randomized 1:1:1 to the D+B+-TACE, D+TACE, or TACE arms. TACE was cTACE or DEB-TACE (investigator choice). Pts received D (1500 mg) or placebo for D (Q4W) plus TACE. After completion of last TACE, pts received D (1120 mg) or placebo for D plus B (15 mg/kg) or placebo for B (Q3W). Primary endpoint was progression-free survival (PFS) for D+B+TACE vs TACE. Secondary endpoints included PFS for D+TACE vs TACE, overall survival (OS), objective response rate (ORR), time to progression (TTP), and safety for D+B+TACE or D+TACE vs TACE. PFS, ORR, and TTP were assessed by blinded independent central review (RECIST v1.1).

**Results:** In total, 616 pts with BCLC Stage A (25.8%), Stage B (57.3%), and Stage C (16.1%) were randomized to D+B+TACE (n=204), D+TACE (n=207), or TACE (n=205). Demographic and baseline characteristics were generally balanced across arms. At final PFS analysis, the primary objective was met: PFS significantly improved for D+B+TACE vs TACE (median [m] PFS 15.0 vs 8.2 months [mo]; hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.61–0.98; *P*=0.032 [threshold 0.0434]). Results were consistent across most prespecified subgroups. The secondary endpoint of PFS for D+TACE vs TACE was not statistically significant (mPFS 10.0 vs 8.2 mo; HR, 0.94; 95% CI, 0.75–1.19; *P*=0.638). ORR was 43.6%, 41.0%, and 29.6%, and mTTP was 22.0, 11.5, and 10.0 mo for D+B+TACE, D+TACE, and TACE, respectively. No new safety signals were identified. In the D+B+TACE (n=154), D+TACE (n=232), and TACE (n=200) safety analysis sets, respectively, 26.6%, 6.5%, and 6.0% of pts had maximum Grade 3/4 treatment-related adverse events (TRAEs); 12.3%, 3.4%, and 3.0% discontinued due to TRAEs; and 0%, 1.3%, and 1.5% died due to TRAEs. Pts continue to be followed for OS.

**Conclusions:** D+B+TACE is the first ICI-based regimen in a global Phase 3 trial to show statistically significant and clinically meaningful improvement in PFS, vs TACE, in pts with embolization-eligible uHCC. Safety was manageable and consistent with the safety profiles of D, B, and TACE in uHCC. D+B+TACE has the potential to set a new standard of care in uHCC.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, Durvalumab, Bevacizumab

THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# Free Paper Presentation 1

| | |
|---|---|
| **FP-1~FP-6** | MASLD, Clinical |
| **FP-7~FP-12** | HCC, Clinical 1 |
| **FP-13~FP-18** | LC & Others, Basic |
| **FP-19~FP-24** | Surgery, Technical Issues |
| **FP-25~FP-30** | HCC, Basic |
| **FP-31~FP-36** | Drug and Toxic Injury |
| **FP-37~FP-42** | ALD & Genetics |
| **FP-43~FP-48** | Autoimmune Disease |

Friday, June 28, 2024, 09:10-10:30

# 1. MASLD, Clinical

## FP-1

### Characteristics and Outcomes of Hepatocellular Carcinoma Related to MASLD versus NAFLD

Sung Won Chung[1], Ye Rim Kim[1], In Hye Song[2], Ha Il Kim[3], Ji Hyun An[3], Gi-Won Song[4], Han Chu Lee[1], Ju Hyun Shim[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Gastroenterology and Hepatology, Hanyang University College of Medicine, Guri, Repulic of Korea; [4]Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

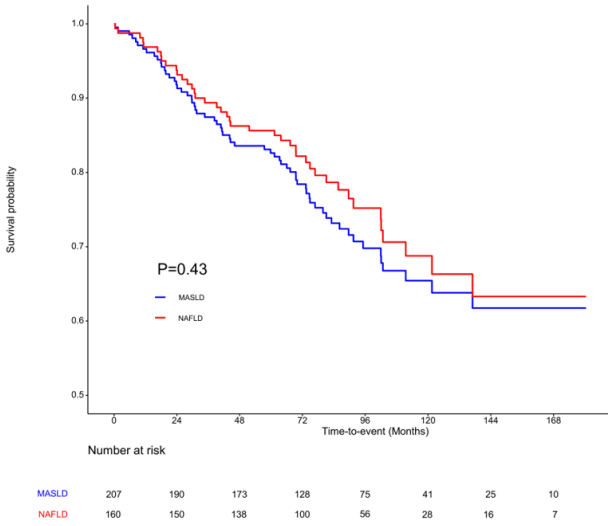
**Aims:** Since the establishment of metabolic dysfunction-associated steatotic liver disease (MASLD), multiple studies have characterized its extent and prognosis in comparison with traditional non-alcoholic fatty liver disease (NAFLD). However, there has been little information on hepatocellular carcinoma (HCC) related to these old and new disease categories. This study aimed to investigate the clinical features and outcomes of NAFLD- versus MASLD-related HCC.

**Methods:** This retrospective cohort study involved non-B, non-C patients who underwent hepatic resection for HCC at Asan Medical Center from January 2008 to December 2019. The included patients had neither autoimmune nor metabolic etiologies of chronic liver disease other than hepatic steatosis. We compared preoperative characteristics and overall survival between patients meeting the NAFLD and MASLD criteria. Hepatic steatosis and cirrhosis, and HCC were based on pathological and/or radiological findings.

**Results:** Among the 233 patients with MASLD (n=207) or NAFLD (n=160), 134 fulfilled both steatotic criteria. Patients with MASLD exhibited a significantly higher incidence of underlying cirrhosis (54.1%) compared to those with NAFLD (26.3%; $P<0.05$). Otherwise, the prevalence of diabetes mellitus (56.5% vs. 43.8%; $P<0.05$) and hypertension (66.2% vs. 55.0%; $P<0.05$) was significantly higher in patients with MASLD compared to those with NAFLD. The 5-year overall survival was 82.6% (77.6%–87.9%) for MASLD patients versus 85.0% (79.6%–90.7%) for NAFLD patients, with no significant difference between the groups (log-rank test: $P$=NS). Among cirrhotic patients, the 5-year overall survival was also comparable at 77.7% (70.3%–85.8%) for MASLD and 81.0% (69.9%–93.7%) for NAFLD ($P$=NS), and among non-cirrhotic patients, it was 88.4% (82.2%–95.1%) for MASLD and 87.3% (81.5%–93.5%) for NAFLD ($P$=NS). The 5-year survival rates in patients with single HCC were 84.1% (78.9%–89.6%) for MASLD and 86.3% (80.9%–92.1%) for NAFLD, while in multiple HCC, the survival rates were 72.0% (56.4%–91.9%) for MASLD and 78.6% (59.8%–100%) for NAFLD ($P$=NS).

**Conclusions:** Patients with MASLD-related HCC had significantly higher rates of hypertension, diabetes mellitus, and cirrhosis compared to those with NAFLD-related HCC, though this did not significantly influence overall survival. Our findings suggest that previous data and experiences on NAFLD-related HCC could be utilized in caring and studying MASLD-related HCC patients, particularly in non-cirrhotics.

**Keywords:** MASLD, NAFLD, Overall survival, Cirrhosis




## FP-2

### Impact of Cardiometabolic Risk Factors and Alcohol Consumption on Mortality in Steatotic Liver Diseases: A Comparative Analysis of MASLD and MetALD

Young Chang, Soung Won Jeong, Jae Young Jang

Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea

**Aims:** Metabolic dysfunction associated steatotic liver disease (MASLD) and MASLD with increased alcohol intake (MetALD) are distinct yet overlapping conditions that significantly impact liver disease progression and mortality. This study aims to delineate the differential impacts of cardiometabolic risk factors and alcohol consumption on hepatic fibrosis, cancer-related mortality, cardiovascular mortality, and all-cause mortality in patients with MASLD and MetALD.

**Methods:** Individuals aged 20–79 years without any history of cancer, cardiovascular disease, or secondary causes of chronic liver disease were selected from the Korean National Health

and Nutrition Examination Surveys from 2007 to 2015. Their mortality data until November 2023 were retrieved from the National Death Registry. MASLD and MetALD were defined based on hepatic steatosis index> 36, cardiometabolic risk factors, and alcohol consumption. Significant fibrosis was defined as fibrosis-4 index ≥ 2.67.

**Results:** MASLD and MetALD patients showed significantly higher risks of cancer-related mortality compared to controls, with hazard ratios (HR) of 2.610 (95% CI: 1.029–6.618, *P*=0.043) and 3.355 (95% CI: 1.097–10.263, *P*=0.034), respectively. High alcohol intake (350-420g/week in male, 280-350g/week in female) was particularly detrimental in MetALD patients, significantly increasing cancer mortality (HR 5.864, 95% CI 3.6-9.6, *P*=0.033). Cardiovascular mortality did not significantly differ between patient groups and controls. All-cause mortality was notably higher in MetALD (HR: 2.085, 95% CI: 1.127–3.860, *P*=0.019), especially among current smokers (HR: 10.612, 95% CI 1.385-81.289, *P*=0.023). Significant fibrosis was especially prevalent in MASLD women (OR 3.463, 95% CI 1.391-8.622, *P*=0.008) and in cases with 5 CMRFs in both diseases, with ORs nearing tenfold in MASLD and 8.5-fold in MetALD.

**Conclusions:** Patients with MASLD and MetALD exhibited increased cancer-related and all-cause mortality rates compared to the healthy control group, particularly in MetALD, indicating that metabolic dysfunction coupled with significant alcohol intake may synergistically amplify the adverse outcomes.

**Keywords:** MASLD, METALD, Cardiometabolic risk factor, Mortality

## FP-3

### Skeletal Muscle Mass Loss According to Sub-Classification of Steatotic Liver Disease: Insights from a Longitudinal Cohort Study

Aryoung Kim[1,2], Danbee Kang[3,4], Sung Chul Choi[5], Dong Hyun Sinn[1], Geum-Youn Gwak[1]

[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [2]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, South Korea; [3]Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, South Korea; [4]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea; [5]Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea.

**Aims:** Identifying risk factors for sarcopenia is important due to its significant effect on health. The association between sarcopenia and the newly proposed steatotic liver disease (SLD) and its sub-classification has largely been unexplored.

**Methods:** This longitudinal cohort study included 67,321 adults who underwent at least two health check-up examinations with bioelectrical impedance analysis and abdominal ultrasound (US) imaging between 2004 and 2020. SLD participants were further categorized as cryptogenic SLD, metabolic dysfunction-associated SLD (MASLD), or MASLD with increased alcohol intake (MetALD). SLD severity was assessed based on fibrosis-4 (FIB-4) score.

**Results:** The average duration of follow-up was 5.9 years. The annual appendicular skeletal muscle mass (ASM) change was −30.9 g (95% CI −32.3, −29.6) and −38.4 g (95% CI −40.4, −36.4) in participants without and with SLD, respectively. When assessed based on SLD severity, annual ASM loss was fastest in SLD participants with FIB-4 score ≥ 1.3, followed by those with FIB-4 score < 1.3 and those without SLD. In multivariable adjusted analysis, annual ASM loss was fastest in subjects with MetALD (−50.0 g; 95% CI −93.7, −6.4), followed by individuals with MASLD (−24.8 g; 95% CI −60.8, 11.2) and those with cryptogenic SLD (reference). This pattern was consistent throughout SLD severity but more pronounced in SLD subjects with FIB-4 score ≥ 1.3.

**Conclusions:** The loss of skeletal muscle mass was fastest in the subjects with MetALD, followed by participants with MASLD and cryptogenic SLD. Particular attention to prevent sarcopenia should be given to MASLD and MetALD patients, especially in case with advanced fibrosis.

**Keywords:** Metabolic dysfunction-associated steatotic liver disease (MASLD), Metabolic dysfunction-associated alcoholic liver disease (METALD), Sarcopenia

## FP-4

### Comparison of Dipeptidyl Peptidase-4 Inhibitor and Sodium-Glucose Cotransporter-2 Inhibitor in Diabetic Patients with Steatotic Liver Disease

Yunmi Ko, Moon Haeng Hur, Youngsu Park, Jeayeon Park, Hyunjae Shin, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Jung-Hwan Yoon, Yoon Jun Kim

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**Aims:** There is currently insufficient evidence to recommend one oral hypoglycemic agent over another for diabetic patients to improve hepatic steatosis or prevent advanced fibrosis. We aimed to evaluate the effectiveness of dipeptidyl peptidase-4 inhibitors (DPP-4i) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) in diabetic patients with metabolic dysfunction-associated fatty liver disease (MAFLD) or metabolic dysfunction-associated steatotic liver disease (MASLD).

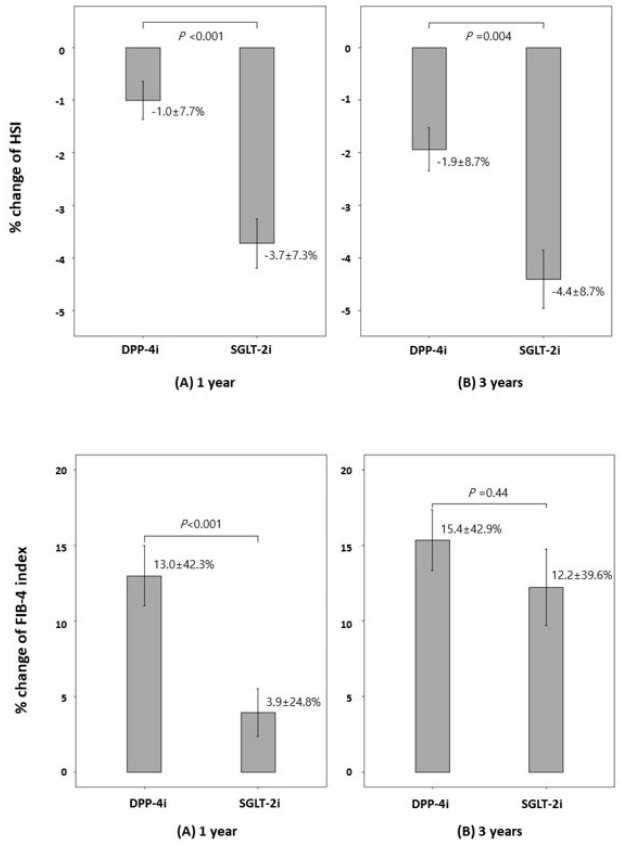
**Methods:** This study included type 2 diabetes mellitus (DM) patients with steatotic liver who newly received either DPP-4i or SGLT-2i as a second-line treatment between 2014 and 2021 at a single tertiary hospital. MAFLD or MASLD was confirmed using radiologic evaluation or hepatic steatosis index (HSI).

Changes in HSI and fibrosis-4 (FIB-4) index were compared after treatment initiation.

**Results:** A total of 3,506 patients were consecutively enrolled: 3,013 and 493 patients received DPP-4i and SGLT-2i treatment, respectively. After applying propensity score matching, the SGLT-2i group showed a significantly greater reduction in HSI after one year of treatment compared to the DPP-4i group among DM-MAFLD population (DPP-4i vs. SGLT-2i: -1.5% vs. -3.5%, $P$<0.001). The FIB-4 indices of both groups increased; however, it was more significant in the DPP-4i group at year 1 (11.7% vs. 4.7%, $P$=0.015). In patients with DM-MASLD, the SGLT-2i group showed more prominent percent changes in terms of HSI (-1.0% vs. -3.7%, $P$<0.001) and FIB-4 index (13.0% vs. 3.9%, $P$<0.001) compared to the DPP-4i group at year 1.

**Conclusions:** In patients with DM-MAFLD or DM-MASLD, SGLT-2i treatment was associated with greater improvement in hepatic steatosis and delayed fibrotic progression compared to DPP-4i treatment.

**Keywords:** Steatotic liver, Type 2 diabetes, Dipeptidyl peptidase-4 inhibitor, Sodium-glucose cotransporter-2 inhibitor




## FP-5

### Sequential Approach Using Combination of Newly Developed HOMA2-IR-ALT-TE-MASH (HALT-M) Score and Magnetic Resonance Elastography for Non-Invasive Identifying at-Risk Metabolic Dysfunction-Associated Steatohepatitis in Obese Subjects

Yoonseok Lee[1], Oh Sang Kwon[1], Yun Soo Kim[1], Ju Hyun Kim[1], Dae Ho Lee[2], Seung Kak Shin[1]

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Gachon University College of Medicine, Gil Medical Center, Incheon, Korea; [2]Division of Endocrinology, Department of Internal Medicine, Gachon University College of Medicine, Gil Medical Center, Incheon, Korea

**Aims:** Presence of metabolic dysfunction-associated steatohepatitis (MASH) and significant fibrosis are associated with increased risk of disease progression and poor clinical outcomes in metabolic dysfunction-associated steatotic liver disease (MASLD) patients. Insulin resistance has been suggested to play a crucial role in the pathogenesis of MASH. However, this has been given little consideration in most of the non-invasive markers for identifying at-risk MASH. This study aimed to develop the non-invasive sequential approach using combination of HOMA2-IR-ALT-TE-MASH (HALT-M) score and magnetic resonance elastography (MRE) for diagnosis of borderline/definite MASH [MASLD activity score (MAS) ≥ 4] and at-risk MASH (MAS ≥ 4 and fibrosis stage ≥ 2).

**Methods:** Obese (BMI ≥ 25 kg/m$^2$) MASLD patients were prospectively enrolled at Gachon University Gil Medical Center between March 2018 and January 2023. All patients underwent histological confirmation. Newly developed HALT-M score consists of three risk factors: 1) presence of HOMA2-IR ≥ 2.35 or DM, 2) increased ALT (men ≥ 35 U/L, women ≥ 25 U/L), 3) transient elastography (TE) > 8.0 kPa. The three factors were given a score of 1 point each, and a score of 0-3 was calculated and used for non-invasive diagnosis of borderline/definite MASH or at-risk MASH. And combination of HALT-M score and MRE (HALTME index) was used for non-invasive diagnosis of at-risk MASH. Diagnostic performance was evaluated based on the areas under the receiver operating characteristic curve (AUCs).

**Results:** A total 84 patients (mean age of 35±11 years; 79.8% of female; mean BMI of 37.6±6.1 kg/m2; 35.7% of DM; 84.5% of bariatric surgery) were finally enrolled. At histological confirmation, 43 (51.2%) and 16 (19.0%) patients were diagnosed with borderline/definite MASH and at-risk MASH, respectively. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of HALT-M score ≥ 2 for diagnosis of borderline/definite MASH were 91%, 60%, 71%, 86%, respectively (AUC 0.753; 95% CI 0.645-0.862, $P$<0.001). The sensitivity, specificity, PPV, and NPV of HALT-M score ≥ 2 for diagnosis of at-risk MASH were 100%, 41%, 29%, 100%, respectively (AUC 0.709; 95% CI 0.594-0.824, $P$<0.001). The sensitivity,

specificity, PPV, and NPV of HALTME index (HALT-M score ≥ 2 plus MRE ≥ 3.6 kPa) for diagnosis of at-risk MASH were 80%, 90%, 63%, 95%, respectively (AUC 0.849; 95% CI 0.723-0.974, *P*<0.001).

**Conclusions:** Newly developed HALT-M score including HOMA2-IR, ALT and TE demonstrated high sensitivity in diagnosis of borderline/definite MASH and at-risk MASH. The sequential addition of MRE value increased the specificity for diagnosis of at-risk MASH, showing good diagnostic performance. A large-scale validation study is warranted.

**Keywords:** MAFLD, MASH, HALT-M score

## FP-6

### Protective Effects of MASLD in Chronic Hepatitis B Patients on the Risk for Hepatocellular Carcinoma, Hepatic Decompensation, and Mortality

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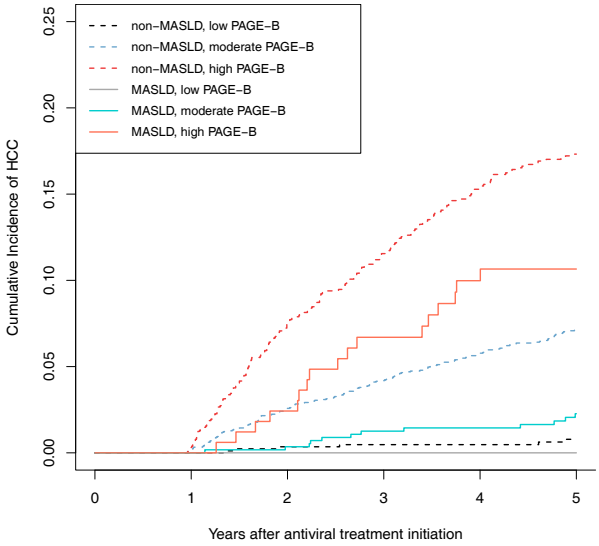
**Aims:** Both metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic hepatitis B (CHB) can proceed to hepatocellular carcinoma (HCC), hepatic decompensation (DCC), and mortality. However, the role of MASLD in CHB patients in this process remains controversial.

**Methods:** This study included 5,614 treatment-naive CHB patients with or without MASLD between 2007 and 2021. We compared the incidence rates and cumulative incidences of HCC, DCC, and mortality between MASLD and non-MASLD patients. To adjust for confounding variables, the inverse probability of treatment weighting (IPTW) was used. Furthermore, patients were stratified by PAGE-B scores to compare the HCC cumulative incidence between MASLD and non-MASLD patients.

**Results:** MASLD patients (n=1,001) had lower incidence rates of DCC (5.4 per 1,000 person-years, hazard ratio [HR] 0.379), HCC (6.8 per 1,000 person-year, HR 0.418), and mortality (1.4 per 1,000 person-year, HR 0.199) compared to non-MASLD patients (n=4,613; 14.3, 16.1, and 7.1 per 1,000 person-years for DCC, HCC, and mortality, respectively). In the analysis after IPTW, the respective adjusted HRs of MASLD were 0.532 (95% confidence interval [CI] 0.288-0.982, *P*=0.043), 0.522 (95% CI 0.306-0.893, *P*=0.018), and 0.432 (95% CI 0.185-1.009, *P*=0.052) for DCC, HCC, and mortality. The results remained consistent even after stratification by PAGE-B. Furthermore, an increase in cardiometabolic risk factors was associated with increased incidences of DCC, HCC, and mortality, with or without stratification by PAGE-B.

**Conclusions:** We explore the effect of newly defined MASLD in the progression of CHB patients to HCC, DCC, and mortality. Concurrent MASLD in CHB patients was associated with a lower risk of DCC, HCC, and mortality in CHB patients after adjustment by IPTW and stratification by PAGE-B. Therefore, different criteria for HCC surveillance could be applied in CHB patients with MASLD.

**Keywords:** Chronic hepatitis B, MASLD, Hepatocellular carcinoma, Decompensation




Friday, June 28, 2024, 13:30-14:50

# 2. HCC, Clinical 1

## FP-7

### Atezolizumab plus Bevacizumab versus Lenvatinib for BCLC-B Stage of Patients with Hepatocellular Carcinoma: A Large Real-Life Worldwide Population

Francesco Vitiello, Margherita Rimini, Mara Persano, Toshifumi Tada, GokiSuda, Shigeo Shimose, Masatoshi Kudo, Jaekyung Cheon, Fabian Finkelmeier, Silvia Foti,Silvia Camera,Ho Yeong Lim, Gianluca Masi, Changhoon Yoo, Sara Lonardi, Federico Rossari, Elisabeth Amadeo, Andrea Casadei-Gardini

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**Aims:** This study is a real-world analysis about patients with Barcelona Clinic Liver Cancer stage B (BCLC-B) hepatocellular carcinoma (HCC) treated with Atezolizumab plus Bevacizumab (A+B) vs Lenvatinib.

**Methods:** The study population included patients affected by intermediate (BCLC-B) HCC not suitable for locoregional therapies (LRTs) from eastern and western populations, who received A+B or Lenvatinib as first-line treatment. Univariate and multivariate analyses were used to evaluate predictor factors for overall survivor (OS) and Time to progression (TTP) while prognostic factors were analyzed by univariate and multivariate analysis using Cox regression model.

**Results:** 919 patients were enrolled: 561 (61%) received Lenvatinib and 358 (39%) received A+B. The median overall survivor (mOS) for Lenvatinib cohort was 21.3 months compared to 15.8 months for A+B cohort as first-line treatment (Lenvatinib Vs A+B): Hazard ratio (HRs) 0.84 *P*=0.22. The median time to progression (mTTP) for Lenvatinib cohort was 7.3 months compared to 8.7 months for A+B cohort as first-line treatment (Lenvatinib vs A+B): HR 1.15 *P*=0.10. The multivariate analysis confirmed no different in terms of mOS and mTTP between the two treatments. Objective response rate (ORR) was 47.1% for Lenvatinib cohort and 27.1% for A+B cohort *P*<0.000001. Lenvatinib cohort showed a significantly higher incidence of hand-foot skin reaction (HFSR), hypertension, diarrhea, fatigue, decrease appetite, hypothyroidism compared to A+B cohort. Favorable prognostic factors for OS in Lenvatinib cohort were, platelets (PLT) > 100.000 (HR 0.68 *P*=0.02), HCC non-alcoholic steatohepatitis/non-alcoholic fatty liver disease (NASH/NAFLD) related (HR 0.53, *P*=0.03). Favorable prognostic factors for TTP in the A+B cohort were in TACE refractory patients (HR 0.76, *P*=0.02), PLT <100.000 (HR 0.62, *P*=0.0067), and Neutrophil-to-lymphocyte ratio (NLR) <3 (HR 0.78, *P*=0.04).

**Conclusions:** The study showed a greater response of Lenvatinib and no statistically significant differences between Lenvatinib and A+B in terms of efficacy.

**Keywords:** HCC, Lenvatinib, First line, Atezolizumab plus bevacizumab

## FP-8

### An Early Increase in IL-10 and TNF-α Levels Following Atezolizumab Plus Bevacizumab Treatment Predicts Survival in Advanced HCC Patients

**Soon Kyu Lee**, Soon Woo Nam, Jung Hyun Kwon

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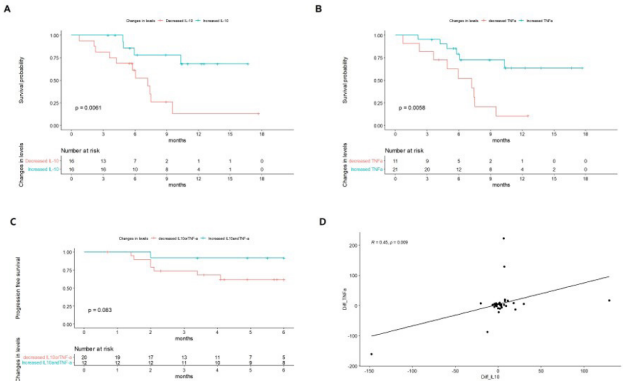
**Aims:** While treatment with atezolizumab plus bevacizumab (Ate/Bev) has demonstrated improved survival rates in patients with advanced hepatocellular carcinoma (HCC), there remains a scarcity of reliable biomarkers for predicting patient outcomes following Ate/Bev treatment. This study aimed to evaluate the impact of cytokine levels and their early changes post-treatment on the clinical outcomes of advanced HCC patients.

**Methods:** We prospectively enrolled 32 consecutive patients with advanced hepatocellular carcinoma (HCC) who were undergoing treatment with atezolizumab plus bevacizumab (Ate/Bev). Following enrolment, initial blood samples were collected from each patient before their first Ate/Bev treatment. Subsequently, follow-up blood samples were taken prior to their second Ate/Bev therapy, scheduled 20 days after the initial treatment. These samples were analyzed to measure the levels of IL-2, IL-6, IL-10, IL-12, IL-17, IFN-$\gamma$, and TNF-$\alpha$, and to calculate the changes in these levels before and after the initial Ate/Bev treatment. The primary outcome measured was overall survival, while secondary outcomes included progression-free survival (PFS) at 6 months and the correlation between cytokine levels and clinical outcomes.




**Results:** Among the 32 patients included in the study, 13 (40.6%) passed away within a median follow-up period of 6.3 months. The mean age was 64.2 years, with the majority being male (93.8%). The average level of alpha-fetoprotein was measured at 77.9 ng/mL, and 17 patients (53.1%) presented with metastasis. Baseline levels of IL-10, IL-17, and TNF-$\alpha$ did not show a significant impact on overall survival. However, patients who experienced an increase in IL-10 (Figure A), IL-17, and TNF-$\alpha$ levels (Figure B) demonstrated significantly better survival compared to those with decreased levels in these cytokines (*P*<0.05 for all). Other cytokines did not show a significant impact on survival outcomes. Furthermore, patients with increased IL-10 and TNF-$\alpha$ levels exhibited marginally better PFS at 6 months compared to those without such increases (Figure C). Interestingly, a significant positive correlation was observed between the changes in IL-10 and TNF-$\alpha$ levels (*P*=0.009; Figure D). Finally, in the multivariable analysis, an increase in IL-10 and TNF-$\alpha$ levels emerged as a significant predictor of improved survival in advanced HCC patients undergoing Ate/Bev treatment (hazard ratio, 0.07; 95% confidence interval, 0.01-0.46; *P*=0.005).

**Conclusions:** Our findings suggest that an early increase in IL-10 and TNF-$\alpha$ levels following Ate/Bev treatment may serve as

a convenient and effective predictive marker for clinical outcomes in advanced HCC patients undergoing this treatment regimen.

**Keywords:** Hepatocellular carcinoma, Immune checkpoint inhibitor, Cytokine, Biomarker

## FP-9

### Long-Term Survival Outcomes of Surgical Resection versus Radiofrequency Ablation for Solitary Hepatocellular Carcinoma Less Than 3cm: A Systematic Review and Meta-Analysis

**Doyoung Lee**, Sanghoon Kim, Byeonggon Na, Sungmin Kim, Rakkyun Oh, Kihun Kim

Liver Transplantation, Asan Medical Center, Republic of Korea

**Aims:** The oncologic outcomes of surgical resection (SR) versus radiofrequency ablation (RFA) in treating early-stage hepatocellular carcinoma (HCC) remains controvisial. The aim of this meta-analysis was to compare the long-term survival outcomes between SR and RFA for patients with solitary HCC less than 3cm.

**Methods:** Electronic databases were searched from January 2000 to July 2023 for studies comparing long-term outcomes between SR and RFA for treatment of HCC. The long-term outcomes including three-, five-, and eight-year overall survival (OS) and recurrence-free survival (RFS) were abstracted. Individual and pooled hazard ratios (HRs) with 95 % confidence interval of each outcome was analyzed.

**Results:** Eighteen studies including randomized controlled or matched cohort studies comprising 5294 patients were analysed. In terms of OS, SR group had better three-year OS (HR: 0.66, 95% CI [0.56, 0.79], $P<0.001$), five-year OS (HR: 0.66, 95% CI [0.57, 0.77], $P<0.001$), and eight-year OS (HR: 0.71, 95% CI [0.57, 0.88], $P=0.002$). For RFS, SR group had better three-year RFS (HR: 0.63, 95% CI [0.55, 0.72], $P<0.001$), five-year RFS (HR: 0.60, 95% CI [0.51, 0.70], $P<0.001$), and eight-year RFS (HR: 0.67, 95% CI [0.60, 0.75], $P<0.001$). In subgroup analysis, open surgical resection showed better long-term outcomes than RFA in OS and RFS and it was not clear whether minimally invasive surgery is superior to RFA for solitary HCC less than 3cm.

**Conclusions:** SR is preferred treatment of solitiray HCC less than 3cm over RFA with a better long-term OS and RFS.

**Keywords:** Surgical resection, Radiofrequency ablation, Hepatocellular carcinoma

## FP-10

### Lenvatinib (L) versus Sorafenib (S) Second-Line Therapy in Hepatocellular Carcinoma (HCC) Patients (P) Progressed to Atezolizumab plus Bevacizumab (AB)

**Mara Persano**[1-2], Margherita Rimini[3], Toshifumi Tada[4], Goki Suda[5], Jaekyung Cheon[6], Changhoon Yoo[7], Federico Rossari[3], Elisabeth Amadeo[3], Francesco Vitiello[3], Silvia Camera[3], Silvia Foti[3], Luigi Mascia[1], Stefano Cascinu[3], Mario Scartozzi[8], Andrea Casadei Gardini[3]

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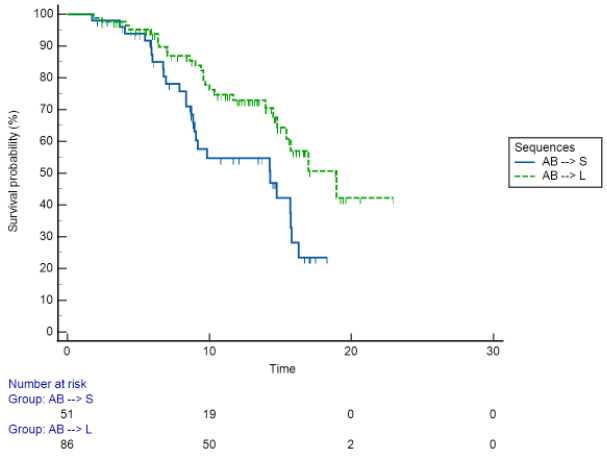
**Aims:** This retrospective multicenter real-world study aims to compare outcomes reached by L and S second-line therapy in HCC P treated with first-line AB.

**Methods:** The overall cohort included 891 HCC P from 5 countries (Italy, Germany, Portugal, Japan, and the Republic of Korea) treated with AB in first-line setting. 53.0% of P had progressive disease after first-line therapy, of which 51.5% received a second-line treatment. Data from 137 P were available: 37.2% received S and 62.8% L.

**Results:** L second-line subgroup achieved a median overall survival (mOS) of 18.9 months, significative longer ($P=0.01$; HR: 2.24) compared to S subgroup that reached a mOS of 14.3 months. Multivariate analysis highlighted ALBI 1 grade [$P<0.01$; hazard ratio (HR): 5.23] and L second-line therapy ($P=0.01$; HR: 2.18) as positive prognostic factor for OS. Forest plot highlighted a positive trend in terms of OS in favor of P treated with L second-line regardless of baseline characteristics before first-line therapy. Regarding first-line outcomes, L second-line subgroup achieved a median progression-free survival (mPFS) of 3.5 months, while S second-line subgroup reached a mPFS of 4.3 months (p 0.42; HR: 1.15). There was no difference in overall response rate (L 26.1% vs. S 19.8%; $P=0.29$) and disease control rate (L 76.8% vs. S 66.4%; $P=0.71$). Among the group of P reaching a first-line PFS inferior to 6.0 months, P treated with L second-line achieved a mOS of 17.0 months significative longer ($P=0.02$; HR: 2.24) compared to those treated with S (9.2 months). Within the group of P reaching a first-line PFS superior to 6.0 months, there was no difference in mOS (S 15.7 months vs. L not reached; $P=0.12$; HR: 2.41).

**Conclusions:** L second-line therapy is superior to S in HCC P progressed to first-line AB.

**Keywords:** Atezolizumab plus bevacizumab, LENVATINIB, Sorafenib, HCC




## FP-11

### Transarterial Radioembolization versus Transarterial Chemoembolization plus External Beam Radiotherapy in Hepatocellular Carcinoma with Portal Vein Thrombosis

**Jae Woong Yoon**[1,*], Hyunjae Shin[1,2,*], Seung Up Kim[3,*], Yuri Cho[2,*], Youngsu Park[1], Yunmi Ko[1], Moon Haeng Hur[1], Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Jung-Hwan Yoon[1], Dong Hyun Sinn[4], Yoon Jun Kim[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [2]Center for Liver and Pancreatobiliary Cancer, National Cancer Center, Goyang, Korea; [3]Department of Internal Medicine and Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [4]Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea;

**Aims:** Transarterial radioembolization (TARE) has become promising therapy in patients with hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT). However, previous treatment with transarterial chemoembolization (TACE) plus external beam radiotherapy (RT) has not been well compared to TARE. We compared the outcomes of TARE and TACE plus RT in treatment-naïve patients with HCC and PVTT, who had no extrahepatic metastasis.

**Methods:** This multicenter study included 187 patients initially treated with TARE (n=125) or TACE plus RT (the TACE-RT group, n=62) between 2005 and 2023. The primary outcome was overall survival (OS) and the secondary outcomes included progression-free survival (PFS), objective response rate (ORR), PVTT response rate. Two groups were also compared utilizing balancing baseline characteristics by propensity score matching (PSM).

**Results:** The median OS of the TARE and TACE-RT groups were 27.5 and 21.0 months, respectively ($P$=0.028). The TARE group exhibited significantly longer OS compared to the TACE-RT group before PSM (hazard ratio [HR]=0.61, 95% confidence interval [CI]=0.39–0.95, $P$=0.029) and after PSM (HR=0.37, 95% CI=0.18-0.78, $P$=0.008). PFS was not inferior in the TARE group compared to the TACE-RT group. In the matched cohorts, the TARE group showed a higher ORR of 43.8%, compared to 27.1% in the TACE-RT group. Additionally, the complete or partial response of PVTT was better in the TARE group, at 35.5%, relative to 25% in the TACE-RT group.

**Conclusions:** In the treatment of locally advanced HCC with PVTT, TARE demonstrated superior OS compared to TACE plus RT.

**Keywords:** Hepatocellular carcinoma, Radioembolization, Chemoembolization, Radiotherapy, portal vein tumor thrombosis

## FP-12

### Comprehensive Multi-Omics Analysis for Resectable Hepatocellular Carcinoma Uncovers Biomarkers to Predict Microvascular Invasion

**Incheon Kang**, Woo Young Kwon, Sung Hwan Lee

Department of Surgery, Bundang CHA, Republic of Korea

**Aims:** Microvascular invasion (MVI) is a key factor in predicting cancer recurrence in resectable hepatocellular carcinoma (HCC). A precision strategy using cancer-specific multi-omics features to predict MVI at HCC diagnosis is needed.

**Methods:** We analyzed gene expression in resected human HCC (Discovery cohort, n=240) to identify a transcriptomic signature predicting MVI. Using the cancer dependency map (DepMap) project data, we conducted comprehensive analyses, including multi-omics characterization, drug sensitivity screening, and in-silico prediction methods. The MVI-predictive transcriptomic signature was validated in independent cohorts (TCGA-LIHC; n=373, KOREA; n=188, TOKYO; n=183, MODENA; n=78, ZHONGSHAN; n=159).

**Results:** A 1028-gene MVI signature was identified, showing significant prediction accuracy in the validation cohort (AUC=0.865, $P$<0.01). Multi-omics analysis highlighted aggressive tumor biology linked to the MVI signature and identified specific biomarkers.

**Conclusions:** Multi-omics profiling in resectable HCC identifies biomarkers predicting MVI, aiding in distinguishing tumors with aggressive biology. This approach could lead to a precision strategy for identifying HCC patients who would benefit most from surgical resection, informed by ongoing clinical trials based on this study.

**Keywords:** Hepatocelluar carcinoma, Microvascular invasion, Prognostic factor

Friday, June 28, 2024, 09:10-10:30

## 3. LC & Others, Basic

### FP-13

### The Hepatic Recovery Effects of Exosomes Derived from Human Chemically Derived Hepatic Progenitor Cells (hCdHs)

**Min Kim**[1], Soraya Salas-Silva[1], Ji Hyun Shin[1], Dongho Choi[1]

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**Aims:** Exosomes, extracellular vesicles facilitating intercellular communication, have gained attention as a promising treatment for liver diseases. Recent research highlights the effectiveness of exosomes derived from stem cells, renowned for therapeutic efficacy in liver conditions, sparking a growing interest in exosome-based treatments. A prior study successfully developed chemically derived human hepatic progenitor cells (hCdHs) through direct lineage reprogramming from human hepatocytes, showcasing their ability to regenerate the liver in disease-model mice following transplantation.

**Methods:** This study focuses on investigating the liver regenerative potential of hCdHs-derived exosomes. hCdHs were cultured on a large scale and exosomes were isolated from the culture supernatant through Ultra-centrifugation. Characterization of the exosomes was conducted through NTA, Western blotting, Flow cytometry, and Cryo-TEM analyses, used in both *in vivo* and *in vitro* experiments. Liver disease induction in mice using CCl4 was followed by the intravenous injection of hCdHs-derived exosomes, and the extent of liver damage mitigation was evaluated through H&E, Sirius red, and IHC analyses.

**Results:** The size and morphology of hCdHs-derived exosomes were assessed using NTA and Cryo-TEM. Confirmation of exosome marker proteins, including CD9, CD63, and CD81, was achieved through Western blotting and Flow cytometry analyses. When these exosomes were injected into mice with liver damage induced by CCl4, liver damage was observed to be alleviated.

**Conclusions:** As hCdHs-derived exosomes were isolated from patient-specific liver stem cells, it appears that exosomes, along with hCdHs cells, can develop into one of the methods to safely restore liver damage to patients.

**Keywords:** Exosome, Hepatic recovery effects, Hepatic progenitor cells

### FP-14

### Catecholamine Induces Hepatocyte Proliferation by Beta-2 Adrenergic Receptor-Mediated YAP Activation in Partial Hepatectomy

**Katherine Po Sin Chung**[1], Kyurae Kim[1], Sung Eun Choi[1], Min Jeong Kim[1], Eunmi Lee[1], Kwang Woo Lee[1], Won-Il Jeong[1,2]

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**Aims:** The entire process of liver regeneration is meticulously coordinated by a cascade of growth factors, inflammatory responses, and complex signaling pathways. Despite of growing research on neurological signals in liver pathophysiology, the role of neurological involvement in liver regeneration remains elusive. Here, we delved into the impact of catecholamines and beta-2 adrenergic receptor (ADRB2) during early stage of liver regeneration following partial hepatectomy (PHx).

**Methods:** To study liver regeneration, 45% PHx was performed to wild-type and ADRB2 knockout mice. Serum catecholamine levels were examined by ELISA. Whole liver tissues were subjected to bulk RNA sequencing, qRT-PCR, western blotting and GeoMx spatial transcriptome analyses. In humans, plasma catecholamine levels of liver donors were evaluated. *In vitro*, primary hepatocytes and cell lines of mouse and human were stimulated with a specific ADRB2 agonist.

**Results:** Serum catecholamine levels increased at 30 minutes and sustained at 60 minutes after PHx. Bulk RNA sequencing analysis revealed significant upregulation of *Adrb2* expression, which was confirmed in isolated hepatocytes by qRT-PCR analysis, suggesting catecholamine-mediated ADRB2 activation. Moreover, proliferating hepatocytes with PCNA and YAP activation were mainly observed at hepatic zone 2 in PHx-operated liver. Accordingly, spatial transcriptomics also demonstrated up-regulation of *Adrb2* and YAP target genes in zone 2 of PHx-operated liver tissues compared to those of sham controls. *In vitro* stimulation of ADRB2 in primary hepatocytes and cell lines showed nuclear YAP translocation and activation. These findings were abolished in *Adrb2* knockout mice and isolated hepatocytes. Similarly, the elevated levels of catecholamine and hepatic YAP activation by ADRB2 stimulation were observed in liver donors and human liver cell lines, respectively.

**Conclusions:** In early liver regeneration, catecholamines may stimulate ADRB2 and promote hepatocyte proliferation via YAP activation, which may provide novel insights in facilitating liver regeneration through neurological signalling pathway.

**Keywords:** Liver regeneration, Beta-2 adrenergic Receptor, Par-

tial hepatectomy, Catecholamines

## FP-15

### Development of Mesenchymal Stem Cell-Derived Exosomes Targeting Liver Sinusoid Endothelial Cells for the Treatment of Chronic Liver Disease

Seul Ki Han[1,2], Ji Won Lee[3], Jin Suk Lee[2], Mi Ra Lee[1], Yong Serk Park[3],Soon Koo Baik[1,2], Moon Young Kim[1,2]

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**Aims:** The prevalence of liver disease is increasing every year, and has a high mortality rate and its treatment process is notoriously complicated. In a healthy liver, blood circulation is facilitated by the exchange of substances between blood and liver tissue through the fenestrae of liver sinusoidal endothelial cells. However, if the perforation is closed and blood circulation is not possible due to liver damage, it can lead to fibrosis and chronic liver disease. Since there is no specific treatment after cirrhosis, it is important to address liver fibrosis in the early stages. In recent studies, mesenchymal stem cell-derived materials have the potential to alleviate fibrosis, so an approach to treating fibrosis has been sought by replacing it with exosomes containing active ingredients for regeneration. Since exosomes inherently lack liver-targeting capabilities, the mannose receptor, which is a scavenger receptor specifically expressed in liver endothelial cells, was utilized as a liver target.

**Methods:** The soup obtained by culturing MSC was obtained by removing cell debris other than exosome through a syringe filter to obtain a filtrate eluant, and then through lysis and washing, other things other than exosome were removed, and the elution buffer was treated to obtain a pure exosome and used in the experiment. After analyzing the physicochemical properties of the prepared particles through particle analysis, toxicity was identified through CCK assay. *In vitro* binding assay used LSEC and RAW 264.7 cells expressing manose receptor, and progressed to HUVEC not expressing manose receptor. And we did biodistribution to see if we can actually target the LSEC of the livers through *in vivo*.

**Results:** In this study, exosomes were PEGylated to enhance their stability, and coupled with mannose molecules to facilitate effective delivery to liver cells. Subsequent *in vitro* transfection demonstrated specific binding to RAW 264.7 and LSEC cells, which highly express mannose receptors. Man-Exo also exhibited a more specific binding affinity for LSEC compared to RAW 264.7 cells in coculture. Furthermore, the biodistribution studies showed that the intravenously administered Man-Exo accumulated longer in the blood and localized higher compared to bare exosomes.

**Conclusions:** These findings suggest the Man-Exo are clinically applicable as a novel targeted delivery system for the regeneration of liver fibrosis.

**Keywords:** Liver sinusoidal endothelial cells-target, Mesenchymal stem cells, Exosomes, Liver fibrosis regeneration

## FP-16

### Mechanisms of Liver Cirrhosis through the Regulation by MCRS1

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**Aims:** Due to the absence of genetic animal models that faithfully reproduce essential clinical manifestations of cirrhosis, the molecular mechanisms underlying its pathogenesis have been insufficiently understood, resulting in limited therapeutic options. Therefore, our objective was to enhance comprehension of the pathological pathways associated with cirrhosis by employing an innovative murine model.

**Methods:** Our study presents the inaugural murine genetic model designed to simulate human cirrhosis through targeted deletion of microspherule protein 1 (MCRS1) specifically within hepatocytes, a constituent of the non-specific lethal (NSL) and INO80 chromatin-modifier complexes. Leveraging this genetic platform in conjunction with additional murine models, cell cultures, and human specimens, coupled with quantitative proteomics, single nuclei/cell RNA sequencing, and chromatin immunoprecipitation assays, we interrogated the underlying mechanisms of cirrhosis.

**Results:** The absence of MCRS1 in murine hepatocytes induces alterations in the expression of bile acid (BA) transporters, notably marked by the decreased expression of Na+-taurocholate cotransporting polypeptide (NTCP), resulting in BA accumulation within sinusoids and subsequent activation of hepatic stellate cells (HSCs) through the farnesoid X receptor (FXR), which is primarily localized in human and murine HSCs. Correspondingly, reintroduction of NTCP in murine models mitigates cirrhosis, while genetic deletion of FXR in HSCs attenuates fibrotic indicators both in murine models and in cell culture systems. Mechanistically, deletion of a putative SANT domain from MCRS1 displaces histone deacetylase 1 from its binding sites on histone H3, leading to increased histone acetylation of BA transporter genes, thereby influencing their expression and disrupting BA flux. In concordance, diminished nuclear expression of MCRS1 and NTCP is evident in human cirrhosis cases.

**Conclusions:** Our findings unveil a novel role for MCRS1 as an essential regulator of histone acetylation, crucial for the maintenance of gene expression and liver equilibrium. Depletion of MCRS1 triggers acetylation of bile acid (BA) transporter genes, disrupting BA flux, and consequently activating the FXR in HSCs. This cascade signifies a pivotal and ubiquitous signaling pathway in cirrhosis, holding substantial therapeutic implications for its treatment.

**Keywords:** Genetic mouse model, Liver cirrhosis

## FP-17

### Akkermansia Muciniphila Improve Cognitive Dysfunction by Regulating BDNF and Serotonin Pathway in Gut-Liver-Brain Axis

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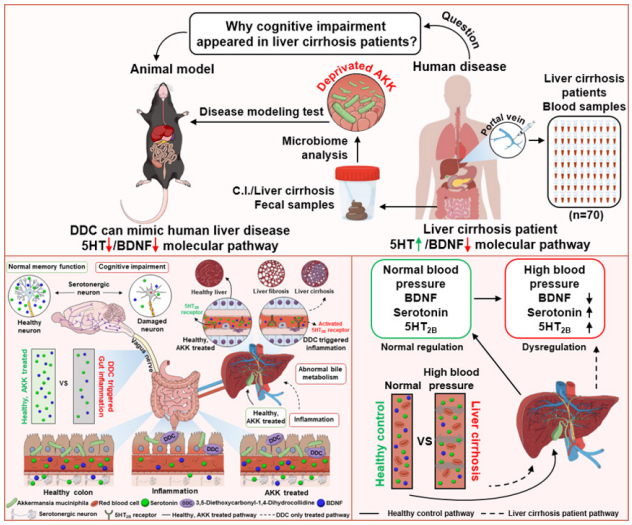
**Aims:** *Akkermansia muciniphila*, a next-generation microbiota, is known as a cornerstone in regulating the gut-organ axis in various diseases, but the mechanism remains poorly understood. Here, we reveal neuronal and antifibrotic mechanisms of *A. muciniphila* on the gut-liver-brain axis in liver injury.

**Methods:** 80 patients were recruited by cognition cohort study, and groups were divided according to cognitive dysfunction, and total analysis of microorganisms in the intestine was performed. *A. muciniphila* selected as the candidate strain was $10^9$ CFU/ml orally gavage to 5 weeks pathogen free male C57BL/6J mice induced by diethoxycarbonyl-1,4-dihydrocollidine (DDC). Histopathological examination and genetic changes were confirmed in liver and brain tissues.

**Results:** To investigate neurologic dysfunction and characteristic gut microbiotas, we performed cirrhosis cohort (154 patients with or without hepatic encephalopathy) and community cognition cohort (80 participants) and validated the existence of cognitive impairment in the 3,5-diethoxycarboncyl-1,4-dihydrocollidine-induced hepatic injury mouse model. Effects of candidate strain on cognition were evaluated in liver injury animal models. Expression of brain-derived neurotrophic factor (BDNF) and serotonin receptors were checked in patients with fibrosis according to the fibrosis grade and hepatic venous pressure gradient. The proportion of *A. muciniphila* was decreased in populations with hepatic encephalopathy and cognitive dysfunction. Tissue staining techniques confirmed gut-liver-brain damage in liver injury, with drastic expression of BDNF and serotonin in the gut and brain. Administration of *A. muciniphila* significantly reduced tissue damage and improved cognitive dysfunction and the expression of BDNF and serotonin. Isolated vagus nerve staining showed recovery of serotonin expression without affecting the dopamine pathway. Conversely, in liver tissue, inhibition of injury through suppression of serotonin receptors (5-hydroxytryptamine 2A and 2B) expression was confirmed. Severity of liver injury was correlated with serotonin, BDNF, and *A. muciniphila* abundance.

**Conclusions:** *A. muciniphila,* next generation probiotics, is a therapeutic candidate to alleviate the symptoms of liver fibrosis and cognitive impairment.

**Keywords:** Hepatic encephalopathy, Liver cirrhosis, Gut-liver-brain axis, Akkermansia muciniphila, Serotonin




## FP-18

### Quasi-Spatial Single-Cell Transcriptome Based on Physical Properties Defines Early Aging Associated Niche in Liver Tissue

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**Aims:** The aim of this study is to specifically and effectively capture microenvironments where fibrotic changes occur in the liver during aging, consequently identifing and characterizing distinct cell populations within the fibrotic niche in the context of natural aging. Furthermore, the study aims to elucidate the spatial distribution of these cell populations near the portal vein and understand their role in age-related fibrosis.

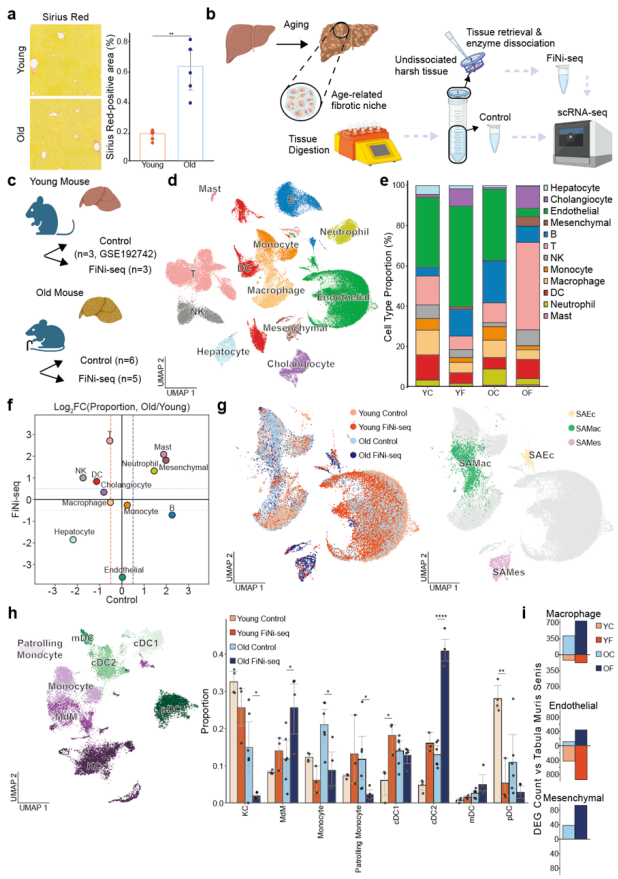
**Methods:** By utillizing special sequencing method, we dissociated aged mouse and young mouse to performe scRNA-seq. Signatures of cells enriched in aged-fibrotic niche were eval-

uated for effectors and cell-cell interaction. These cells were also projected into spatial transcriptomics and verified using RNAscope assay. Further analysis on regulators were done performing scATAC-seq.

**Results:** Fibrosis promoting scar populations are prevalent with aging. Especially endothelial cells undergo loss of cell fate and becomes senescent while expressing SASP factors, recruting active immune cells. Fibroblast also form the niche and have Wnt-modulating traits while also responding to hypoxic microenvironment. Age-related senescent cells are located along the portal vein, and expansion of the niche is observed in portal-vein injury model.

**Conclusions:** Aging accompanies increase in ECM matrix within the liver, where senescent cells colocalize forming a mosaically distributed hotspots of aging. These spots form hypoxic microenvironment with cell type shift driven by NFkB, ultimately forming portal vein distributed senescent niche.

**Keywords:** Liver, Aging, Fibrosis, Senescence




Friday, June 28, 2024, 13:30-14:50

## 4. Surgery, Technical Issues

### FP-19

### Artificial Intelligence-based Analysis Using Surface-Enhanced Raman Spectroscopy Profiles of Plasma Extracellular Vesicles to Develop an Early Diagnosis Method for Cholangiocarcinoma

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**Aims:** Cholangiocarcinoma is usually asymptomatic until it reaches an advanced stage. Early diagnosis is crucial for being a candidate for curative treatment and achieving a better prognosis. This study demonstrates a novel detection technique for cholangiocarcinoma using surface-enhanced Raman spectroscopy (SERS) profiles of plasma extracellular vesicles (EV) with artificial intelligence-based analysis.

**Methods:** This study analyzed preoperative blood samples from 50 patients who underwent surgical resection for pathologically proven cholangiocarcinoma. Using a size-exclusion chromatography kit, EV were isolated from the patient's plasma samples. SERS signals were measured and analyzed using a deep learning-based multi-cancer early detection algorithm (ExoPred Multi) of EXoPERT corporation.

**Results:** The artificial intelligence-based analysis using SERS signals of plasma EV (EV-SERS-AI) effectively identified cholangiocarcinoma samples with 100% sensitivity in a cancer presence detection model. Tissue of origin (TOO) prediction models to identify six different cancer types analyzed most of the cholangiocarcinoma samples as negative. (ROAUC lung 0.991, breast 0.795, colorectal 0.781, liver 0.853, pancreas 0.962, and stomach 0.880, respectively) Additionally, the cholangiocarcinoma-specific TOO prediction model, which learned partial sample data, effectively identified 24 validation samples that were not used for training.

**Conclusions:** We introduced a novel method and its capabilities for early diagnosis of cholangiocarcinoma using integrated EV-SERS-AI. Although further validation using larger cohorts is necessary to prove the clinical applicability, we expect that this approach could be a novel blood analysis for an accurate and earlier diagnosis of cholangiocarcinoma.

**Keywords:** Cholangiocarcinoma, Diagnosis

## FP-20

### Initial Experience of Minimal Invasive Living Donor Liver Transplantation: From Hybrid Surgery to Totally Laparoscopic Approach

Jinsoo Rhu, Gyu-Seong Choi

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**Aims:** As minimal invasive surgery is increasingly performed, the procedure is starting to expand throughout the world. Among them, minimal invasive surgery for the recipient is started to be performed in leading centers.

**Methods:** Retrospective data acquisition was performed from Samsung Medical Center database. Among living donor liver transplantation, minimal invasive recipient surgeries were included. Hybrid surgery which is performed as laparoscopic explant hepatectomy combined with open procedures were included as well as totally laparoscopic living donor liver transplantation. Donor and recipient information as well as time consumed during each procedures were calculated. Donor and recipient complication during the 30-day postoperative period were collected.

**Results:** During the period of July 2023 to November 2023, 8 cases of minimal invasive living donor liver transplantations were performed. Among Five laparoscopic transplantations, one open conversion case was included. For totally laparoscopic approach, partial clamping of the inferior vena cava was performed to maintain venous return to the heart, and not to disturb the vital sign of the recipient during anhepatic phase. Portal flow control was performed at the latest time to minimize bowel congestion. The mean operation time of hybrid cases was 314±38 minutes while that of totally laparoscopic cases was 477±169 minutes. One hepatic artery stenosis which required balloon angioplasty occurred in one patient. One patient experienced Pfannenstiel site bleeding.

**Conclusions:** Minimal invasive liver transplantation is technically feasible and can be performed within acceptable time. However, further refinement of procedure is required to minimize operation time. Further research is required to observe long-term results.

## FP-21

### Development and Validation of a Novel Model for Surgical Instrument Recognition during Laparoscopic Cholecystectomy Using AI-Based Automated Surgical Instrument Detection System

Jae Hyun Kwon[1], Taeyong Park[2], Soeui Kim[2], Jung-Woo Lee[1], Jong Woo Lee[1], Bum-Joo Cho[2]

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**Aims:** To enhance the efficiency of surgical procedures and avoid complications such as retained instruments, it is crucial to identify the required surgical tools accurately. However, this process is often time-consuming and poses a challenge for researchers. To address this, we developed a system for detecting laparoscopic surgical instruments during laparoscopic cholecystectomy through virtual image creation. We aim to evaluate the system's performance and establish an effective method for instrument detection during this surgery.

**Methods:** Virtual laparoscopic surgical video images were generated by combining images of laparoscopic surgical instruments with background images from laparoscopic cholecystectomy videos. Background images underwent random adjustments in brightness and contrast, while laparoscopic surgical instruments underwent diverse modifications, including changes in brightness, contrast, width cropping, rotation, cutting, scaling, flipping, and perspective transformations. These transformations aimed to create realistic virtual images.

**Results:** The training dataset comprised 4100 virtual images extracted from 41 laparoscopic cholecystectomy videos, with an additional 578 real images from 48 patients serving as external validation datasets. After 500 iterations of training, the mean average precision (mAP) for instrument detection in the internal and external validation testing datasets was 0.993 and 0.841, respectively, with an intersection over union (IoU) of 0.25. For instrument classification, the mAP for the internal and external validation testing datasets was 0.999 and 0.959, respectively, with an IoU of 0.25.

**Conclusions:** This laparoscopic surgical instrument detection system offers a valuable tool for clinical and research communities, potentially enhancing the efficiency of video review processes in various minimally invasive surgeries.

**Keywords:** Artificial intelligence, Minimally invasive surgery, Surgical instrument detection

## FP-22

### From Ideas to Clinical Application of Tunnel Technique in Laparoscopic-Endoscopic Cooperative Surgery for Biliary and Pancreatic Stones

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[1]Department of Hepatobiliary and Pancreatic Surgery Institute of Digestive Surgery; [2]Vin University, Vietnam

**Aims:** From practical problems in laparoscopic biliary stones surgery, using an intraoperative cholangioscope will be difficult due to unstable access, and the risk of infection. We have improved and modified the endotracheal tube to become a channel connecting from the abdominal wall to the common bile duct, and this tube also has many manipulation channels

to increase efficiency. After a period of practical application to biliary stones, we apply this tunnel technique to cases of pancreatic stones, helping achieve two purposes: first is to increase the dispersion efficiency. The second is the ability to place a pancreatic-duodenal stent, so there is no need for pancreatico-jejunostomy, which helps to preserve the normal anatomical structure of the digestive tract.

**Methods:** We describe the step-by-step application of the tunnel technique using newly design instruments in laparoscopic-endoscopic cooperative surgery for biliary stones and pancreatic stones.

**Results:** From June 2019 to March 2023, laparoscopic-endoscopic cooperative surgery through the tunnel was used to remove stones from the pancreatic ducts of 2 cases of pancreatic stones and 31 patients with hepatolithiasis and choledocholithiasis, respectively. The total clearance rate for pancreatic and biliary stones was 100% and 83.8%, respectively. Two cases of postoperative complications involving minor bile leakage required no treatment. 70,9% of cases of biliary stones and 100% pancreatic stones were cleared in a single session, respectively. Postoperative hospital stay was 7.3±2.4 (days).

**Conclusions:** The tunnel technique using newly manufactured instrument may be considered as standard treatment for selected patients with biliary stones or pancreatic stones.

**Keywords:** Tunnel technique, Laparoscopic-endoscopic cooperative surgery

## FP-23

### Resectability as a Prognostic Indicator in BCLC Stage B Hepatocellular Carcinoma: Challenging Current Treatment Paradigms

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Department of Surgery, Seoul National University College of Medicine

**Aims:** Current 2022 guidelines predominantly recommend non-surgical interventions for Barcelona Clinic Liver Cancer (BCLC) stage B hepatocellular carcinoma (HCC), omitting curative surgical options. This study challenges existing protocols by evaluating the prognostic impact of tumor resectability in these patients.

**Methods:** This retrospective study involved 1,342 HCC patients treated at a tertiary center from 2015 to 2017. Resectability assessments were independently conducted by four expert liver surgeons. Patients were categorized accordingly, and electronic medical records were analyzed to identify prognostic indicators.

**Results:** Of the 223 patients in BCLC stage B, 130 were deemed resectable. The resectable group showed significantly higher 1-year (97.4%) and 3-year (91.3%) survival rates compared to the unresectable group (83.3% and 73.2%, respectively; $P<0.001$). Treatment modalities varied, with 15.4% undergoing surgery, which suggested a non-significant trend toward better outcomes compared to TACE ($P=0.075$). Multivariate analysis identified surgical candidacy, high serum albumin levels, female gender, and lower PIVKA scores as significant predictors of improved survival.

**Conclusions:** This findings emphasize the prognostic significance of resectability in BCLC stage B HCC, suggesting that reconsideration of surgical interventions could benefit selected patient subgroups. This study advocates for integrating surgical options into treatment guidelines to enhance survival outcomes.

**Keywords:** Hepatocellular carcinoma, Resectability, BCLC B

## FP-24

### Minimally Invasive Hepatopancreatoduodenectomy for Locally Advanced Gallbladder Cancer

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**Aims:** Hepatopancreatoduodenectomy (HPD) can offer a survival advantage in selected patients with locally advanced gall bladder cancer (GBC). As HPD is a complex procedure, a minimally invasive approach was not commonly used. Short and medium-term outcomes of patients who underwent minimally invasive HPD are reported in this study.

**Methods:** Retrospective analysis of patients who underwent minimally invasive(robotic/laparoscopic) HPD (pancreatoduodenectomy with segment IVb and V liver resection) between October 2021 and October 2023. Patients who require major hepatectomy are not considered for the minimally invasive approach. Robotic procedures are performed with davinci Xi robotic system.

**Results:** During the study period, eight patients underwent minimally invasive HPD (laparoscopic-3, robotic-5). The indications of HPD are duodenopancreatic involvement in three patients and extensive bile duct involvement in five patients. The median (range) operative time and blood loss were 510 (460-650) minutes and 400 (275-950) mL respectively. Two patients had grade B postoperative pancreatic fistula and three patients had grade B delayed gastric emptying in the postoperative period. No patient had postoperative liver failure. At a median follow-up of 13 (2-24) months, two patients developed systemic metastasis.

**Conclusions:** The feasibility of minimally invasive HPD for locally advanced GBC reported in the present case series needs to be documented in a larger multicenter series.

**Keywords:** Gallbladder cancer, Hepatopancreatoduodenectomy

Friday, June 28, 2024, 14:50-16:10

## 5. HCC, Basic

### FP-25

### Exosomal miRNA as a Useful Biomarker for Predicting the Response of Atezolizumab and Bevacizumab Combination Therapy in Patients with Advanced Hepatocellular Carcinoma

Eunho Choi[1], Young-Sun Lee[1], Jeong-An Gim[2], Wonhyo Seo[3], Yang Jae Yoo[1], Seong Hee Kang[1], Sun Young Yim[1], Young Kul Jung[1], Ji Hoon Kim[1], Yeon Seok Seo[1], Hyung Joon Yim[1], Jong Eun Yeon[1], Kwan Soo Byun[1]

[1]Department of Internal Medicine, Korea University College of Medicine, South Korea; [2]Department of Medical Science, Soonchunhyang University, South Korea; [3]College of Pharmacy, Ewha Womans University, South Korea

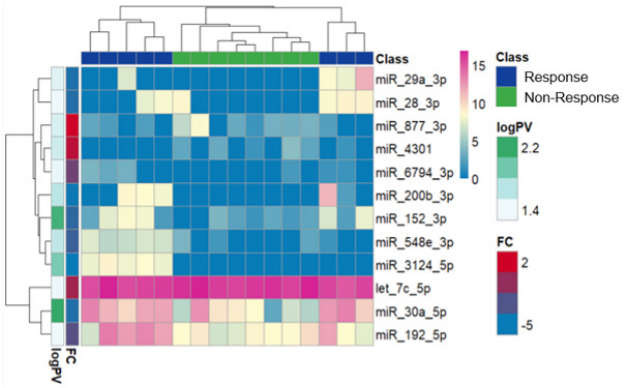
**Aims:** Atezolizumab and bevacizumab combination therapy is currently used as first-line therapy for patients with advanced hepatocellular carcinoma, but the effective biomarker for response to systemic therapy with atezolizumab and bevacizumab is unknown. This study aimed to find exosomal miRNA biomarkers to predict good response to combination therapy.

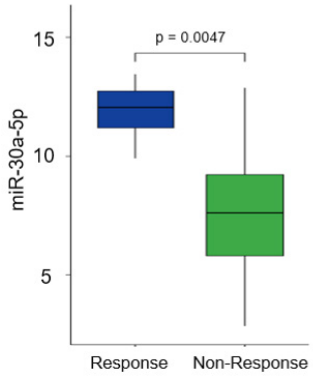
**Methods:** Sera were collected from patients with advanced hepatocellular carcinoma before the first cycle treatment of atezolizumab and bevacizumab. The patients were divided into two groups; the response group comprised patients showing stable disease, partial or complete response, while the non-response group consisted of patients showing progressive disease. The serum was concentrated with a qEV concentration and isolation kit. Exosomal RNA was extracted from isolates and small RNA sequencing using next-generation sequencing (NGS) was performed. We selected miRNAs that effectively distinguished between response or non-response using decision tree analysis among the top 100 in the order of most expressed. T-test was used to verify decision tree results.

**Results:** Eight patients each (7 male, and 1 female) were included in the response and non-response group. Seven out of 8 patients had viral etiology of hepatocellular carcinoma for both groups. A total of 1076 miRNAs were obtained from NGS. Among 1076 miRNAs, 12 miRNAs showed a significant difference in expression between the response group and the non-response group. Three miRNAs significantly increased and 9 miRNAs significantly decreased in the response group. Significantly increased miRNAs in the response group were let7c-5p, miR-30a-5p, and miR192-5p. Out of the top 100 most read miRNAs, 30 miRNAs were selected by decision tree analysis. miR-30a-5p levels were significantly higher in the response group ($P$=0.0047). In validation using Quantitative reverse transcription PCR, the response group showed significantly increased expression of miR-30a-5p compared with the non-response group. When we transfected miR-30a-5p to HepG2 cells, HepG2 cells decreased migration and proliferation.

**Conclusions:** Exosomal miRNAs could be used as a biomarker for predicting response to atezolizumab-bevacizumab therapy.

**Keywords:** Hepatocellular carcinoma, Exosome, Atezolizumab Bevacizumab, Biomarker




### FP-26

### NOX2 Regulates EMT Signaling through SREBP2 and Induces HCC Development

Hei Gwon Choi[1,2,3], Ha Neul Kim[1,2,3], Soon Ok Kim[3], Hyuk Soo Eun[3,4,5]

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**Aims:** Nicotinamide adenine dinucleotide phosphate oxidase (NOX) family enzymes play a pivotal role in generating reactive oxygen species (ROS), contributing significantly to the development of various cancers, including hepatocellular carcinoma (HCC). Specifically, NOX2 has been identified as being activat-

ed by palmitate in multiple cell types. However, research regarding NOX2 in relation to HCC has not been conducted yet.

**Methods:** The HCC cell line HepG2 was analyzed using Western blot, PCR, and FACS. NOX2 activity was induced by palmitate. The mouse HCC model was induced using transposon technology to promote HCC development. Tissues from HCC patients were analyzed by Western blot to assess the protein levels between tumor (N=149) and paired tissues (N=149).

**Results:** Palmitate-mediated NOX2 activity induces sterol regulatory element-binding protein 2 (SREBP2) activity and generates ROS. In HCC, inhibition of NOX2 expression led to increased fatty acid oxidation (FAO), particularly pronounced in HCC cell lines compared to normal hepatocyte cells. Furthermore, NOX2 activity was predominantly induced at the plasma membrane. Cell debris induces NOX2 and SREBP2 activity, indicating that lipid components are crucial in this process. This suggests that HCC obtains lipid components from dead cells, inducing the expression and activation of NOX2. Overexpression of NOX2 resulted in increased migration, whereas its inhibition led to decreased migration and increased FAO. Inhibition or decreased expression of SREBP2 resulted in decreased epithelial–mesenchymal transition (EMT) signaling and migration. Additionally, depletion of NOX2 in the liver in animal models reduced both the size and number of HCCs, accompanied by a decrease in SREBP2 activity and EMT signaling in HCC. Moreover, an association between NOX2 or N-cadherin expression and SREBP2 activity was observed in patient samples.

**Conclusions:** In HCC, NOX2 activity induces migration through SREBP2-mediated EMT signaling, exacerbating the progression of HCC.

**Keywords:** HCC, NOX2, SREBP2, EMT

## FP-27

### Application of CRISPR/Cas9 Technology for Constructing a Hepatocellular Carcinoma Model Using Human Chemically Derived Hepatocytes

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**Aims:** Hepatocellular carcinoma (HCC) poses challenges for direct examination in patient samples due to its molecular complexity, heterogeneity, and limited accessibility. Employing hepatic progenitor cells, we replicate genetic changes in HCC, providing insights into tumor initiation and progression. Previous studies have demonstrated that introducing TP53 and BAP1 mutations into human chemically derived hepatocytes (hCdHs) results in a cholangiocarcinoma cell line. While Sox9 is expressed in hepatocytes, the precise roles of Sox9+ hepatocytes in HCC remain elusive. Our research investigates the impact of SOX9 gene knockout in HCC context.

**Methods:** Human primary hepatocytes were reprogrammed using a medium supplemented with HGF, A83-01, and CHIR99021, yielding hCdHs. Sequential CRISPR/Cas9-mediated mutations were introduced into TP53, BAP1, and SOX9 genes. The resultant cell line was utilized to generate organoids. Subsequently, analysis of the cell line was conducted through real-time PCR.

**Results:** The new cell line exhibited downregulated SOX9 mRNA expression. Hepatocyte markers (HNF4$\alpha$ & AFP) were upregulated, while HCC marker ARID1A was downregulated, and CD44, HCC stem cell marker, was upregulated. Cholangiocyte markers (EpCAM & Ck19) and extrahepatic cholangiocarcinoma markers (SOX4, SOX17, & Jag1) were downregulated. Taken together, these results suggest a shift toward hepatocyte-like properties. New cell-derived organoids exhibited diverse morphologies, unlike the control organoids, while maintaining a PCR profile consistent with the 2D cell line, confirming the preservation of their cellular nature.

**Conclusions:** This preliminary data highlights the potential of CRISPR/Cas9 technology for generating an HCC disease model using hCdHs. Further investigations are essential to validate the true characteristics of this new cell line.

**Keywords:** CRISPR/CAS9 technology, Hepatocellular carcinoma (HCC) model, Genetic changes in HCC

## FP-28

### Identification and Functional Evaluation of LINC01446 and AK7 in Hepatocellular Carcinoma Progression and Metastasis

Min Ji Kang[1,2], Geum Ok Baek[1], Moon Gyeong Yoon[1], Ji Hyang Weon[1,2], Su Jin Kim[1,2], Ji Yi Choi[1,2], Se Ha Jang[1,2], Ji Eun Han[1], Hyo Jung Cho[1], Soon Sun Kim[1], Jae Youn Cheong[1], Jung Woo Eun[1]

[1]Department of Gastroenterology, Ajou University, School of Medicine, Suwon, South Korea; [2]Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, South Korea

**Aims:** Hepatocellular carcinoma (HCC) is a leading cause of cancer-related mortality worldwide, with limited treatment options and poor prognosis. Long non-coding RNAs (lncRNAs) have emerged as critical regulators in various cancers, including HCC. However, the specific roles and underlying mechanisms of lncRNAs in HCC progression and metastasis remain poorly understood. In this study, we aimed to identify and evaluate the functional significance of lncRNA LINC01446 and its downstream target AK7 in HCC pathogenesis.Hepatocellular carcinoma (HCC) is a leading cause of cancer-related

mortality worldwide, with limited treatment options and poor prognosis. Long non-coding RNAs (lncRNAs) have emerged as critical regulators in various cancers, including HCC. However, the specific roles and underlying mechanisms of lncRNAs in HCC progression and metastasis remain poorly understood. In this study, we aimed to identify and evaluate the functional significance of lncRNA LINC01446 and its downstream target AK7 in HCC pathogenesis.

**Methods:** We conducted a comprehensive analysis of three public omics datasets (GSE77314, GSE94660, GSE124535) to identify dysregulated lncRNAs in HCC. Among them, LINC01446 was confirmed by qRT-PCR analysis of tissue and blood samples. Functional studies were performed using *in vitro* assays, including cell growth, wound healing, migration, and invasion assays, following LINC01446 knockdown in HCC cell lines. Furthermore, *in vivo* experiments using xenograft and tail vein metastasis models were conducted.

**Results:** Our analysis revealed that LINC01446 expression was significantly elevated in HCC tissues and correlated with poor prognosis in HCC patients. Knockdown of LINC01446 impaired HCC cell migration, invasion, and epithelial-mesenchymal transition (EMT) *in vitro* without affecting cell growth at both *in vitro* and *in vivo*. Additionally, AK7 was identified as a downstream target of LINC01446, and its knockdown inhibited metastasis *in vitro* and *in vivo*. Patients with concurrent upregulation of LINC01446 and AK7 exhibited poor prognosis across multiple survival metrics, including overall survival (OS), progression-free survival (PFS), disease-specific survival (DSS), and disease-free survival (DFS).

**Conclusions:** Our findings demonstrate the critical roles of LINC01446 and its downstream target AK7 in HCC progression and metastasis. LINC01446 may serve as a potential prognostic marker and therapeutic target for HCC and targeting the LINC01446/AK7 axis could be a promising strategy for inhibiting HCC metastasis and improving patient outcomes.

**Keywords:** Long non-coding RNAs (LNCRNAS), Hepatocellular carcinoma (HCC), LINC01446, AK7

## FP-29

### Landscape of Circulating Immune Cells after Atezolizumab plus Bevacizumab Treatment in Advanced Hepatocellular Carcinoma

Ha Seok Lee[1], Young-Sun Lee[1], Seong Hee Kang[2], Sun Young Yim[3], Yang Jae Yoo[1], Young Kul Jung[2], Ji Hoon Kim[1], Yeon Seok Seo[3], Hyung Joon Yim[2], Jong Eun Yeon[1]

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**Aims:** Atezolizumab and bevacizumab combination therapy is being used as first-line therapy in patients with advanced hepatocellular carcinoma. However, factors that predict which patients will respond well to treatment are still unknown.

**Methods:** Patients who treated with atezolizumab and bevacizumab were enrolled in this study. Blood samples were collected before treatment of first cycle atezolizumab and bevacizumab and 14 days after first cycle atezolizumab and bevacizumab. We used Lymphocyte Separation Medium (Corning Inc., Corning, NY, USA) to isolate PBMCs by density gradient centrifugation and cryopreserved until use. scRNA-seq of PBMC samples at baseline and post-treatment was performed. Of the eight patients, four patients responded well to treatment and the other four patients did not respond well to treatment.

**Results:** scRNA sequencing were performed using PBMC from 8 patients who treated with atezolizumab and bevacizumab. Four patients had complete response (CR) or partial response (PR) and the other four had progressive disease (PD) at first response evaluation. We obtained landscapes of circulating immune cells before and after treatment. In pre-treatment PBMC, patients with a favorable prognosis tended to have higher frequencies of $\gamma\ \delta$ T cells, $CD4^+$ T cells, classical monocytes, $CD8^+$ T cells, and non-classical monocytes compared to patients with a poor prognosis. And there was a significant increase in proliferating lymphocytes after treatment in patients with a favorable prognosis. In the $CD8^+$ T cell subgroup, cluster 4, which highly expresses the proliferation marker *MKI67* and inhibitory checkpoint genes such as *PDCD1*, *HAVCR2*, and *CTLA4*, tends to be present in greater frequency in patients with better prognosis in pre-treatment PBMCs, and a greater increase in frequency is observed after treatment in patients with better prognosis.

**Conclusions:** In summary, the current study provided a landscape for heterogeneous populations of circulating immune cells after treatment. And this study suggested a subpopulation of $CD8^+$ T cells to be a candidate biomarker for predicting the treatment response.

**Keywords:** ScRNA-seq, Hepatocellular carcinoma, Immunotherapy, Biomarker

## FP-30

### Transcobalamin 1 (TCN1) Regulated Hypoxia-Driven Cancer Stemness via ITGA3-Mediated Notch Signaling Pathway in Hepatocellular Carcinoma

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[1]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, [2]State Key Laboratory of Chemical Biology and Drug Discovery, The Hong Kong Polytechnic University

**Aims:** Hepatocellular carcinoma (HCC) is a disease with poor clinical outcomes, necessitating a better understanding of the mechanisms that lead to cancer stemness, which is regarded as the root of tumor recurrence and therapy resistance. This study aims to investigate the crucial pathways involved in the process.

**Methods:** Liver tumor-initiating cells (T-ICs) enrichment was achieved through multiple sphere passages under chemotherapy and analyzed using RNA sequencing. TCN1's functional role was assessed using T-IC functional assays, while molecular pathways were identified using ChIP assay, western blotting analysis, and pathway analysis. The role of secretory TCN1 was evaluated by ELISA and recombinant TCN1.

**Results:** Transcriptome profiling revealed that transcobalamin 1 (TCN1), a vitamin B12-binding protein, was the most significantly upregulated molecule in enriched T-IC populations, and a consistent pathway in the stem cell signature was enriched in TCN1$^{high}$ HCC samples from the clinical dataset. Using lentiviral shRNA overexpression and knockdown approaches, we identified a critical role of TCN1 in regulating the properties of T-ICs, including self-renewal, invasiveness, tumorigenicity, and drug resistance, through *in vitro* and *in vivo* assays. HCC cells secrete TCN1, which regulates cancer stemness via paracrine secretion. Clinically, we also observed a substantial increase in *TCN1* mRNA signatures in HCC samples, which was associated with poor prognosis of HCC patients. Strikingly, TCN1 protein and its secretory levels were augmented by hypoxia, as its expression was regulated by a hypoxia-inducible element via ChIP assay. By analyzing TCGA dataset with confirmation by immunoprecipitation, we report for the first time that TCN1 directly interacts with integrin subunit alpha 3 (ITGA3), thereby regulating the Notch signaling pathway.

**Conclusions:** Our study provides new insights into the function of TCN1 in HCC, revealing its non-canonical role beyond vitamin B12-binding. This reveals our understanding of the complex relationship between hypoxia and cancer stemness in HCC.

**Keywords:** Hepatocellular carcinoma, Tumor-initiating cells, TCN1

Friday, June 28, 2024, 09:10-10:30

## 6. Drug and Toxic Injury

### FP-31

### Personalized Prediction of Drug-Induced Liver Injury Using the Transformer Architecture

Harim Kim[1], Hyo Jung Cho[2], Soon Sun Kim[2], Ji Eun Han[2], Jae Youn Cheong[2], Charmgil Hong[1]

[1]Department of Computer Science and Electrical Engineering, Handong Global University, [2]Department of Gastroenterology, School of Medicine, Ajou University

**Aims:** Drug-Induced Liver Injury (DILI) is a condition characterized by liver damage resulting from the adverse effects of medications. Our study hypothesizes that the manifestation of DILI is intricately linked with individual patient diagnostic information, as well as one's medication records. We investigate predictive methodologies that take into account the interplay within electronic medical records (EMRs) to foresee the occurrence of DILI.

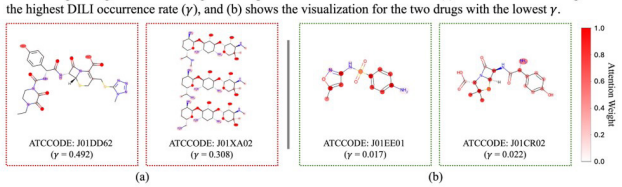
**Methods:** Our research involved reviewing EMR data from Hospital A, spanning from 2016 to 2020, which included 970 DILI-possible and 12,595 DILI-negative cases. We developed a deep learning model utilizing a Transformer-based structure, a concept gaining traction in the field of artificial intelligence, to facilitate the prediction of DILI using comprehensive patient diagnosis and medication data. The model features two primary components: the Drug Channel, which analyzes the intricate structures of drug molecules, and the Patient Channel, which processes diagnostic information. Integrating the outputs from both channels, our model is fine-tuned to predict the potential for DILI.

**Results:** To validate our method, we conducted non-parametric statistical tests and visual analytics. As a result, our method has achieved superior performance with an AUROC of 73.0% and an AUPRC of 20.2%, marking improvements of up to 3% and 3.8%, respectively, over existing methods (Table 1). Additionally, the visual analytics provide chemical insights into the molecular structures of drugs associated with DILI (Figure 1). These results show the effectiveness of method in improving DILI prediction by considering both the patient's unique profile and drug interactions.

Table 1. The result of performance comparison (mean±std). The baseline consists of graph neural network-based and Transformer-based methods.

| | AUROC | AUPRC |
|---|---|---|
| MLP (structured) | 0.714±0.028 | 0.177±0.032 |
| GCN [Kipf and Welling, 2016] | **0.728±0.021** | 0.190±0.039 |
| GAT [Velickovic *et al.*, 2017] | 0.704±0.022 | 0.164±0.030 |
| SAGE [Hamilton *et al.*, 2017] | **0.731±0.022** | 0.191±0.034 |
| GIN [Xu *et al.*, 2018] | 0.700±0.022 | 0.168±0.029 |
| M-Transformer [Choi *et al.*, 2023] | **0.728±0.020** | 0.172±0.036 |
| Ours | **0.730±0.019** | **0.202±0.027** |

Figure 1. The results of attention visualization on the input drug molecular structures in the proposed method. Atoms assigned higher attention weights are depicted in a more intense red color. (a) visualizes the two drugs with the highest DILI occurrence rate ($\gamma$), and (b) shows the visualization for the two drugs with the lowest $\gamma$.




**Conclusions:** We have proposed a personalized model for pre-

dicting DILI that utilizes the EMR data. Our model has been developed to enhance the ability to see how drugs might affect each patient's unique health condition. We anticipate that our approach will enable more precise and safer medication choices for patients.

**Keywords:** Drug-induced liver injury, Electronic medical records, Deep learning, Transformer

## FP-32

### Evaluation of Hepatoprotective and Antioxidant Properties of Phytosterols against Carbon Tetrachloride-Induced Hepatic Fibrosis in Mice

**Gireesh Dayma**, Dinesh Dayma

Department of Applied Sciences, Manipal University, India

**Aims:** Phytosterols, plant sterol and stanol esters found in plant cell membranes, structurally resemble cholesterol and inhibit its absorption in the human body. Dietary sugar richness triggers inflammation and insulin resistance mainly via alterations in gut microbiota. This study aimed to assess the hepatoprotective and antioxidant activity of phytosterols against carbon tetrachloride (CCl4)-induced hepatic fibrosis in mice.

**Methods:** Mice were randomly assigned to 6 groups: normal control, model, silymarin tablets (positive control), and phytosterols at doses of 100, 200, and 400mg/kg. After 8 weeks, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides (TG), hyaluronic acid (HA), and laminin (LN) activities were measured. Antioxidant enzyme levels such as superoxide dismutase (SOD), glutathione (GSH), and glutathione peroxidase (GSH-Px) were determined post-phytosterol administration. Hydroxyproline (HYP) and malondialdehyde (MDA) levels, along with histopathological examinations of hepatocyte fibrosis, were also conducted.

**Results:** Results indicated that phytosterol administration significantly mitigated CCl4-induced liver injury. Phytosterols notably reduced serum levels of hepatic enzyme markers AST, ALT, HA, and LN ($P$<0.01). SOD and GSH-Px levels increased significantly, while MDA levels decreased remarkably in mice receiving medium (200mg/kg) and high doses (400mg/kg) of phytosterols ($P$<0.01). Histological liver examinations revealed partial healing of lesions, including necrosis, lymphocyte infiltration, and fatty degeneration, with phytosterol treatment. Protein expression studies demonstrated phytosterols' inhibition of $\alpha$-SMA and TGF-$\beta$1 protein expression ($P$<0.01). Moreover, phytosterols significantly decreased cytochrome P450 2E1 (CYP2E1) expression and production of pro-inflammatory markers such as inducible nitric oxide synthase (iNOS), interleukin-1$\beta$ (IL-1$\beta$), cyclooxygenase-2 (COX-2), and nitric oxide (NO) in CCl4-treated mouse livers.

**Conclusions:** These findings suggest that phytosterols' protective effect against CCl4-induced hepatic fibrosis may stem from their ability to reduce oxidative stress and enhance drug metabolizing enzyme activity in the liver.

**Keywords:** Carbon tetrachloride-induced hepatic fibrosis, Phytosterols, Mice

## FP-33

### Understanding of the Underlying Mechanisms of CXCL1-Associated Neutrophil Migration in APAP-Induced Liver Injury

**Jisoo Kang**, Wonhyo Seo

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**Aims:** Drug-induced liver injury (DILI) has emerged as a significant concern in the field of public health due to issues such as the withdrawal of approved drugs. Among these drugs, acetaminophen (APAP) is a prominent medication known to cause acute liver injury when consumed in overdose. Infiltration of neutrophil is a well-recognized key factor in the progression of APAP-induced liver injury. Recent studies have revealed the involvement of CXCL1, a major adhesion molecule involved in neutrophil infiltration, in APAP-induced liver injury, however, the underlying mechanisms have not been fully eluciated. Therefore, we have investigated the underlying mechanisms via the involvement of CXCL1 in APAP-induced liver injury.

**Methods:** High dose APAP (400 mg/kg) was administered intraperitoneally to C57BL/6N male mice, followed by euthanasia after 6 hours. Subsequently, blood and liver tissue samples were collected for further experiments.

**Results:** The administration of APAP induced a dramatic elevation of hepatocyte damage, hepatocyte necrosis, the infiltration of neutrophils. In addition, the expression of Cxcl1 in hepatocytes was significanty induced after the treatment of APAP. The gene expression of CXCR2, the receptor for CXCL1, also increases concomitantly with the elevation of CXCL1 expression. To support this finding, liver-specific CXCL1 KO mice were used to investigate the involvement of CXCL1 in APAP-induced liver injury. Experiments liver-specific CXCL1 KO mice exhibited a dramatic improvement of liver injury after APAP treatment. Freshly isolated hepatocytes were treated with APAP (5 mM) and co-cultured with neutrophils using transwell. Migtaion of neutrophils and hepatotoxicy were lower in Cxcl1 deficient hepatocytes compared to WT hepatocytes.

**Conclusions:** In conclusion, APAP-induced liver injury occurs via the association of CXCL1, leading to neutrophil infiltration, hepatic inflammation, oxidative stress, and cell death. Therefore, the inhibition of Cxcl1 could be a novel therapeutic approach to improve DILI.

**Keywords:** Acetaminophen, CXCL1, Infiltration of neutrophil,

Drug-induced liver injury

## FP-34

### Ameliorative Effects of Punica Granatum (Pomegranate) Seed Oil Extract on Ethanol-Induced Gastric and Hepatic Disorders in Animal Models

**Assiya Karaltayeva**

Department of Medicine, Al-Farabi Kazakh National University, Almaty, Kazakhstan

**Aims:** Pomegranate (Punica granatum) seed oil extract is known for its richness in phytoestrogen and antioxidant compounds. This study aimed to investigate the beneficial effects of Punica granatum seed oil extract (PGSO) on stomach and liver disorders against ethanol-induced gastric injury in female rats.

**Methods:** Female Wistar rats aged 2-4 months were divided into four groups: control, ethanol-treated, and two PGSO pre-treated groups (at doses of 50 mL/kg and 100 mL/kg). Various parameters including gastric pH, gastric mucus analysis, hepat index, liver enzymes (ALT, AST, ALP, GGT), total bilirubin, and antioxidant levels (SOD, malondialdehyde, CAT) were measured. Histopathological examination of stomach and liver tissues was also conducted.

**Results:** Pre-treatment with PGSO significantly reduced ulcer index, oxidative stress, and restored liver enzyme levels and total bilirubin induced by ethanol. Additionally, PGSO pre-treatment elevated antioxidant activity and reduced mucosal NF κ B protein expression and caspase 3 activities, while increasing antiapoptotic Bcl-2 gene expression. Histopathological findings revealed ethanol-induced damage to multiple organs, including the stomach and liver. However, PGSO treatment, particularly in group 4, protected these tissues from ethanol-induced damage in a dose-dependent manner.

**Conclusions:** These results highlight the hepatoprotective effects of PGSO against ethanol-induced oxidative and mucosal damage, suggesting its potential therapeutic utility in mitigating alcohol-related gastrointestinal and hepatic disorders.

**Keywords:** Liver disorders, Ethanol-induced gastric injury, Female rats

## FP-35

### Analysis of Drug Inducing Liver Injury: A Graph-Based Machine Learning Approach

**Geonyeong Choi**, Charmgil Hong

Department of Computer Science and Electrical Engineering, Handong Global University, Pohang, Korea

**Aims:** Drug-induced liver injury (DILI) represents liver damage caused by medications, often resulting from idiosyncratic reactions that remain poorly understood. Our study seeks to uncover the chemical properties and biological interactions of drugs related to DILI. This investigation will deepen our understanding of the underlying mechanisms of DILI.

**Methods:** Our approach employed Graph Neural Networks (GNNs) to predict the chemical properties of drugs and specifically analyzed the statistical differences between DILI-positive and DILI-negative drugs (Fig. 1). For training GNNs, we harnessed publicly available datasets. We included ToxCast (Richard et al., 2016), which measures bioactivity related to nuclear receptors and stress response pathways. We also employed PubChem BioAssay (PCBA) (Wang et al., 2012), which documents the biological activities of small molecules identified through high-throughput screening.

**Results:** Our results confirmed that lipophilicity presents a statistically significant difference (Fig. 2), as in previous research (Chen et al., 2013). Specifically, drugs with high solubility and increased off-target effects are prone to penetrate hepatocytes and undergo metabolism. Furthermore, we discovered a significant difference in drug solubility. Notably, no DILI-positive drugs were found with solubility below -100, indicating a potential link between drug absorption rates and toxicity (Fig. 3). Additionally, our analysis indicated significant variations in the induction of cell cycle arrest and DNA damage in hepatocytes. This highlights the critical role that specific drug properties and biological effects can play in liver damage.

**Conclusions:** We examined significant chemical features and biological responses of drugs that are influential in the development of DILI. We anticipate that personalized drug evaluations can facilitate drug toxicity assessments, contribute to identifying causes of DILI, and aid in the development of safer drug administration protocols.

**Keywords:** Drug induced liver injury, DILI, Graph neural networks

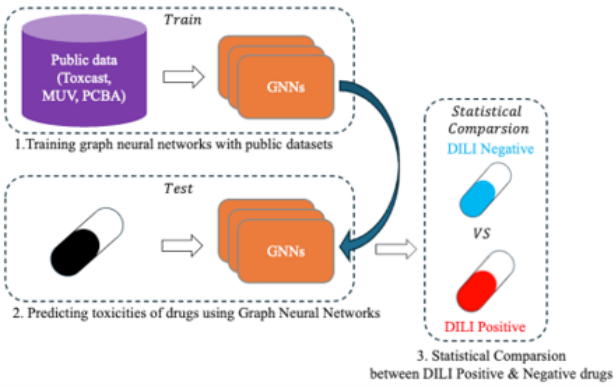


**Figure 1.** Overall Structure of the Model

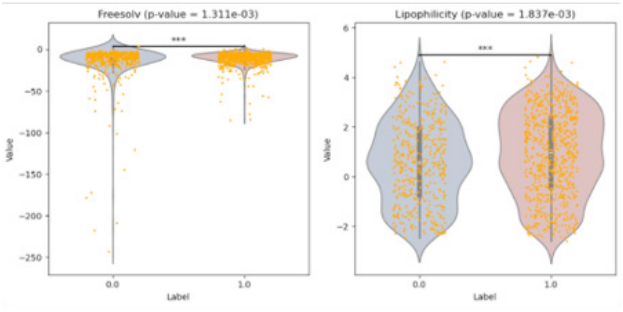


**Figure 2.** Statistical Comparsion of Lipophilicity anmd FreeSolv

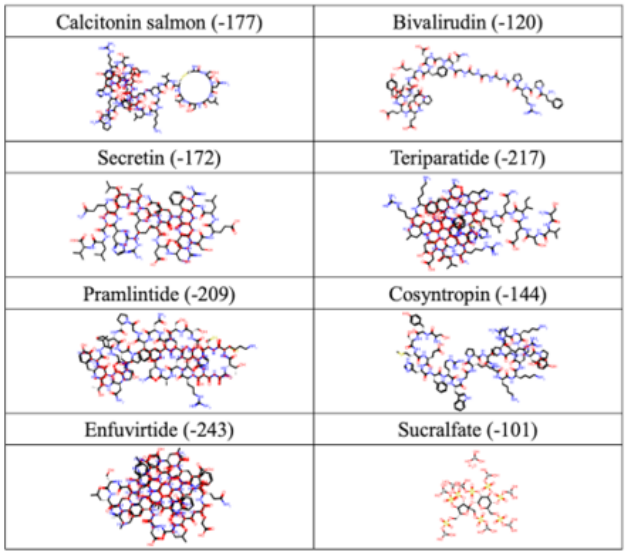


**Figure 3.** Molecules with a FreeSolv of -100 or lower and their predicted FreeSolv values

## FP-36

### Pre-Clinical Evaluation of Hepatoprotective Effects of Lutein Against DMBA-Induced Hepatotoxicity in Experimental Rats

Yogesh Dayma, Shewta Choudhary

Life Sciences, Jawaharlal Nehru University, New Delhi, India

**Aims:** Humans are regularly exposed to 7,12-dimethyl-Benz[a] anthracene (DMBA), a highly lipophilic environmental organic pollutant. Lutein, a carotenoid found in citrus fruits, possesses antioxidant and anti-inflammatory properties, making it an emerging nutraceutical. Both human and laboratory studies have highlighted the therapeutic potential of lutein in various health conditions, including heart disease, vascular disorders, metabolic disorders, and neurodegenerative diseases. This study aimed to investigate the hepatoprotective role of lutein against DMBA-induced hepatotoxicity using a rat model.

**Methods:** Fifty male rats were divided into five groups: GI (control), GII (olive oil, vehicle for DMBA), GIII (DMBA), GIV (DMBA + lutein), and GV (lutein). After 12 weeks, changes in body weight and mortality were assessed. Histological and ultrastructural examinations of liver tissue were conducted, and the expressions of p53, TGF $\beta$2, TNF-$\alpha$, S6K2, and c20orf20 were evaluated using RT-PCR.

**Results:** Post-treatment with lutein increased both body weight and the survival rate of rats exposed to DMBA. Lutein demonstrated significant protection against the pathological effects of DMBA on the liver. Ultrastructurally, lutein ameliorated or prevented most of the toxic effects of DMBA on hepatocytes, including irregularities in the nuclear envelope, clumping and margination of heterochromatin aggregates, segregated nucleoli, and mitochondrial pleomorphism. Lutein administration resulted in the downregulation of p53, c20orf20, and S6K2 mRNA levels, and upregulation of TNF-$\alpha$ and TGF $\beta$2.

**Conclusions:** In conclusion, lutein exhibited a protective effect against DMBA-induced liver toxicity in albino rats. Thus, lutein supplementation may mitigate polycyclic aromatic hydrocarbons-induced hepatotoxicity and could potentially enhance human health when included in the diet.

**Keywords:** Lutein, Hepatotoxicity, Rat model

Friday, June 28, 2024, 13:30-14:50

## 7. ALD & Genetics

## FP-37

### Expansion of Effector Regulatory T Cells in Steroid Responders of Severe Alcohol-Associated Hepatitis

Min Woo Kang[1], Soon Kyu Lee[1,2], Ji Won Han[1,3], Jung Hyun Kwon[1,2], Soon Woo Nam[1,2], Jeong Won Jang[1,3], Jong Young Choi[1,3], Seung Kew Yoon[1,3], Pil Soo Sung[1,3*]

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**Aims:** While steroid therapy is the preferred treatment for severe alcohol-associated hepatitis, the role of effector regulatory T (eTreg) cells and their association with steroid response and clinical outcomes in these patients remains to be elucidated.

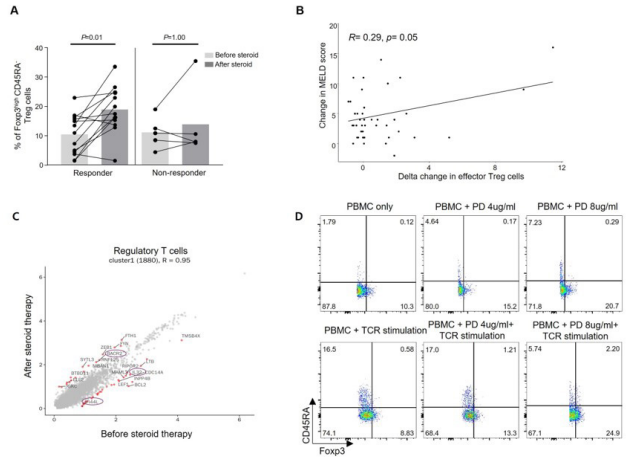
**Methods:** We prospectively enrolled 47consecutive patients with alcohol-associated hepatitis, consisting of severe alcohol-associated hepatitis treated with steroid (n=18; steroid-treated group) and mild alcohol-associated hepatitis

(n=29; non-treated group). After isolating peripheral blood mononuclear cells (PBMCs) from the patients at enrollment and again 7 days later, eTreg cells frequency was examined using flow cytometry. Single-cell RNA sequencing analysis was conducted using paired PBMCs. *In vitro* experiments were also performed to assess phenotype changes and the suppressive function of Treg cells following steroid treatment.

**Results:** The steroid-treated group exhibited significantly higher Model for End-Stage Liver Disease (MELD) scores than the non-treated group ($P$<0.01). Within the steroid-treated group, the proportion of eTreg cells significantly expanded in the steroid responders (n=13; $P$=0.01; Figure A). Furthermore, a significant positive correlation was observed between the decrease in MELD score and the increase in eTreg cells ($P$<0.05; Figure B). Single-cell RNA sequencing using paired peripheral blood mononuclear cells (pre- and post-steroid therapy) from a steroid responder revealed gene expression changes in T cells (Figure C) and monocytes, suggesting enhancement of Treg cell function. *In vitro* results showed an elevation in eTreg cells proportion after steroid therapy (Figure D).

**Conclusions:** In conclusion, our findings suggest that the efficacy of steroid therapy in patients with severe alcohol-associated hepatitis is mediated by an increase in the number of eTreg cells.

**Keywords:** Alcohol-associated hepatitis, Effector regulatory T cells, Steroids




## FP-38

### Dysbiotic change in intestinal microbiome in Korean alcoholic liver disease patients

Young Youn Cho[1], Hochan Seo[1], Hyung Jun Kim[1], Yoon-Keun Kim[2], Jae Gyu Kim[1]

[1]Department of Internal Medicine, Chung-Ang University College of Medicine; [2]MD Healthcare R&D Institute

**Aims:** Although there is great interest in the role of the intestinal microbiome, the exact mechanism is generally unknown. The aim of our study is to identify changes in the intestinal microbiome during different stages of alcoholic liver disease, from alcoholic hepatitis to liver cirrhosis (LC).

**Methods:** We prospectively enrolled 90 patients: 17 patients in the alcoholic control group, 17 patients in the alcoholic hepatitis group, 36 patients in the compensated LC group, and 20 patients in the decompensated LC group. Differences in microbial diversity and composition were analyzed using 16S rRNA gene profiling and the next-generation sequencing method. Tax4Fun was employed to predict possible functional pathways.

**Results:** The microbial composition differed significantly among the four groups. Alpha diversity was highest in the alcoholic hepatitis group. The alcoholic hepatitis group exhibited differential enrichment with the genera Blautia, Collinsella, and Romboutsia, whereas the decompensated LC group showed enrichment with the genera Bifidobacterium and Lactobacillus.

**Conclusions:** Significant changes were observed in the diversity and composition of the intestinal microbiome during different stages of alcoholic liver disease.

**Keywords:** Alcoholic liver disease, Microbiome, Liver cirrhosis

## FP-39

### Effect of Diabetes on Mortality and Liver Transplantation in Patients with Alcoholic Liver Cirrhosis

Jihye Lim[1], Sung-Eun Kim[2], Aj Jeong Jo[3], Jung Hee Kim[2], Seul Ki Han[4], Tae Hyung Kim[2], Hyung Joon Yim[5], Young Kul Jung[5], Do Seon Song[1], Eileen L. Yoon[6], Hee Yeon Kim[1], Seong Hee Kang[7], Young Chang[8], Jeong-Ju Yoo[9], Sung Won Lee[1], Jung Gil Park[10], Ji Won Park[2], Soung Won Jeong[8], Young Joo Jin[11], Hyoung Su Kim[2], Ki Tae Suk[2], Moon Young Kim[4], Sang Gyune Kim[9], Won Kim[12], Jae Young Jang[8], Jin Mo Yang[1], Dong Joon Kim[2] on behalf of The Korean Acute on-Chronic Liver Failure (KACLiF) Study Group

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**Aims:** Few studies have investigated the influence of diabetes on alcoholic liver cirrhosis patients, leaving its impact unclear. Thus, we conducted a study to reveal diabetes' impact on the clinical outcomes of such patients.

**Methods:** We conducted an analysis of prospective multicenter data pertaining to 965 patients diagnosed with alcoholic liver cirrhosis, all of whom were admitted due to acute decompensation between 2015 and 2019. Risk of major precipitating factors and incidences of death or liver transplantation in patients with and without diabetes was comparatively assessed. Propensity score (PS) matching was performed at a 1:2 ratio for accurate comparisons.

**Results:** The mean age was 53.4 years, and 81.0% of the patients were male. Diabetes was prevalent in 23.6% of the cohort and was positively correlated with hepatic encephalopathy and upper gastrointestinal bleeding, although not statistically significant. Over a median follow-up of 903.5 person-years (PYs), 64 patients with and 171 without diabetes died or underwent liver transplantation, with annual incidence of 33.6/100 PYs and 24.0/100 PYs, respectively. In the PS-matched cohort, the incidence of death or liver transplantation was 36.8/100 PYs and 18.6/100 PYs in the diabetes and matched control group, respectively. After adjusting for various factors, coexisting diabetes significantly increased the risk of death or liver transplantation in the short and long term, in addition to prolonged prothrombin time, low serum albumin, elevated total bilirubin and creatinine, and decreased serum sodium levels.

**Conclusions:** Diabetes increases the risk of death or liver transplantation in patients with alcoholic liver cirrhosis.

**Keywords:** Liver transplantation, Precipitating factor, Prognosis, Diabetes mellitus

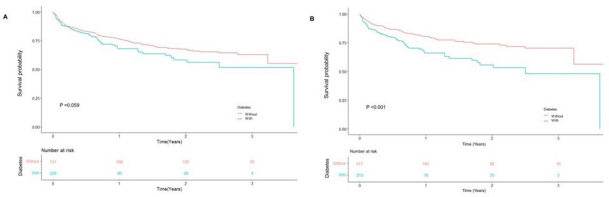

**Figure.** Cumulative risk of composite outcome. (A) the total and (B) propensity score-matched cohorts

## FP-40

### Anthraquinone Analogues for Alcoholic-Induced Liver Fibrosis Therapy Targeting TGF-β Receptor: Bibliometric and Molecular Docking Evidence

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Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Palangka Raya, Central Kalimantan, Indonesia

**Aims:** Alcoholic liver disease results in the development of liver fibrosis. The discovery of intriguing natural substances for the treatment of liver fibrosis remains captivating. Bibliometric analysis provides insights into the current trends in liver fibrosis therapy and identifies the target protein. Additionally, our earlier research revealed that the anthraquinone molecule exhibited the greatest binding affinity for the key fibrosis regulator, the TGF-$\beta$ receptor, compared to other phytochemicals. This work aimed to identify a potential targeted therapy for liver fibrosis using a bibliometric and molecular docking analysis on anthraquinone analogs.

**Methods:** Bibliometric analysis was performed by retrieving the Scopus database with the keyword "liver-fibrosis-therapy" in the range 2013 to 2024 followed by analysis using the VOS viewer 1.6.20. The molecular docking was conducted on 100 anthraquinone analogs from the ZINC database by AutoDock Vina and compared to Galunisertib. The visualization was using Biovia Discovery Studio. SwissADME and pkCSM were utilized to predict the pharmacokinetics and safety of the compound.

**Results:** Our bibliometric analysis uncovered that alcohol-induced fibrosis is associated with TGF-$\beta$ signaling and remains the primary focus in cases of fibrosis (Figure 1a). Based on the analysis of anthraquinone analogs, the chemical ZINC000003896802 had the most favourable binding energy of -9.9 kcal/mol towards the TGF-$\beta$ receptor compared to Galunisertib (-6.7 kcal/mol). The amino acid residues Asp351, Val219, Ile211, Tyr249, His283, and Glu245 were essential for molecular binding. The molecule predominantly engages with the TGF-$\beta$ binding site via hydrogen bonding and Pi interactions with the aromatic ring. The adjacent nitrogen ring increases the attraction for binding to the receptor (Figure 1b-c). This molecule was found to exhibit drug-like properties, demonstrated good gastrointestinal absorption, and exhibited no toxicity.

**Conclusions:** The anthraquinone scaffold shows promise as a pharmacophore for inhibiting TGF-$\beta$ receptors, which could assist researchers in creating new and innovative lead molecules for liver fibrosis.

**Keywords:** Liver fibrosis, TGF-B, Anthraquinone

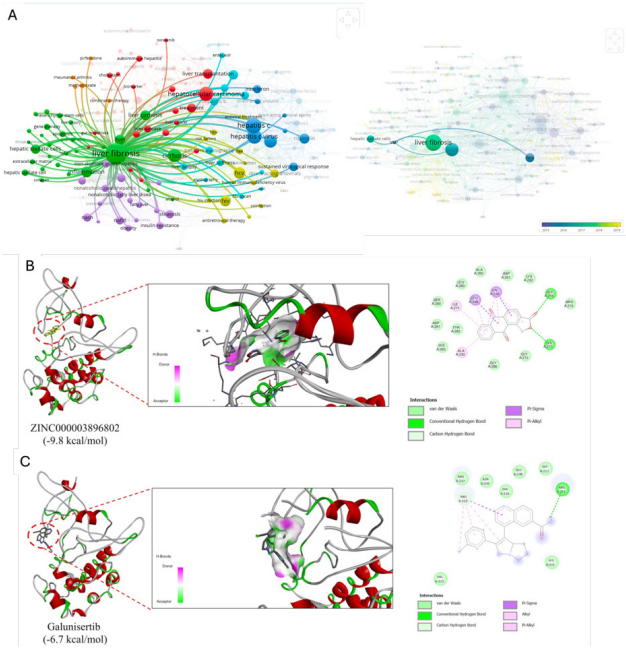


Figure 1. (A) The relationship of fibrosis and TGF-β , (B) the molecular interaction of anthraquinone derivative ZINC000003896802 into the TGF-β active site, (C) Galunisetib

## FP-41

### The Prognostic Impact of Psychiatric Intervention on Alcohol-Associated Liver Disease: A Prospective Study of the UK Biobank Cohort

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**Aims:** Alcohol-associated liver disease (ALD) is a public health concern. ALD patients often have psychiatric comorbidities, but the effects of psychiatric interventions on ALD are not well-established. This study explores the prognostic impact of psychiatric intervention on ALD within UK Biobank cohort.

**Methods:** This prospective study included a total of 502,370 participants. Psychiatric intervention was defined by a consultation with psychiatrists during hospitalization or a history of medication related to alcohol use disorder and psychiatric comorbidities. Survival analysis was conducted, incorporating propensity score matching (PSM) and doubly robust (DR) estimation, to precisely assess the impact of psychiatric intervention.

**Results:** Among 2,417 ALD patients in the final analysis, those with F10 codes had poorer survival outcomes. Psychiatric intervention significantly improved the outcomes of both all-cause and liver-related mortality and reduced the incidence of liver cirrhosis. In subgroup analyses or 2-year landmark analyses, psychiatric intervention consistently showed a survival benefit in ALD patients. In the multivariate analysis, psychiatric intervention was identified as a favorable prognostic factor (hazard ratio, 0.780; $P$=0.002 after PSM). Furthermore, the average treatment effects from DR estimation provided detailed insights into the impact of psychiatric intervention (2.9 years, $P$<0.001 after PSM).

**Conclusions:** This study demonstrates the favorable effect of psychiatric intervention in ALD patients with psychiatric comorbidities. These findings emphasize the importance of integrated management for ALD patients to address both their medical and psychiatric aspects. Therefore, we suggest the potential benefits of early psychiatric interventions in improving survival outcomes in ALD.

**Keywords:** Alcohol-associated liver disease, Psychiatric comorbidities, Psychiatric medication, Psychiatric consultation

## FP-42

### The Causal Linkage Between Telomere Attrition and Cirrhosis: A Mendelian Randomization Study

Hyunjae Shin[1,2], Sung Won Chung[3*], Moon Haeng Hur[1], Yun Bin Lee[1], Eun Ju Cho[1], Su Jong Yu[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Jeong-Hoon Lee[1,4]

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**Aims:** Liver cirrhosis is a major worldwide health concern, attributed to various established factors such as viral hepatitis, alcohol abuse, and metabolic dysfunction-associated steatotic liver disease. Nonetheless, the role of aging in the development of liver cirrhosis remains poorly understood.

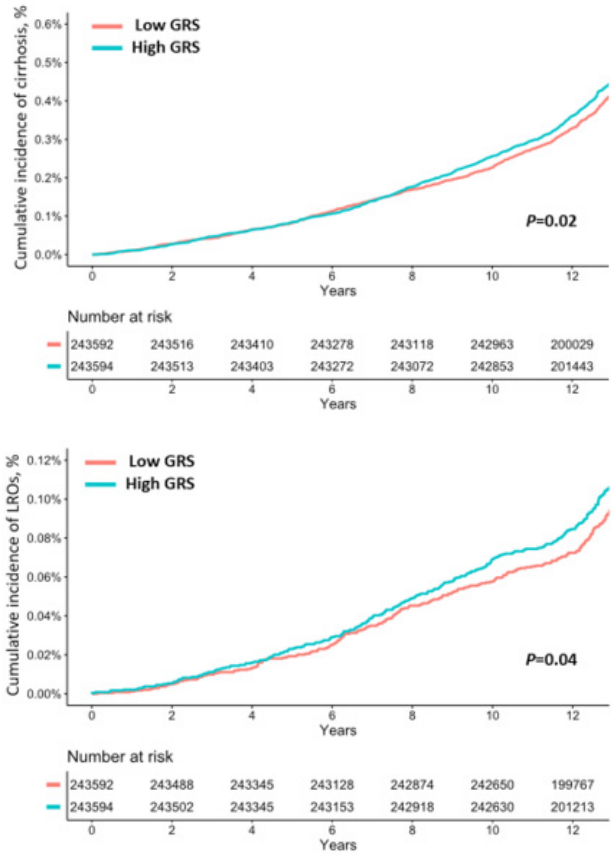
**Methods:** We conducted a Mendelian randomization (MR) study to explore the causal linkage between aging and liver cirrhosis. Genetic instruments for leukocyte telomere length served as proxies of aging. Our approach included two-sample bidirectional MR analysis and one-sample genetic risk score (GRS)-based MR analysis, utilizing data from two extensive European cohorts: summary-level data from the FinnGen and individual-level data from the UK Biobank. For the bidirectional analysis, we selected 47 single-nucleotide polymorphisms (SNPs) representing telomere attrition, and 5 SNPs indicative of liver cirrhosis. We examined obesity and alcoholic liver disease with MR as potential confounding factors due to horizontal

pleiotropy.

**Results:** Our MR analysis employing the inverse variance-weighted method, indicating that telomere attrition significantly increased the risk of liver cirrhosis (odds ratio=1.45, 95% confidence interval [CI]=1.13–1.77; *P*=0.02). The MR–Egger intercept P value supported the absence of significant directional pleiotropy (intercept *P*=0.54). In the GRS analysis with the UK Biobank data, a higher GRS for telomere shortening was significantly associated with an increased risk of liver cirrhosis (hazard ratio=1.05, 95% CI=1.01–1.10; *P*=0.02) and liver-related outcomes including hepatic decompensation, hepatocellular carcinoma development, or liver-related death (hazard ratio=1.09, 95% CI=1.00–1.10; *P*=0.04). Conversely, the reverse-direction MR analysis found no significant association between genetic predisposition to liver cirrhosis and telomere attrition.

**Conclusions:** Our findings highlighted a causal linkage between telomere shortening and liver cirrhosis, emphasizing aging as a risk factor for cirrhosis and indicating potential need for screening cirrhosis in elderly.

**Keywords:** Telomerase, Leukocyte telomere length, Senescence

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## 8. Autoimmune Disease

### FP-43

### Risk Factors Affecting Non-Response and Biochemical Response in Autoimmune Hepatitis: A Multicenter Cohort Study

Soon Kyu Lee[1], Sook-Hyang Jeong[2], Gwang Hyeon Choi[2], U IM Chang[3], Ahlim Lee[3], Jeong-Ju Yoo[4], Ja Kyung Kim[5], Hye Yeon Chon[5], Seung Kak Shin[6], Kyung-Ah Kim[7], Hae Lim Lee[8], Ji-Won Park[9], Young-Joo Jin[10], Heechul Nam[11], Jung Hee Kim[12], Bo Hyun Kim[13], Jung Hyun Kwon[1], Hyung Joon Yim[14*]

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**Aims:** Recently published guidelines for autoimmune hepatitis (AIH) emphasize evaluating treatment responses, underscoring their impact on patient survival. Despite this, studies identifying factors that influence treatment response, particularly among Asian populations, remain limited.

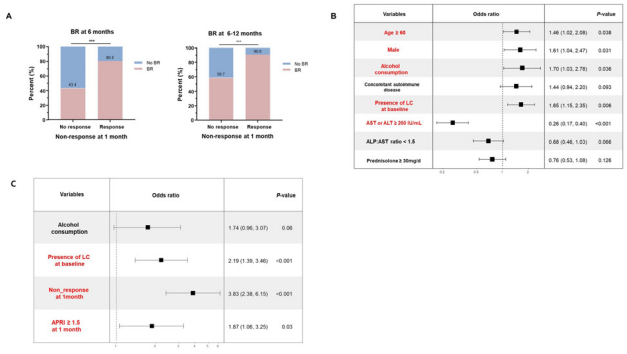
**Methods:** This study encompassed 1,401 newly diagnosed AIH patients from 14 Korean centers between January 2010 and December 2021. Of these, 1,133 patients (867 with liver histology) were included in the final analysis. The primary outcomes assessed were treatment responses, categorized as non-response at 1 month and biochemical responses (BR) between 6

and 12 months. Secondary outcomes involved identifying risk factors for non-response and biochemical responses both in the entire cohort and specifically in patients with liver histopathology at diagnosis.

**Results:** The mean age of the included patients was 59.6 years, with approximately 85% (n=960) being female. At diagnosis, 356 patients (31.4%) had liver cirrhosis. After treatment, approximately 69.1% of patients responded at 1 month, while 68.3% exhibited a BR at 6 months. In terms of BR at 6 and 6-12 months, patients who did not respond at 1 month had significantly lower rates of BR at these times ($P$<0.001 for both; Figure A). Multivariate analysis revealed that older age (≥ 60), male sex, alcohol consumption, presence of liver cirrhosis at baseline, and high AST or ALT levels (≥ 200 IU/mL) were significant risk factors for non-response at 1 month ($P$<0.05 for all, Figure B). Similar factors were also confirmed in patients with liver histology. Furthermore, the presence of liver cirrhosis at baseline, non-response at 1 month, and a high APRI score (≥ 1.5) at 1 month significantly impacted the failure to achieve a BR at 6-12 months ($P$<0.05 for all, Figure C) in both the entire population and patients with liver histology, highlighting the influence of initial non-response on later BR.

**Conclusions:** Utilizing a large multicenter cohort study, this research is the first to identify significant risk factors for non-response at 1 month and biochemical response (BR) at 6-12 months. Particularly, it highlights the impact of initial non-response on subsequent BR.

**Keywords:** Autoimmune hepatitis, Liver cirrhosis, Non-response, Biochemical response




## FP-44

### Risk of Extrahepatic Malignancies in Patients with Autoimmune Hepatitis: A Nationwide Cohort Study

Sung Won Chung[1], Ye-Jee Kim[2], Jihye Lim[3], Jonggi Choi[1], Danbi Lee[1], Ju Hyun Shim[1], Kang Mo Kim[1], Young-Suk Lim[1], Han Chu Lee[1], Sehee Kim[2], Won-Mook Choi[1]

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**Aims:** Nationwide, population-based data on the risk of extrahepatic malignancy in patients with autoimmune hepatitis (AIH) in Asian countries are scarce. This study aimed to examine the risk of developing extrahepatic malignancies in a nationwide cohort of patients with AIH.

**Methods:** Using claims data from the Korean National Health Insurance Service database between 2007 and 2020, patients with AIH (n=7,382) were matched in a 1:8 ratio with an age- and sex-matched control population (n=58,320) to compare the incidence of extrahepatic malignancies. We compared the incidence rates (IRs) and hazard ratios (HRs) of overall and specific extrahepatic malignancies between the two groups, while also examining the impact of immunosuppressant use.

**Results:** During a median follow-up period of 5.4 years, a total of 3,713 extrahepatic malignancies developed. The IR of extrahepatic malignancy in AIH patients (990.8 cases per 100,000 person-years) was comparable to that in the matched controls (937.6 cases per 100,000 person-years), with an HR of 0.93 (95% CI, 0.81–1.07; $P$=0.30). However, a significantly higher risk of hematologic malignancies, particularly lymphoma or myeloma (HR, 2.66; 95% CI, 1.70–4.17; $P$<0.001), was observed. The use of glucocorticoids (HR, 1.09; 95% CI, 0.87–1.38; $P$=0.44) or azathioprine (HR, 0.92; 95% CI, 0.73–1.17; $P$=0.51) had no impact on the risk of lymphoma or myeloma in patients with AIH.

**Conclusions:** In this nationwide, population-based cohort in South Korea, AIH was not associated with an increased risk of overall extrahepatic malignancy compared with age- and sex-matched controls. However, AIH itself increased the risk of lymphoma or myeloma, independent of immunosuppressant use.

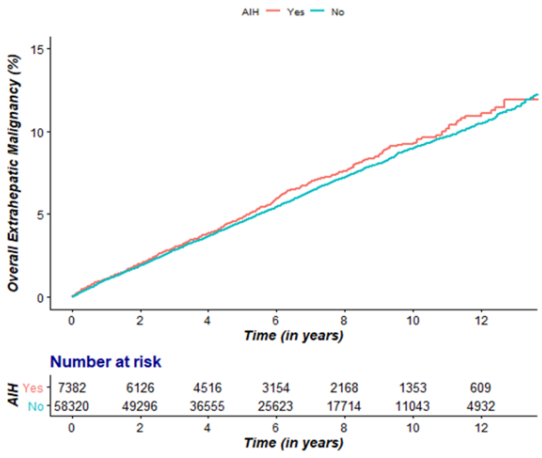


**Figure.** Cumulative risks of overall extrahepatic malignancy in patients with autoimmune hepatitis and their matched controls.

**Keywords:** Lymphoma, Myeloma, Thyroid cancer, Azathioprine

## FP-45

### Decoding the Role of Long Non-Coding RNAs in Autoimmune Hepatitis Progression: A Machine Learning Approach

Rifaldy Fajar[1], Prihantini Prihantini[2], Sahnaz Vivinda Putri[3], Elfiany Elfiany[4], Andi Nursanti Andi Ureng[5]

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**Aims:** Autoimmune Hepatitis (AIH) is a complex liver disorder marked by the immune system attacking liver cells, which can lead to liver failure. Long non-coding RNAs (lncRNAs) are emerging as important players in how the immune system functions and in the development of autoimmune diseases, but their specific roles in AIH are still not fully understood. This research aims to utilize machine learning (ML) techniques to explore how lncRNAs are involved in the progression of AIH. By doing so, we plan to identify certain lncRNAs that could potentially be used as new markers for detecting the disease or as targets for treatment.

**Methods:** We conducted a comprehensive analysis using high-throughput RNA sequencing data from liver biopsy samples of 300 AIH patients at different stages of the disease and 200 healthy controls. A ML framework was employed, comprising data preprocessing for normalization, feature selection to identify differentially expressed lncRNAs, and a combination of unsupervised and supervised learning algorithms (including clustering for pattern recognition and Random Forest for classification). The algorithms were fine-tuned and validated through a 5-fold cross-validation strategy to optimize performance and ensure generalizability.

**Results:** Our ML model distinguished AIH stages with an accuracy of 88.3%, sensitivity of 87.5%, and specificity of 89.1%. We identified 120 significantly differentially expressed lncRNAs associated with AIH progression, of which 10 were highly predictive of disease severity stages and response to immunosuppressive therapy. These lncRNAs were involved in pathways critical to immune response regulation, hepatocyte apoptosis, and liver regeneration. The model's predictive for therapeutic response was 84.2%, with a precision of 85.3% and recall of 84.2%. The 95% confidence interval (CI) for staging accuracy ranged from 87.1% to 89.5%.

**Conclusions:** This study reveals a new understanding of long non-coding RNAs (lncRNAs) and their connection to Autoimmune Hepatitis (AIH) progression, particularly their potential as indicators for how the disease develops and responds to treatment. By using machine learning (ML) to investigate how lncRNAs affect AIH, we are making important strides towards more personalized healthcare. This research opens up possibilities for improved diagnosis and treatment methods for this complex autoimmune disease.

**Keywords:** Autoimmune hepatitis (AIH) progression, Long non-coding RNAs (lncRNAs), Machine learning techniques, Biomarkers and therapeutic targets

## FP-46

### Development of a Nomogram for Predicting Survival in Patients with Autoimmune Hepatitis: A Multicenter Cohort Study

Soon Kyu Lee[1], Gwang Hyeon Choi[2], U IM Chang[3], Ahlim Lee[3], Jeong-Ju Yoo[4], Ja Kyung Kim[5], Hye Yeon Chon[5], Hyung Joon Yim[6], Seung Kak Shin[7], Kyung-Ah Kim[8], Hae Lim Lee[9], Ji-Won Park[10], Young-Joo Jin[11], Heechul Nam[12], Jung Hyun Kwon[1], Jung Hee Kim[13], Bo Hyun Kim[14], Sook-Hyang Jeong[2*]

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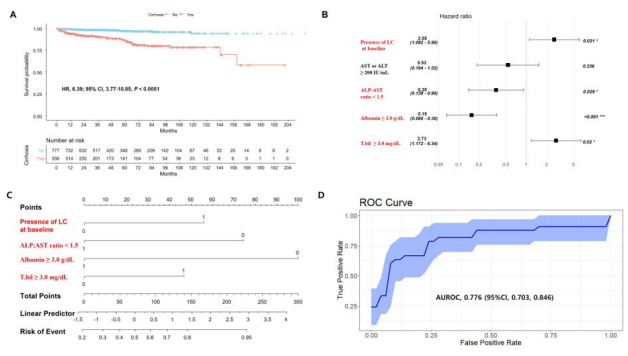
**Aims:** Although most patients with autoimmune hepatitis (AIH) exhibit a favorable prognosis, some progress to mortality, particularly those with liver cirrhosis (LC). Using a multicenter cohort study, this research aimed to identify risk factors and stratify risks for survival in AIH patients.

**Methods:** The study included 1,401 newly diagnosed AIH patients from 14 Korean centers, collected between January 2010 and December 2021. A total of 1,133 patients (867 with liver histology) were included in the final analysis. The primary outcome was the survival of AIH patients, analyzed according to liver cirrhosis and histologic fibrosis stages. Secondary outcomes focused on identifying risk factors for survival and developing a nomogram to predict it. Additionally, we assessed the impact of liver fibrosis on the development of liver-related events, including decompensated LC and hepatocellular carcinoma.

**Results:** During a mean follow-up of 58.6 months, a total of 69 patients died, including 19 with hepatitis and 50 with LC at baseline. Patients with LC exhibited significantly lower survival compared to those without LC ($P$<0.001, Figure A). This trend persisted among patients with liver histology, with those showing F4 fibrosis (cirrhosis) having lower survival rates than those with F3 or F0-2 fibrosis ($P$<0.001). In multivariate analysis, the presence of LC at baseline, a high ALP:AST ratio (≥ 1.5), low albumin levels (< 3.0 g/dL), and high bilirubin levels (≥ 3.0mg/dL) emerged as significant predictors of survival (Figure B). Subsequently, using these four variables, a predictive nomogram for survival was constructed (Figure C), which demonstrated good reliability with an AUROC of 0.776, according to bootstrap analysis (Figure D). These results were corroborated by a similar, reliable predictive model that incorporated comparable variables among patients with liver histology. Regarding liver-related events, patients with F4 fibrosis showed significantly lower survival, followed by those with F3 and F0-2 fibrosis ($P$<0.05 for all)

**Conclusions:** Utilizing a large multicenter cohort study, this research is the first to identify significant predictive factors for survival and to develop a reliable nomogram for predicting survival in patients with AIH.

**Keywords:** Autoimmune hepatitis, Survival, Liver cirrhosis, Liver-related event




## FP-47

## Vibration-Controlled Transient Elastography-Based Scores in Autoimmune Hepatitis for Predicting Liver Fibrosis Stage and Liver-Related Events

Kunhee Kim[1], Jae Seung Lee[1,2,3], Mi Na Kim[1,2,3], Beom Kyung Kim[1,2,3], Seung Up Kim[1,2,3], Do Young Kim[1,2,3], Sang Hoon Ahn[1,2,3], Hye Won Lee[1,2,3]

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**Aims:** Monitoring fibrosis progression in autoimmune hepatitis (AIH) is crucial. Recently, vibration-controlled transient elastography (VCTE)-based scores has been developed for monitoring fibrosis and has been confirmed to be predictive of predict liver-related events (LREs) in metabolic dysfunction-associated steatotic liver disease. However, the predictive performance of VCTE-based scores in AIH are unknown.

**Methods:** This study involved 308 patients with autoimmune hepatitis. We compared the area under the receiver operating curve (AUROC) of liver stiffness measurement (LSM), Agile 3+, Agile 4, and serologic scores for predicting fibrosis stage. We also compared the concordance index (c-index) and AUROC for 3-year and 5-year LREs, defined as hepatic decompensation, hepatocellular carcinoma, liver transplantation, and mortality.

**Results:** Overall, VCTE-based scores showed superior performance for the prediction of fibrosis stage and LREs, compared to serologic scoring systems. For predicting fibrosis stage 3 (F3), the AUROC of LSM, Agile 3+, and Agile 4 were 0.864 (95% confidence interval (95% CI) 0.818-0.910), 0.870 (95% CI 0.823-0.918), and 0.866 (95% CI 0.817-0.916), which were higher than those of FIB-4 (0.709 (95% CI 0.640-0.779)), NFS (0.766 (95% CI 0.704-0.829)), AST/ALT ratio (0.640 (95% CI 0.568-0.712)), BARD (0.710 (95% CI 0.646-0.773)), and APRI (0.559 (95% CI 0.484-0.635)). The AUROCs of LSM, Agile 3+, and Agile 4 for predicting 5-year LREs was 0.854 (95% CI 0.796-0.912), 0.867 (95% CI 0.806-0.928), 0.868 (95% CI 0.806-0.930), which was higher than those of FIB-4 (0.749 (95% CI 0.668-0.830)), NFS (0.789 (95% CI 0.710-0.868)), AST/ALT ratio (0.789 (95% CI 0.710-0.868)), BARD (0.712 (95% CI 0.629-0.794)), and APRI (0.602 (95% CI 0.511-0.694)). A similar trend was observed in AUROCs for prediction of F4 and 3-year LREs, and the c-index for prediction of 3-year and 5-year LREs.

**Conclusions:** VCTE-based scores are effective for predicting fibrosis stage and LREs in AIH and should be considered for clinical use.

**Keywords:** Autoimmune hepatitis, agile 3+, Agile 4, Fibrosis, Liver-related events

FP-48

## Multicenter Study on Incidence and Risk Factors of Hepatocellular Carcinoma in Patients with Autoimmune Hepatitis

Jiwon Yang[1], Hye Won Lee[2], Sang Hoon Ahn[2], Jonggi Choi[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Gastroenterology, Yonsei University College of Medicine, Seoul, Republic of Korea

**Aims:** A recent European multicenter study found a low incidence of hepatocellular carcinoma (HCC) in autoimmune hepatitis (AIH), even after cirrhosis development (annual incidence of 0.14/100 patient-years [PYs]). We aimed to evaluate the incidence and predictors of HCC in Asian patients with AIH.

**Methods:** We conducted a multicenter, retrospective study on adult patients diagnosed with AIH between 2007 and 2023. AIH diagnosis was based on international guidelines and confirmed via the registration of rare intractable disease registry of the Korean National Health Insurance Database. Patients with <6 months of follow-up or those with hepatitis B virus or hepatitis C virus infection were excluded. Primary outcome was the incidence of HCC with a median follow-up period of 5.1 years.

**Results:** Of 1,174 patients with AIH, 737 (64.3%) were from Asan Medical Center and 437 (37.2%) were from Yonsei University Severance hospital. Mean age was 57.0 years and 999 (85.1%) patients were female. Cirrhosis at diagnosis was present in 184 (15.7%) patients. During follow-up period, 48 (4.2%) patients developed HCC with an annual incidence of 0.65/100 PYs. Cumulative incidence of HCC at 3, 5, 7, and 10 years were 2.5%, 3.8%, 5.2%, and 6.2%, respectively. Risk factors for HCC included male gender (adjusted hazard ratio [AHR]: 2.87, 95% confidence interval [CI]: 1.50–5.49), cirrhosis at baseline (AHR: 3.57, 95% CI: 1.89–6.76), and diabetes (AHR: 2.65, 95% CI: 1.48–4.73).

**Conclusions:** Our multicenter AIH cohort showed a higher HCC incidence than the European study. Predictive factors associated with HCC included male gender, cirrhosis, and diabetes at baseline.

**Keywords:** Autoimmune hepatitis, Hepatocellular carcinoma, Risk factor, Survival

# The Liver Week 2024

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THE LIVER WEEK 2024

DAY 3: June 29 (Sat)

# Free Paper Presentation 2

| | |
|---|---|
| **FP-49~FP-54** | HBV |
| **FP-55~FP-60** | HCC, Clinical 2 |
| **FP-61~FP-66** | Liver Transplantation 1 |
| **FP-67~FP-72** | MASLD, Basic |
| **FP-73~FP-78** | HBV & HCV |
| **FP-79~FP-83** | LC, Clinical & Liver Failure |
| **FP-84~FP-89** | Liver Transplantation 2 |

Saturday, June 29, 2024, 09:10-10:30

## 9. HBV

### FP-49

### Impact of Maternal Chronic HBV Infection on the Neurodevelopment of Children: A Comprehensive Korean Cohort Study

Yewan Park[1,2], Jihye Heo[3,4], Danbee Kang[3,4], Geum-Youn Gwak[5]

[1]Department of Internal Medicine, Kyung Hee University Hospital, Seoul, Korea; [2]Department of Digital Health, SAIHST, Sungkyunkwan University, Seoul, Korea; [3]Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, South Korea; [4]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea; [5]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

**Aims:** Previous studies have indicated a potential association between maternal Hepatitis B virus (HBV) infection and impaired neurodevelopment in offspring. This study aimed to evaluate the relationship between maternal HBV infection and neurodevelopmental disorders (NDD) in children.

**Methods:** A retrospective cohort study was conducted utilizing data from the Korean National Health Insurance Service database, encompassing live births from 2005 to 2019. The cohort comprised children born to mothers who underwent HBsAg testing. Subsequent diagnoses of NDD were monitored in these children. Propensity score matching, at a 1:3 ratio, was employed to compare children born to HBV-infected mothers with those born to uninfected mothers. This matching method adjusted for various maternal and pregnancy-related variables.

**Results:** The study encompassed 263,904 children born to HBV-infected mothers and 791,712 matched controls. Offspring of HBV-infected mothers exhibited a slightly elevated risk of NDD development (HR 1.03, 95% CI: 1.01–1.04). Remarkably, children who were themselves infected with HBV demonstrated a further increased risk (HR 1.18, 95% CI: 1.09–1.28).

**Conclusions:** Children born to HBV-infected mothers, particularly those directly infected, displayed a modestly heightened risk of NDD. These findings underscore the necessity for further investigation into the impact of maternal HBV infection on offspring neurodevelopment and the formulation of targeted interventions.

**Keywords:** Hepatitis B virus, Neurodevelopmental disorders, Pediatric outcomes

### FP-50

### A Machine Learning Model to Predict Liver-Related Outcomes after the Functional Cure of Chronic Hepatitis B

Moon Haeng Hur[1], Seung Up Kim[2], Hyun Woong Lee[2], Han Ah Lee[3], Hyung-Chul Lee[4], Sang Hoon Ahn[2], Beom Kyung Kim[2], Hwi Young Kim[3], Yeon Seok Seo[5], Hyunjae Shin[1], Jeayeon Park[1], Yunmi Ko[1], Youngsu Park[1], Yun Bin Lee[1], Su Jong Yu[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Jeong-Hoon Lee[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea; [3]Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea; [4]Department of Anesthesiology, Seoul National University College of Medicine, Seoul, Korea; [5]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea

**Aims:** The risk of hepatocellular carcinoma (HCC) and hepatic decompensation persists after hepatitis B surface antigen (HBsAg) seroclearance. This study aimed to develop and validate a machine learning model to predict the risk of liver-related outcomes (LROs) following HBsAg seroclearance.

**Methods:** A total of 2,046 consecutive patients who achieved HBsAg seroclearance between 2000 and 2022 were enrolled from 6 centers in South Korea. A new model (designated as PLAN-C) was developed using variables based on the results of multivariable Cox analysis and a gradient-boosting machine (GBM) algorithm. The primary outcome was the development of LRO (i.e., HCC, cirrhosis-related complications, and liver-related death), and the first LRO confirmed after HBsAg seroclearance was counted as an event.

**Results:** During a median follow-up of 55.2 (interquartile range=30.1–92.3) months, 123 LROs were confirmed (1.1%/person-year). The PLAN-C was constructed using 6 variables: age, sex, diabetes, alcohol consumption, cirrhosis, and platelet count. Compared to previous HCC prediction models, the PLAN-C showed significantly superior predictive accuracy in both the training (c-index: 0.85 vs. 0.63–0.70, all $P<0.001$) and the validation (0.84 vs. 0.61–0.81; all $P<0.05$ except for CU-HCC, $P=0.09$) cohorts. The calibration plots demonstrated a close correlation between the predicted and observed risks of LRO (Hosmer–Lemeshow test $P>0.05$ in both cohorts). When entire patients were divided into 3 groups according to the risk predicted by PLAN-C, the low-risk group had a significantly lower 5-year incidence of LRO (0.8%), compared to the intermediate-risk (4.0%) and high-risk (22.8%) groups (both $P<0.001$).

**Conclusions:** This novel machine learning model consisting of 6 variables provides reliable risk prediction of LRO after HBsAg seroclearance that can be used for personalized surveillance.

**Keywords:** Surface antigen, Seroclearance, Liver cancer, Artificial intelligence

## FP-51

### A Nationwide Seroepidemiology Study of Hepatitis D Virus Infection in South Korea

Ju-Yeon Cho[1], Sung Won Lee[2,3], Jeong Won Jang[2,4*], Ji Won Han[2,4], Jung Hyun Kwon[2,5], Chang Wook Kim[2,6], Myeong Jun Song[2,7], Hee Yeon Kim[2,3], Moon Young Kim[8], Seul Ki Han[8], In Hee Kim[9], Young-Kul Jung[10], Kwang Il Seo[11], Jeong-En Song[12], Jin Dong Kim[13]

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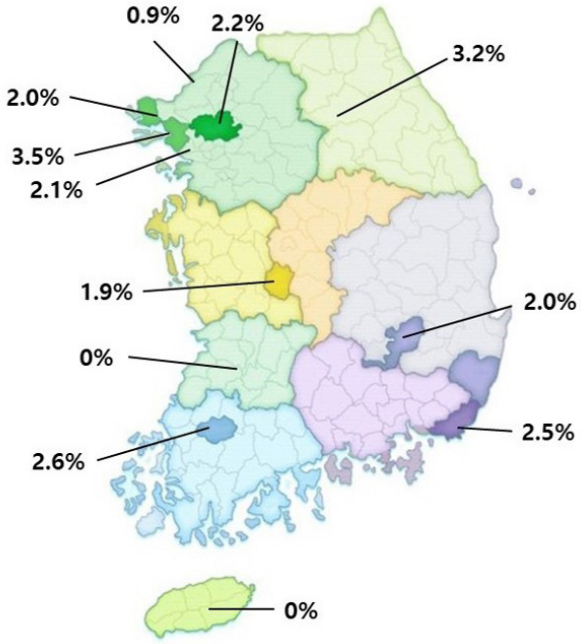
**Aims:** Hepatitis D Virus (HDV) infection which requires the presence of hepatitis B virus leads to a more aggressive disease course in chronic hepatitis B (CHB) patients leading to an increased healthcare burden. The estimated anti-HDV prevalence is reported to be 4.5% among all HBsAg-positive people, but data regarding the prevalence rate of HDV in Korea is lacking. This study aimed to elucidate the prevalence of HDV infection among chronic hepatitis B patients residing in South Korea.

**Methods:** This prospective, multicenter cohort enrolled 2,009 patients with CHB infection in twelve tertiary centers in South Korea. Demographic, biochemical characteristics including liver disease status were reviewed. Competitive enzyme and chemiluminescence immunoassays were used to detect anti-HDV antibodies at a central lab.

**Results:** The CHB patients had a mean age of 56.4 years and 62.6% of the patients were male. Forty-three patients (2.14%) had positive anti-HDV tests. Co-infection with HCV and HIV was noted in 30 patients (1.5%) and 2 patients (0.1%), respectively. The anti-HDV positive rates varied according to geographical region. (Fig1) The seroprevalence ranged from 0 to 3.5%. The highest prevalence rates were seen in Bucheon and Gangwon-do. Jeonbuk and Jeju had no patients with HDV co-infection. Among the foreign residents residing in Korea (6.2%, n=106), positive anti-HDV tests were significantly higher compared to Korean nationals. (7.4% vs 1.9%, *P*=0.001) Positive anti-HDV test was noted in 2.7% and 1.8% of CHB patients with and without liver cirrhosis, respectively. (*P*=0.108) Patients with and without hepatocellular carcinoma were positive for anti-HDV test in 1.8% and 2.3%, respectively (*P*=0.343) The proportion of patients with liver cirrhosis and hepatocellular carcinoma was not significantly different according to the presence of anti-HDV.

**Conclusions:** The national anti-HDV seroprevalence rate in South Korea was lower than that of the global estimate. However, there was a difference in the prevalence rate according to the geographical region and in the foreign residents of Korea. Further studies to determine the impact of HDV co-infection on the disease progression in an HBV endemic area is needed.

**Keywords:** Hepatitis D virus, Prevalence rate, Korea




## FP-52

### Effectiveness of Solanum Procumbens Combined with Tenofovir Disoproxil Fumarate in Treatment of Chronic Hepatitis B

Le Thi Thu Hien[1], Le Quoc Tuan[2], Pham Như Quynh[1], Nguyen Quoc Anh[2], Dinh Cong Tiep[2], Tran Thi Tuyet Nhung[2]

[1]Thai Nguyen University of Medicine and Pharmacy; [2]103 Cam Khe Clinic

**Aims:** Evaluating the effectiveness of Solanum procumbens

(SP) combined with Tenofovir disoproxil fumarate (TDF) in the treatment of hepatitis B virus (HBV).

**Methods:** Study on a randomized controlled clinical trial in HBeAg (+) 150 HBV patients at Cam Khe Clinic from May 2019 to November 2023, who divided into 3 groups treated with: TDF 300mg, TDF 300mg combined with SP 300mg and SP 300mg.

**Results:** Percentages of ALT, AST ≤ 40 UI/L after 6, 12, 18 months of SP-TDF group were higher than the TDF group and SP group ($P$<0.01). Early response of HBV DNA in the SP -TDF group were higher than in the TDF group and SP group ($P$<0.01). The rates of response to reduce HBV DNA below the detection threshold in the SP -TDF group after 6, 12, 18 months were higher than TDF group and SP group ($P$<0.01). The rate of the seroconversion from HBeAg (+) to HBeAg (-) in the SP-TDF group after 6, 12, 18 months were higher than the TDF group and SP group ($P$<0.01). The rate of HBeAg (-) and anti HBe (+) in the SP -TDF group after 6,12, 18 months were higher than the TDF group and SP group ($P$<0.01). It quickly reduce AST, ALT values returned to normal in the SP group. Some patients had side effects of headache and epigastric pain in SP-TDF groups.

**Conclusions:** The combination of SP and TDF is more effective than TDF or SP alone in the treatment of HBV.

**Keywords:** Chronic hepatitis B, Solanum procumbens (SP), Tenofovir disoproxil fumarate (TDF), Treatment, Effective

## FP-53

### Factors Predictive of Improvement of Renal Function after Switching to Tenofovir Alafenamide from Tenofovir Disoproxil Fumarate in Patients with Chronic Hepatitis B

Hyeyeon Hong[1], Won-Mook Choi[1], Danbi Lee[1], Ju Hyun Shim[1], Kang Mo Kim[1], Young-Suk Lim[1], Han Chu Lee[1], Jonggi Choi[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

**Aims:** Switching from Tenofovir disoproxil fumarate (TDF) to Tenofovir alafenamide (TAF) is known to improve renal function in chronic hepatitis B (CHB) patients. However, the factors influencing this improvement remain unclear. We aimed to identify predictors of renal function improvement after switching.

**Methods:** We retrospectively analyzed 942 CHB patients who switched from TDF to TAF between 2017 and 2024 at Asan Medical Center, Seoul, Republic of Korea. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The primary outcome was an improvement of eGFR ≥ 5% from baseline at 6 months post-switch. Multivariable logistic regression analysis assessed predictive factors. Longitudinal changes in eGFR after the switch were also assessed.

**Results:** Mean age was 58.4 years and 504 (53.5%) were male. The baseline eGFR was 69.8 ml/min/1.73m$^2$. Reasons of switching from TDF to TAF were low eGFR < 60 ml/min/1.73m$^2$ (45.4%), osteoporosis (30.5%), and other causes (24.1%), such as partial virologic response or switching from combination to single therapy. Median eGFR increase post-switch: 2.0 ml/min/1.73 m$^2$ (interquartile range: -2-7). 372 (39.5%) patients showed ≥ 5% eGFR improvement; 251 (26.6%) had ≥ 10% eGFR improvement at 6 months post-switch. Baseline eGFR < 60 ml/min/1.73 m$^2$ (adjusted odds ratio: 3.80, 95% confidence interval: 2.73–5.29, $P$<0.001) was significantly associated with eGFR improvement post-switch. Serial eGFR changes indicated significant improvement post-switch in patients with baseline low eGFR, age ≥ 60 years, and diabetes.

**Conclusions:** In the present study, baseline low eGFR <60 ml/min/1.73m$^2$ was a predictive factor for renal function improvement post-switch from TDF to TAF in patients with CHB. Older age and diabetes may also indicate greater benefit from the switch.

**Keywords:** Chronic Hepatitis B, Renal function, Tenofovir alafenamide, Tenofovir disoproxil fumarate

## FP-54

### Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate in Chronic Hepatitis B: Liver-Related Clinical Outcomes and Subgroup Analysis by Liver Cirrhosis Status

Soon Sun Kim[1], Gi Hyeon Seo[2], Ji Eun Han[1], Hyo Jung Cho[1], Eunju Kim[3], Eileen Yoon[4], Eun Sun Jang[5], Jong-In Chang[3], Young Youn Cho[6], Hyun Woong Lee[7], Jae Youn Cheong[1], Hyung Joon Kim[6]

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**Aims:** This study evaluates the differential impacts of tenofovir alafenamide (TAF) versus tenofovir disoproxil fumarate (TDF) on liver-related clinical outcomes in patients with chronic hepatitis B (CHB), with a particular focus on subgroup analyses according to the presence of liver cirrhosis.

**Methods:** A total of 23,074 patients with CHB treated with either TAF (n=11,537) or TDF (n=11,537) were analyzed after

propensity score matching (PSM) for age, sex, liver cirrhosis, diabetes mellitus, hypertension, and the quarter of the year when treatment was initiated. Of these patients, 24.8% had liver cirrhosis. Liver-related clinical outcomes (hepatocellular carcinoma [HCC], decompensation, and liver transplantation [LT] or death) were followed for a mean of 34.8 months.

**Results:** The incidence of HCC was lower in the TAF group (0.72 per 100 person-years) than in the TDF group (0.93 per 100 person-years), with a hazard ratio (HR) for HCC development in the TAF group of 0.77 (95% CI: 0.65–0.92, *P*=0.003). The incidence of decompensation was lower in patients receiving TAF than in those on TDF (0.84 vs. 1.14 per 100 person-years; HR: 0.74, 95% CI: 0.63–0.86, *P*<0.001). TAF treatment was associated with a reduced risk of LT or death compared to TDF treatment (incidence: 0.12 vs. 0.29 per 100 person-years; HR: 0.43, 95% CI: 0.30–0.62, *P*<0.001). Subgroup analysis revealed that among patients with liver cirrhosis, TAF treatment significantly reduced the risk of LT or death (HR: 0.55, 95% CI: 0.35–0.88, *P*=0.012), although the difference in the reduction of HCC incidence between TAF and TDF did not reach statistical significance (*P*=0.063).

**Conclusions:** TAF treatment in patients with CHB was associated with significantly lower risks of HCC, LT or death, and decompensation compared to TDF treatment. In patients without cirrhosis, treatment with TAF decreases the risks of HCC, decompensation, and LT or death. However, for those with cirrhosis, although TAF reduces the likelihood of decompensation and LT or death, it does not significantly alter the risk of HCC when compared to the TDF group. These findings suggest the potential of TAF as a preferred treatment option in CHB management, regardless of the presence of liver cirrhosis.

**Keywords:** Tenofovir, Hepatitis B, Chronic, Liver neoplasms, Liter transplantation

Saturday, June 29, 2024, 13:40-15:00

## 10. HCC, Clinical 2

### FP-55

### Peripheral Blood Inflammatory Score Using a Cytokine Multiplex Assay Predicts Clinical Outcomes in Unresectable HCC Patients Treated with Atezolizumab/Bevacizumab

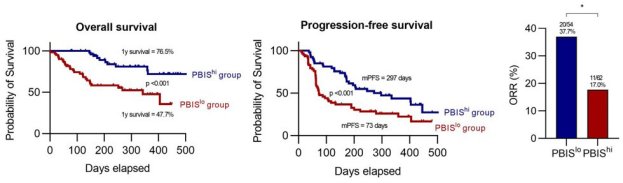
Hee Sun Cho[1,2], Ji Won Han[1,2], Pil Soo Sung[1,2], Jong Yong Choi[1,2], Seung Kew Yoon[1,2], Jeong Won Jang[1,2]

[1]The Catholic University Liver Research Center, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea; [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul 06591, Republic of Korea

**Aims:** Several serum cytokines have been proposed as biomarkers for predicting outcomes in hepatocellular carcinoma (HCC) patients receiving tyrosine kinase inhibitors. However, their role in Atezolizumab/Bevacizumab (AB) treatment is unclear.

**Methods:** We examined serum cytokines, including interferon-γ (IFN-γ), interleukin-10 (IL-10), IL-12, IL-17, IL-2, IL-6, and tumor necrosis factor (TNF), using a Luminex cytokine multiplex assay before AB treatment in prospectively-enrolled 116 AB-treatment patients. We collected baseline characteristics, including neutrophil-lymphocyte ratio (NLR) and C-reactive protein (CRP), and prospectively observed clinical outcomes.

**Results:** Among various peripheral blood inflammatory markers, high NLR, CRP, IL-2, and IL-12 were significantly associated with poor progression-free survival (PFS) and overall survival (OS). Optimal cut-offs identified by Cox-regression analysis were as follows; NLR > 3.5, CRP > 0.13 mg/dL, IL-2 > 3.2 pg/mL, and IL-12 > 11.6 pg/mL. With the sensitivity analysis, we could define a high peripheral blood inflammatory score (PBIS) group who had 2 or more factors among high NLR, CRP, IL-2, and IL-2. High PBIS was an independent risk factor associated with poor OS, PFS, and objective response rate (ORR) in the multivariate analyses. However, it was not a predictive factor regarding OS, PFS, and ORR in lenvatinib-treated patients. The low PBIS group (n=54) showed 1-year OS, median PFS, and ORR of 76.5%, 297 days, and 37.0%, whereas the high PBIS group (n=62) showed 1-year OS, median PFS, and ORR of 47.7%, 97 days, and 17.7%, respectively.




**Conclusions:** These results suggest that the cytokine-multiplex assay-based scoring system significantly predicts clinical outcomes in AB-treated HCC patients. This non-invasive blood base biomarker needs to be validated in multicenter, large-sized cohorts.

**Keywords:** HCC, Atezolizumab plus bevacizumab, Biomarker, Cytokine

### FP-56

### Durvalumab Plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer: A Large Real-Life Worldwide Population

Margherita Rimini[1], Lorenzo Fornaro[2], Mario Domenico Rizzato[3], Daniele Lavacchi[4-5], Masafumi Ikeda[6], Emiliano Tamburini[7], Changhoon Yoo[8], Ilhwan Kim[9], Anna Diana[10], Mario Scartozzi[11], Gerald Prager[12], Jin Won Kim[13], Lukas Perkhofer[14-15], Stephen L

Chan[16], Annamaria Pessino[17], Nicola Personenni[18], Ingrid Garajova[11], Lorenza Rimassa[19], Andrea Casadei-Gardini[1], Mara Persano[1]

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**Aims:** The TOPAZ-1 phase 3 trial demonstrated a survival advantage with the anti-PD-L1 durvalumab, when used with gemcitabine and cisplatin for patients with advanced biliary tract cancer (BTC). To gain a broader understanding of the efficacy and tolerability of this combination, we performed a worldwide multicenter retrospective analysis to investigate the efficacy and safety of this new first-line standard treatment in a real-word setting.

**Methods:** The analyzed population included patients (pts) with unresectable, locally advanced or metastatic BTC treated with durvalumab, gemcitabine and cisplatin at 38 sites from 10 countries in Europe, United States, and Asia. The primary endpoint of the study was OS.

**Results:** 618 pts were enrolled. At data cutoff (January 20, 2024), the median duration of follow-up was 8.5 months (95% CI: 7.9-9.4), 327 patients (52.9%) discontinued the treatment due to disease progression, and 188 patients (30.4%) died. Patient demographics and disease characteristics are reported in table 1. Median OS was 15.1 months (95% CI 13.4-29.1) and median PFS 8.1 months (95% CI 7.5-8.7). By considering chemoimmuno cycles and maintenance cycles with single-agent durvalumab, the median number of administered cycles was 9 with a range of 1-26 cycles. 222 (35.9%) patients were free from disease progression after 8 cycles of chemotherapy plus durvalumab, receiving subsequent maintenance therapy with durvalumab monotherapy. ORR was 31.7% (CR 2.5%, PR 29.6%), SD 46.7%, and DCR 78.8%. Any grade AEs occurred in 92.8% of pts. Grade 3-4 AEs in 46.0%. The most common AEs were fatigue (55.1%), anemia (48.7%), neutropenia (46.0%), and thrombocytopenia (38.5%). The rate of immune-mediated AEs (imAEs) was 19.7%. Grade 3-4 imAEs occurred in 2.5% of the patients. CEA normal value (*P*=0.0009,HR:0.66),ECOG PS 0 (*P*=0.0014,HR:0.67), locally advanced disease (*P*=0.0010,HR:0.47), and NLR < 3 (*P*=0.0002,HR:0.53) were correlate with better outcome.

**Conclusions:** The results reported in this first worldwide real-world analysis mostly confirmed the results achieved in the TOPAZ-1 trial and further support the combination of gemcitabine plus cisplatin and durvalumab as a standard of care for the first-line treatment of pts with advanced BTC.

**Keywords:** Cholangiocarcinoma, Durvalumab, Immunotherapy, Real-world evidence, Biliary tract cancer, Advanced disease

## FP-57

### Increased Variceal Bleeding Risk Associated with Atezolizumab plus Bevacizumab Dose Not Affect Survival Outcomes in Unresectable Hepatocellular Carcinoma: Concurrent Endoscopy and Computed Tomography Screening

Jeayeon Park[1], Dong Ho Lee[2,3], Moon Haeng Hur[1], Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[1],Yoon Jun Kim[1], Jung-Hwan Yoon[1], Su Jong Yu[1]

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**Aims:** The IMbrave150 trial has led first-line systemic therapy for unresectable hepatocellular carcinoma (HCC) to include immunotherapy, remarkably improving life expectancy. However, the use of atezolizumab plus bevacizumab is often challenged due to the increased risk of variceal bleeding. In this study, we aimed to identify factors associated with bleeding events during the treatment with atezolizumab plus bevacizumab, as well as factors that affect OS.

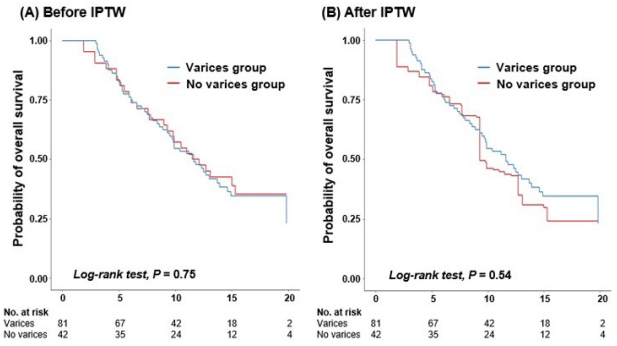
**Methods:** We retrospectively included consecutive patients who treated with atezolizumab plus bevacizumab as first-line systemic therapy for unresectable HCC from October 2020 to December 2022 at a tertiary referral center. Primary endpoint was the incidence of the first bleeding event during treatment. Secondary endpoint included overall survival (OS).

**Results:** A total of 124 patients were included: 82 had varices found on either esophagogastroduodenoscopy (EGD) or computed tomography (CT) (varices group), while 42 showed no varices on both EGD and CT (no varices group). Prior to treatment with atezolizumab plus bevacizumab, no high-risk varices were noted. During the median follow-up duration of 11.1 months (interquartile range, 6.1–14.9), bleeding events occurred in 15 patients. The cumulative incidence of bleeding in the varices group was 12.5%, 21.1%, and 31.0% at 6, 12, and 18 months, respectively, significantly higher than the 0.0% incidence at the corresponding time points in the no varices group (*P*=0.003). The median OS was 11.6 months (95% confidence interval [CI], 9.5–14.6) in the varices group and 11.8 months (95% CI, 9.3–not estimated) in the no varices group (*P*=0.70 by log-rank test). There was no statistically significant difference in OS according to the presence of varices (adjusted

hazard ratio [aHR], 0.92; 95% CI, 0.56–1.51; *P*=0.74). Baseline PIVKA level ≥ 1000 mAu/mL (aHR 1.98; 95% CI, 1.21–3.25; *P*=0.007) and neutrophil to lymphocyte ratio ≥ 3 (aHR 1.77; 95% CI, 1.12–2.81; *P*=0.01) were significant independent predictors of OS.

**Conclusions:** The presence of varices on baseline imaging study was significantly associated with an increased risk of bleeding events during treatment with atezolizumab plus bevacizumab, although the OS was similar regardless of the presence of varices.

**Keywords:** Immunotherapy, PD-L1, Variceal bleeding, Liver cancer




## FP-58

### A Machine Learning Model to Predict De Novo Hepatocellular Carcinoma Beyond Year 5 of Antiviral Therapy

Yeonjung Ha[1], Seungseok Lee, BEng[2], Jihye Lim[3], Kwanjoo Lee[1], Young Eun Chon[1], Joo Ho Lee[1], Kwan Sik Lee[1], Kang Mo Kim[4], Ju Hyun Shim[4], Danbi Lee[4], Dong Keon Yon[5], Jinseok Lee[2], Han Chu Lee[4]

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**Aims:** This study aims to develop and validate a machine learning (ML) model predicting hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients after the first 5 years of entecavir (ETV) or tenofovir (TFV) therapy.

**Methods:** CHB patients treated with ETV/TFV for > 5 years and not diagnosed with HCC during the first 5 years of therapy were selected from two hospitals. We used 36 variables, including baseline characteristics (age, sex, cirrhosis, and type of antiviral agent) and laboratory values (at baseline, at 5 years, and changes between 5 years) for model development. Five machine learning algorithms were applied to the training dataset and internally validated using a testing dataset. External validation was performed.

**Results:** In years 5-15, a total of 279/5,908 (4.7%) and 25/562 (4.5%) patients developed HCC in the derivation and external validation cohorts, respectively. In the training dataset (n=4,726), logistic regression showed the highest area under the receiver operating curve (AUC) of 0.803 and balanced accuracy of 0.735, outperforming other ML algorithms. An ensemble model combining logistic regression and random forest performed best (AUC, 0.811 and balanced accuracy, 0.754). The results from the testing dataset (n=1,182) verified the good performance (AUC, 0.784 and balanced accuracy, 0.712). External validation confirmed the predictive accuracy of our model (AUC, 0.862 and balanced accuracy, 0.771). A web-based calculator was developed.

**Conclusions:** The proposed ML model excellently predicted HCC risk beyond year 5 of ETV/TFV therapy and, therefore, could facilitate individualized HCC surveillance based on risk stratification.

**Keywords:** Machine learning, Chronic hepatitis B, Hepatocellular carcinoma, Prediction

## FP-59

### Effect of Preoperative Transarterial Chemoembolization for Resectable Single Hepatocellular Carcinoma: A Single-Center Cohort Study

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**Aims:** The efficacy of preoperative transarterial chemoembolization (TACE) for resectable hepatocellular carcinoma (HCC) remains unclear. This study aims to evaluate the impact of preoperative TACE on long-term outcomes after surgical resection for single HCC.

**Methods:** This retrospective cohort study included 4997 patients undergoing hepatectomy for resectable single HCC between December 2008 and March 2019 in Asan Medical Center in Seoul. Survival outcomes were compared before and after propensity score matching (PSM) according to different tumor size between patients who underwent preoperative TACE and patients who did not. Univariable and multivariable Cox regression analyses were performed to identify independent risk factors associated with overall-survival (OS) and recurrent-free survival (RFS).

**Results:** Of 4997 patients, 425 (8.5%) underwent preoperative TACE. Preoperative TACE group showed significantly better RFS (*P*<0.001) than upfront surgery group, but did not signifi-

cantly improve OS except for HCC with size of 3-5cm (*P*=0.046). A total of 1489 patients were included after 1:3 PSM. In the matched cohort, preoperative TACE significantly improved OS (*P*=0.025) and RFS (*P*=0.015) only in HCC with size of 3-5cm. The multivariate regression analysis showed preoperative TACE (*P*=0.003, Hazard ratio 0.52, 95 % Confidence interval 0.34-0.80) was significantly associated with improved RFS.

**Conclusions:** Preoperative TACE can be recommended as routine treatment for resectable single HCC, especially when the tumor size is between 3 cm and 5 cm, given its clear benefits of both RFS and OS. Further studies with large sample size and randomized controlled trials are necessary to clarify the effectiveness of preoperative TACE.

**Keywords:** Preoperative tace, Hepatocellular carcinoma, Long-term outcome

## FP-60

### Geriatric Nutritional Risk Index as a Prognostic Cactor in Patients with Hepatocellular Carcinoma: Based on Korea Nationwide Cancer Registry

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**Aims:** Despite the importance of nutritional status of patients with hepatocellular carcinoma (HCC) in clinical practice, the predictive value of nutritional index is not well established.

**Methods:** Data collected from the Korean Primary Liver Cancer Registry, a representative cohort of patients newly diagnosed with HCC in Korea between 2008 and 2019, were analyzed. Nutritional assessment in this study utilized the geriatric nutritional risk index (GNRI), which was calculated based on serum albumin levels, body weight, and height. Overall survival (OS) according to tumor stage, liver function and nutritional index was analyzed.

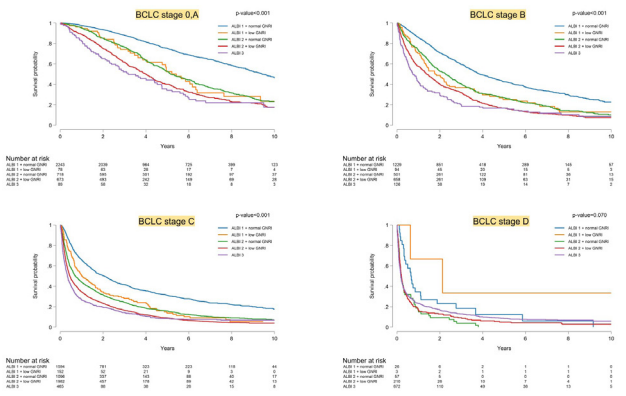
**Results:** The study included 16,416 patients, with a median age of 61 years, of whom 79.2% were male. Patients were classified into four GNRI risk groups: normal (> 98; n=10,107), mild risk (92–98; n=2,528), moderate risk (82-92; n=2,670), and severe risk (<82; n=1,111). Median OS for all patients was 3.1 years (95% CI; 3.0-3.2). Median OS varied significantly across GNRI groups: normal: 4.95 years (95% CI: 4.77–5.13); mild risk: 1.87 years (95% CI: 1.68–2.08); moderate risk: 0.86 years (95% CI: 0.79–0.98); and severe risk: 0.46 years (95% CI: 0.39-0.51) (*P*<0.001) (refer to Table 1). The impact of GNRI on survival was further assessed within each BCLC stage. In every BCLC stage (except stage D), subgroups composed of 'ALBI grade 1 and normal GNRI' exhibited notably better OS, with a p-value of <0.001 in each stage (refer to Figure 1). Multivariate Cox regression analyses, adjusted for age, sex, BMI, BCLC stage, ALBI grade, and etiology, revealed that patients with normal GNRI were associated with better OS (HR 0.85; 95% CI 0.80-0.90, *P*<0.001).

**Table 1.** Overall survival based on GNRI group

| GNRI group | Number | median OS (year) | *P*-value |
|---|---|---|---|
| Normal (≥ 98) | 10107 | 4.95 (4.77-5.13) | <0.001 |
| Mild (92-98) | 2528 | 1.87 (1.68-2.08) | |
| Moderate (82-92) | 2670 | 0.86 (0.79-0.98) | |
| Severe (<82) | 1111 | 0.46 (0.39-0.51) | |
| Total | 16416 | 3.13 (3.03-3.22) | |

**Conclusions:** Nutritional status of HCC patients showed a substantial correlation with survival. Particularly, patients exhibiting ALBI grade 1 and normal GNRI demonstrated a notably favorable prognosis in each BCLC stage. Incorporating nutritional index into the prognostic evaluation of HCC patients could lead to more accurate prognostic predictions.

**Keywords:** Hepatocellular carcinoma, Nutritional assessment, Korea nationwide cancer registry




Saturday, June 29, 2024, 09:10-10:30

## 11. Liver Transplantation 1

## FP-61

### Long-Term Outcomes of Liver Retransplantation: A 31-Year Korean Single-Center Experiences

Sang-Hoon Kim, Deok-Bog Moon, Sung-Gyu Lee, Shin Hwang, Chul-Soo Ahn, Ki-Hun Kim, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung, Gil-Chun Park, Young-In Yoon, Woo-Hyoung Kang, Eun-Kyoung Jwa, Byeong-Gon Na, Sung Min Kim, Rak-Kyun Oh, Hyo Jung Ko

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public of Korea

**Aims:** As the number of liver transplant (LT) increases, graft loss is expected to increase. Liver retransplantation (Re-LT) is the only treatment option for patients with liver graft failure. We aimed to identify the post-retransplant long-term outcomes in recipients using living or deceased donor liver grafts and favorable prognostic factors.

**Methods:** This is a retrospective study of a series of 343 cases of Re-LT for 305 adults and 38 children (<18 years of age) at Asan Medical Center from January 1998 to August 2023. Survival analyses were performed according to recipient type, graft type, allograft dysfunction, time interval from primary to re-LT, technical failure, and preoperative recipient conditions. Univariate and multivariate analyses were evaluated to identify favorable prognostic factors for long-term survival.

**Results:** The most common cause of re-LT was acute or chronic rejection. Five-year overall survival rates were presented according to recipient type (adult vs. pediatric; 58.6% vs. 78.1), graft type (living vs. deceased; 68.7% vs.58.5%), allograft dysfunction (early vs. chronic; 45.5% vs. 75.1%), time interval from primary to re-LT (> 1 year vs. < 30 days vs. 1-12 months; 72.1% vs. 45.5% vs. 58.6%), and technical failure (none vs. present; 62.7% vs. 46.9%). Multivariate analysis showed chronic allograft dysfunction, absence of technical failure, preoperative non-ICU admission, absence of sepsis, and low MELD score were favorable prognostic factors.

**Conclusions:** Considering the poor prognosis of recipient undergoing re-LT in an early period after primary LT, liver transplant surgeon requires to overcome the technical obstacles and intensive post-transplant management, especially for rejection is necessary.

**Keywords:** Retransplantation, Long-term outcome, Liver transplantation

## FP-62

### 3D Auto-Segmentation of Biliary Structure of Living Liver Donors Using Magnetic Resonance Cholangiopancreatography

**Jinsoo Rhu**

Department of Surgery, Samsung Medical Center, Republic of Korea

**Aims:** This study was designed to build a automated segmentation of biliary structure based on magnetic resonance cholangiopancreatography using deep learning model.

**Methods:** Living liver donors with magnetic resonance cholangiopancreatography gradient and spine echo technique and underwent three-dimensional modeling were eligible for this study. The three-dimensional residual U-Net model was implemented for deep learning process. Training set and test set were allocated in 9:1 ratio. For evaluation of the performance, dice similarity coefficient score was evaluated between the ground truth and inference of the auto-segmentation model.

**Results:** A total of 250 cases were included to the study. There was no difference in the baseline characteristics between the train set (n=225) and test set. (n=25) The overall mean dice similarity coefficient was 0.80±0.20 between the ground truth and inference result. The qualitative assessment of the model showed relatively high accuracy especially for common bile duct (88%), common hepatic duct (92%), hilum (96%), right hepatic duct (100%) and left hepatic duct (96%), while the third order branch of right hepatic duct (18.2%) showed low accuracy.

**Conclusions:** The auto-segmentation model of biliary structure based on magnetic resonance cholangiopancreatography using deep learning method showed high performance and shows promising results for future development of automation.

**Keywords:** Deep learning, Artificial intelligence

## FP-63

### Oxygen Delivery and Consumption during Hypothermic Oxygenated Machine Perfusion and Their Impact on Post-Liver Transplant Outcome

**Luca Del Prete**[1], Eloisa Franchi[1], Bianca Taglione[1], Michele Battistin[2], Francesca Marcon[1], Arianna Zefelippo[1], Barbara Antonelli[1], Lucio Caccamo[1], Daniele Dondossola[1]

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**Aims:** While authors recommend maintaining pO2 > 600 mmHg(80KPa) for sufficient oxygenation during liver hypothermic oxygenated machine perfusion (HOPE), recent studies have underscored the adverse relationship between increased carbon dioxide(CO2) production and graft damage. This study aims to investigate the dynamic relationship between oxygen delivery(DO2) and consumption(VO2) during HOPE and assess their impact on post-transplant(LT) outcomes.

**Methods:** DHOPE cases performed at our Foundation were selected and divided according to perfusate pO2 > 600 mmHg(H-DO2) and <600 mmHg(L-DO2). PO2<600 mmHg was obtained by titration of post-liver pO2(> 120 mmHg). DO2 and VO2 were calculated using the modified Fick equation.

**Results:** Twenty-seven transplanted livers underwent DHOPE, comprising 12 from brain-dead and 15 from cardiac-dead donors. Among these cases, 13(48.1%) were classified in the L-DO2 group, while 14(51.9%) were in the H-DO2 group. In L-DO2 grafts, DO2 measured 1.46±1.07ml/min(pO2 233±89

mmHg), with VO2 at 0.82±0.44ml/min. In H-DO2 grafts, DO2 was > 5.06±1.95 ml/min(pO2 > 600 mmHg), and VO2 was > 0.56±1.14ml/min. The increase in DO2 was directly correlated with VO2(r=0.56; *P*=0.056) and both showed associations with portal flow(r=0.81, *P*=0.001;r=0.58; *P*=0.047), but portal flow was not different in the two study groups(*P*=0.214). Importantly, early allograft dysfunction was observed in grafts with a higher DO2(*P*=0.021), but not VO2(*P*=0.451). Grafts with steatosis ≤ 30% exhibited higher VO2(0.933±0.216 ml/min) than those with steatosis > 30%(0.594±0.233 ml/min) (*P*=0.038).

**Conclusions:** During DHOPE, DO2 was more influenced by portal flow than pO2. Elevated DO2 may impact graft function post-LT, while steatosis may affect graft metabolic activation during HOPE. Consequently, titrating pO2 to achieve lower DO2, especially in grafts with high portal flow, should be considered.

**Keywords:** Machine perfusion, Metabolism, Viability

## FP-64

### Anatomical Study of the Paracaval Branch of Caudate Lobe: Implication of Caudate Preserving Right Hepatectomy for Donors with Marginal Remnant Liver Volume (with Video)

Na Reum Kim, Gi Hong Choi

Department of Surgery, Division of Hepato-biliary And Pancreatic Surgery, Severance Hospital, Republic of Korea

**Aims:** In living donor liver transplantation, remnant liver volume(RLV) is important to select a donor, usually exceeding 35%. However, there is no study on preservation of the caudate lobe in donors with marginal RLV. This study aimed to analyze paracaval branch of the caudate lobe, proposing a modified donor right hepatectomy preserving the caudate lobe.

**Methods:** eeding 35%. However, there is no study on preservation of the caudate lobe in donors with marginal RLV. This study aimed to analyze paracaval branch of the caudate lobe, proposing a

**Results:** Among the 87 donors, paracaval branch originated from the right PV in 41(47.1%), left PV in 37(42.5%), and bifurcation of the main PV in 9(10.3%). In 46 left or bifurcation-type donors, 21(45.7%) had a large size, 13(28.3%) had a medium size, and 12(26.1%) had a small size. The mean paracaval area volume, excluding two donors with poor image quality, was 38.0 mL, constituting 2.9% of the total liver volume(TLV). The expected preserved liver volume after modified right hepatectomy was 27.3mL, representing 2.1% of the TLV. Three donors in our center underwent paracaval branch-preserving right hepatectomy.

**Conclusions:** The paracaval portion of caudate lobe preserving right hepatectomy is feasible for donors with left or bifurcation types, expected to preserve 2.1% of the liver volume in those with marginal RLV, enhancing donor safety and expanding donor pool.

**Keywords:** Donor hepatectomy, Caudate lobe, Marginal donor

## FP-65

### The Impact of Tacrolimus Level and Its Intrapatient Variability on the Development of Chronic Kidney Disease Following Liver Transplantation

Soon Kyu Lee[1], Ho Joong Choi[2], Young Kyoung You[2], Jung Hyun Kwon[1], Pil Soo Sung[3], Jeong Won Jang[3], Seung Kew Yoon[3], Jong Young Choi[3*]

[1]Division of Hepatology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [3]Division of Hepatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

**Aims:** Although potent immunosuppressants (ISs), such as tacrolimus, has significantly improved the long-term management of liver transplantation (LT) patients, prolonged use of these ISs post-LT has been linked to several complications, including chronic kidney disease (CKD), consequently affecting survival rates compared to healthy individuals. This study aimed to identify the risk factors for CKD and end-stage renal disease (ESRD) following LT, with a specific focus on tacrolimus levels and intrapatient variability (IPV).

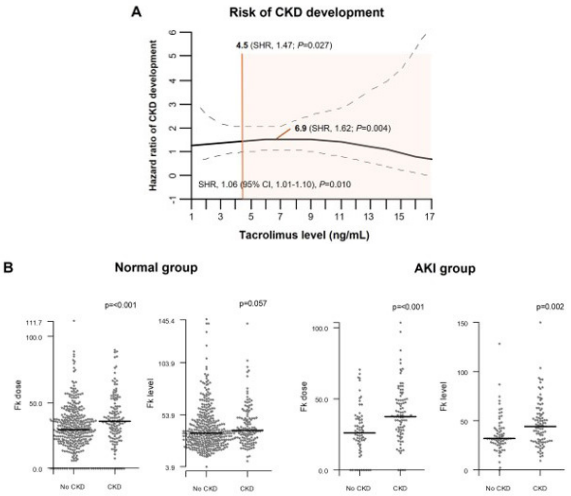
**Methods:** Among the 1,076 patients who underwent LT between 2000 and 2018, 952 were included in the analysis. The tacrolimus doses and levels were recorded every 3 months, and the IPV was calculated using the coefficient of variability. The cumulative incidence rates of CKD and ESRD were calculated based on baseline kidney function at the time of LT. The impact of tacrolimus levels and their IPV on the development of CKD and ESRD was evaluated, and the significant risk factors were identified.

**Results:** Within a median follow-up of 97.3 months, the 5-year cumulative incidence rates of CKD (0.58 vs. 0.24) and ESRD (0.07 vs. 0.01) were significantly higher in the acute kidney injury (AKI) group than in the normal glomerular filtration rate (GFR) group. In the normal GFR group, the tacrolimus levels were identified as a risk factor for CKD, with a level of ≤ 4.5 ng/mL suggested as optimal for minimizing the risk of CKD (Figure A). Both in the normal and AKI groups, patients with CKD development demonstrated higher IPV in the drug dose and level compared to patients without CKD during follow-up (Figure B). Furthermore, the IPV of tacrolimus levels and doses emerged as a significant risk factor for CKD development in both groups (*P*<0.05), with tenofovir disoproxil fumarate also

being a risk factor in HBV-infected patients. The IPV of tacrolimus levels was also a significant factor in ESRD development ($P$<0.05).

**Conclusions:** This study elucidated the optimal tacrolimus through level and highlighted the impact of IPV on the CKD and ESRD development post-LT.

**Keywords:** Liver transplantation, Chronic kidney disease, Tacrolimus, End-stage renal disease




## FP-66

### Attenuation of Hepatic Ischemia-Reperfusion Injury Associated with Liver Transplantation by Curcumin in Rodents via Anti-Inflammatory Action

**Ekta Yadav**

Shalom Institute of Health and Allied Sciences

**Aims:** Curcumin is a natural polyphenol obtained from *Curcuma longa* having significant potential against oxidative stress, inflammation, cancer and hepatic toxicity. In present study we focused on the protective effect of curcumin on hepatic ischemia-reperfusion injury by using *in vitro* and *in vivo* evaluation.

**Methods:** Male Sprague-Dawley rats were divided into five groups and administered with curcumin by an intraperitoneal route at three dose levels, i.e., 5, 10 and 20 mg/kg, for 14 days and subjected to liver transplant. RAW 264.7 cells under hypoxia/reoxygenation model were used and treated with curcumin at 1, 10, and 20 M. Curcumin potential against hepatic ischemia-reperfusion injury was estimated by determining liver enzymes, cytokine status, hepatocyte apoptosis level and TUNEL (Terminal deoxynucleotidyl transferase dUTP nick-end labeling), neutrophil and pro-inflammatory cytokines protein, and mRNA expression were detected.

**Results:** Results of *in vivo* study revealed that pathological liver alterations, level of serum aminotransferase as well as proinflammatory cytokines (IL-1, IL-18 and TNF-) were significantly decreased by curcumin in a dose-dependent manner. Moreover, reduced protein expression levels of TLR-4, p-IB, p-IKK, p-IKK, p-IKK, NLRP3, p-P65MyD88, TNF-$\alpha$, cleaved caspase-1, IL-1, IL-6 and IL-18 which are basically associated with TLR-4/NF-B/NLRP3 inflammatory signaling pathway was observed in rats with liver transplantation. Dose-dependent inhibition of protein expression associated with TLR-4/NF-B/NLRP3 inflammatory pathway in the RAW264.7 cells with hypoxia/reoxygenation model in curcumin-treated group was observed.

**Conclusions:** Curcumin exerts an anti-inflammatory effect in hepatic ischemia-reperfusion injury in liver transplantation by regulating the TLR-4/NF-B/NLRP3 inflammatory signaling pathway.

**Keywords:** Oxidative stress

Saturday, June 29, 2024, 09:10-10:30

# 12. MASLD, Basic

## FP-67

### Omentin-1 in Visceral Adipose Tissue: Implications on Its Role in Diabetes and Metabolic Dysfunction- Associated Steatotic Liver Disease

**Noel Salvoza**[1,2,3], Pablo Giraudi[2], Maria Melissa Milito[2,3], Silvia Gazzin[2], Deborah Bonazza[4], Silvia Palmisano[2,5], Nicolo de Manzini[5], Fabrizio Zanconati[4], Alan Raseni[6], Francesca Sirianni[6], Claudio Tiribelli[2], Natalia Rosso[2]

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**Aims:** Obesity and diabetes are tightly linked to metabolic dysfunction-associated steatotic liver disease (MASLD). Here, we explore the potential role of VAT omentin-1, identified through *in silico* analysis, in the context of obesity-related MASLD and diabetes.

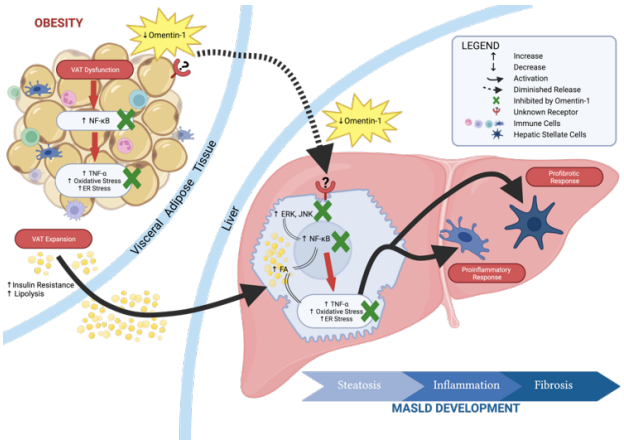
**Methods:** Omentin-1 levels were measured in obese patients with biopsy-proven MASLD and mice fed with high fat-diet (HFD). *In vitro* and/or *ex vivo* studies were conducted to investigate the effects of omentin-1 on MASLD-related pathogenesis, including steatosis, inflammation, ER stress, oxidative stress, and glucose-insulin modulation. We also analyzed the levels of omentin-1 in diabetic patients before and after 1 year of bariatric surgery.

**Results:** VAT and plasma omentin-1 levels exhibit a significant

stepwise reduction in MASLD patients, depending on disease severity but independent of fibrosis status. Likewise, HFD-fed mice with histological signs of MASH exhibited significantly reduced omentin-1 levels compared to their control diet counterpart. *In vitro* and *ex vivo* experiments using fat-laden hepatocytes and VAT explants, respectively, showed that omentin-1 did not affect steatosis but significantly reduced TNF-$\alpha$ levels, ER stress, and oxidative stress. Furthermore, omentin-1 significantly decreased the mRNA expression of *NF-κB* and mitogen-activated protein kinases. *Ex vivo* VAT explants showed that D-glucose and insulin significantly reduced omentin-1 mRNA expression and protein levels. Notably, diabetic patients exhibited a significant increase in plasma omentin-1 levels one year following bariatric surgery.

**Conclusions:** Our findings suggest that reduced omentin-1 levels contribute to the development of diabetes and MASLD. Therefore, further research is warranted to explore its role as a potential therapeutic target and/or biomarker.

**Keywords:** NAFLD, MASLD, Diabetes, Metabolic, Biomarkers




## FP-68

### The Genome-Wide Association Study of Metabolic Dysfunction-Associated Steatotic Liver Disease in Korean Large Population Cohort

Hayoung Oh[1], Sooyeon Oh[1], Jooho Lee[2], Min-ji Ahn[2], Sukyung Chun[2], Ja-Eun Choi[3], Sang-Woon Choi[1], Kyung-Won Hong[3]

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**Aims:** MASLD (metabolic dysfunction-associated steatotic liver disease) is defined as hepatic steatosis accompanied with at least one out of five cardiometabolic criteria. This new nomenclature was suggested because previously used non-alcoholic fatty liver disease (NAFLD) did not accurately capture the etiology of the disease. MASLD puts more emphasis on the role of metabolic dysfunction and does not require the exclusion of significant alcohol intake or other chronic liver disease. Although, MASLD and NAFLD share common grounds, there may be genetic traits distinctively inclined to the occurrence of MASLD compared to NAFLD. Thus, we aimed to discover those genes that are more specifically associated with MASLD. Since MASLD does not exclude steatotic liver disease with alcohol intake, we included MetALD (MASLD and increased alcohol intake) into our analyses to scrutinize the genetic susceptibility associated with alcohol. We believe this study will be the foundation toward understanding the pathophysiology of MASLD and eventually toward the development of a pharmacological treatment.

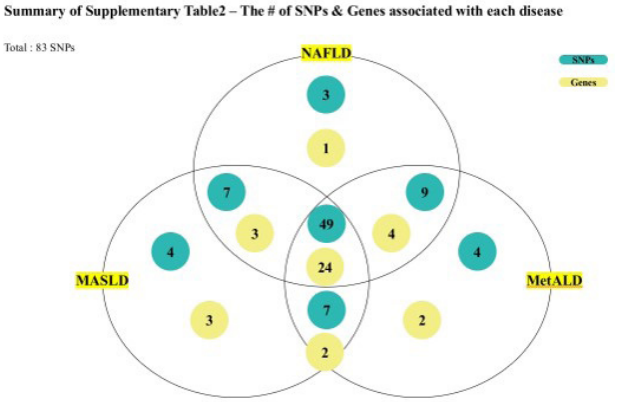
**Methods:** We obtained a large dataset of Korean Genome and Epidemiology Study cohort (n=48,978) from the Korea Biobank. The dataset included genomic data and medical records. 2,837 cases of MASLD, 4,275 cases of NAFLD 1,266 cases of MetALD and 4,912 cases of healthy controls were included. We performed genome-wide association study (GWAS) to investigate single nucleotide polymorphisms (SNP) that are associated with MASLD, NAFLD or MetALD development by comparing each steatotic liver disease group with healthy control group.

**Results:** There were 4 genes associated with MASLD, 4 genes associated with NAFLD and 3 genes with MetALD. MASLD and NAFLD shared 3genes, MASLD and MetALD shared 2 genes, and NAFLD and MetALD shared 2 genes. The rs651821 (*APOA5* gene) *C* allele increased the risk of MASLD (Adjusted OR=1.3; *P*=2.22E-10) and NAFLD (Adjusted OR=1.212; *P*=7.52E-08). The rs11065905 (*ATXN2* gene) *G* allele increased the risk of MASLD (Adjusted OR=1.214; *P*=2.54E-07) and MetALD (Adjusted OR=1.503; *P*=3.42E-12). The rs671 (*ALDH2* gene) *A* allele increased the risk of NAFLD (Adjusted OR=1.743; *P*=1.79E-38), however, decreased the risk of MASLD and MetALD (Adjusted OR=0.403 and 0.101, respectively). The rs688671 (*MC4R* gene) *G* allele increased the risk of NAFLD (Adjusted OR=1.183; *P*=4.45E-06) and MASLD (Adjusted OR=1.197; *P*=1.84E-5). The rs1861412 (*LINC01122* gene) *G* allele increased the risk of MetALD (Adjusted OR=1.339; *P*=7.48E-07).

**Conclusions:** We discovered that the three steatotic liver disease groups had distinctive genetic features although they largely shared the common genetic backgrounds: MASLD and NAFLD shared genetic associations with metabolic syndrome and lipid metabolism (*APOA5, MC4R* genes), while MASLD and MetALD shared genetic associations with alcohol metabolism (*ALDH2, ATXN2* genes). Identifying shared or isolated genetic associations, this work serves as a groundwork for future studies to investigate specific pathways that are involved with the development of each steatotic liver disease.

**Keywords:** Metabolic dysfunction-associated steatotic liver dis-

ease, Korean, Genome-wide association study, Non-alcoholic fatty liver disease




## FP-69

### Nintedanib Alleviates Metabolic-Associated Fatty Liver Disease in Mice by Elimination of Activated Fibroblasts

Sung Woo Cho[1], Jong Geun Park[1], Pil Soo Sung[1,2]

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**Aims:** In the alleviation of metabolic-associated fatty liver disease(MAFLD), the elimination of activated fibroblasts plays a pivotal role. In this study, our focus was on investigating the potential alleviation of MAFLD through the effect of nintedanib, a treatment used for idiopathic pulmonary fibrosis (IPF), on the elimination of activated fibroblasts.

**Methods:** Fibroblasts were isolated from the liver of MAFLD patients. *In vitro* nintedanib treatment on cultured patient-derived fibroblasts was done. A choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) as a dietary MAFLD model with rapidly progressing fibrosis was used.

**Results:** Through *in vitro* experiments utilizing patient-derived fibroblasts, cell viability measurements confirmed that nintedanib induces more elimination of activated fibroblasts compared to sorafenib. Additionally, we confirmed a decrease in phosphorylated-AKT and phosphorylated-ERK, proteins involved in inflammation and liver fibrosis, through western blotting analysis in nintedanib treated fibroblasts. *In vivo* experiments using CDAHFD mouse model demonstrated that increased level of FAP+PD-L1+ fibroblasts were found in the 4th week livers. The treatment of nintedanib selectively killed these activated fibroblasts at a very low concentration, suggesting that nintedanib may be used to treat MAFLD involving activated fibroblasts.

**Conclusions:** Our study suggests that nintedanib could be a promising treatment for MAFLD by targeting activated fibroblasts. Both *in vitro* and *in vivo* experiments showed nintedanib's effectiveness in eliminating activated fibroblasts.

**Keywords:** MAFLD, MASH, Fibroblast, Nintedanib

## FP-70

### Identification of Causal Genes for Nonalcoholic Fatty Liver Disease Using Single-Cell eQTL Analysis

Sung Eun Hong[1], Kyung-Suk Suh[2], Won Kim[3], Murim Choi[1]

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) is a liver disease associated with metabolic syndrome with increasing medical and socioeconomic burdens. Lack of effective treatment drugs urges the discovery of novel therapeutic targets. This study utilizes single-cell expression quantitative trait loci (sc-eQTL) based analysis to discover biomarkers and therapeutic targets of NAFLD.

**Methods:** Liver biopsy samples obtained from 23 control individuals and 25 NAFLD patients were subjected to single nucleus RNA-sequencing (snRNA-seq). DNA samples obtained from the same participants were genotyped by low coverage whole genome sequencing. snRNA-seq profiles of the NAFLD livers were analyzed using various bioinformatics tools. sc-eQTL were mapped via poisson mixed effects model. sc-eQTLs were tested for interaction with various cell level phenotypes. Colocalization with genome-wide association studies (GWAS) were conducted.

**Results:** A total of 250K cells were detected, including hepatocytes and various non-parenchymal cells. Differential gene expression analysis and intercellular interaction analysis revealed cell type-specific changes in NAFLD. Gene modules discovered by network analysis were associated with distinct pathophysiology of liver cells. Multiple sc-eQTL signals were detected and replicated. Disease-interacting sc-eQTLs were identified. Numerous loci colocalizing with NAFLD GWAS were characterized.

**Conclusions:** We present transcriptomic profile of NAFLD in a single-cell resolution. sc-eQTL analysis identified NAFLD-associated genes and their regulatory variants in relevant cell types. The role of putative regulatory genes and variants will be subjected to functional validation.

**Keywords:** Precision medicine, Genomics, Single cell, EQTL

## FP-71

### Knockout of LPS Inactivator Ameliorates NASH Progression in Mice Model

So-Jin Sim, Han-Na Lee, Yong-Hyun Han

Laboratory of Pathology and Physiology, College of Pharmacy, Kangwon National University, Chuncheon, Korea

**Aims:** Lipopolysaccharide (LPS), a major component of gram-negative bacterial endotoxins, consisting of lipid A and polysaccharide chains, triggers inflammatory responses within the host. Acyloxyacyl hydrolase (AOAH), a host lipase, has been identified for its role inactivating LPS-induced inflammation by detaching secondary acyl chains. Non-alcoholic steatohepatitis (NASH), a severe condition of non-alcoholic fatty liver disease, is marked by an abnormal accumulation of fat in the liver, ensuing in persistent inflammation and cellular death. We investigated the role of LPS inactivator in NASH.

**Methods:** This study assessed the phenotype of Kupffer cells exhibiting endotoxin tolerance and conducted comparative analyses between wild-type Kupffer cells and those deficient in AOAH *in vitro*. Utilizing both WT and AOAH-knockout mice, we investigated the effects of LPS inactivator using a fat, phosphate, and cholesterol (FPC) diet and a methionine-choline-deficient (MCD) diet and examined ALT, AST, inflammatory & fibrotic indicators in and histology

**Results:** In studies involving mouse models with NASH induced by FPC and MCD, an increase in AOAH mRNA expression was observed in both the liver and other tissues. This rise in AOAH levels has also been noted in humans diagnosed with NASH, indicating a strong association with hepatic inflammation. Moreover, when Kupffer cells (liver macrophages) and bone marrow-derived macrophages were exposed to bacterial elements, there was a significant induction in AOAH expression, highlighting the role of macrophages in increasing AOAH mRNA in livers suffering from NASH after a bacterial challenge. Strikingly, in AOAH-deficient mice subjected to NASH via FPC and MCD diets, a significant reduction in disease progression was observed through histological assessments. Additionally, the Knockout of AOAH led to decreased levels of plasma ALT and AST, along with reductions in mRNA levels of inflammatory cytokines, collagen markers, and inflammatory cells within the liver

**Conclusions:** These findings implicate AOAH as having a detrimental role in NASH advancement and underscore the potential of targeting AOAH mechanisms as a novel therapeutic approach in NASH management.

**Keywords:** AOAH, NASH, LPS, Kupffer cell

## FP-72

### Therapeutic Potential of miR-660-5p and miR-125a-5p Antagonists in Attenuating Liver Fibrosis: Insights from Next-Generation Sequencing and Experimental Validation

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Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea

**Aims:** Liver fibrosis is associated with changes in microRNA (miRNA) expression, identifying these miRNAs could provide insights into potential therapeutic targets. This study aims to evaluate the therapeutic potential of specific miRNAs in modulating the progression of liver fibrosis.

**Methods:** Next-generation sequencing (NGS) was employed to analyze circulating miRNAs correlated with liver fibrosis stages in a human cohort from liver biopsies (n=20). Mice with steatohepatitis were divided into control and treatment groups, each administered specific miRNA modulators. An *in vitro* cell model using co-cultured Huh7 and LX-2 cells, treated with free fatty acids and LPS to simulate steatohepatitis, supplemented the *in vivo* experiments.

**Results:** NGS analysis highlighted significant differences in the expressions of miR-660-5p and miR-125a-5p across different stages of liver fibrosis. *In vivo*, treatment with miR-660-5p and miR-125a-5p antagonists (3 mg/kg, twice weekly for 12 weeks) significantly reduced liver fibrosis, decreasing markers such as collagen 1A, $\alpha$-SMA, fibronectin, and TGF-$\beta$ at the protein level. These findings were supported by liver histologic assessment using Sirius Red and $\alpha$-SMA immunohistochemistry staining. Similar reductions in fibrosis markers at both protein and mRNA levels were observed in the steatohepatitis cell model, demonstrating the consistent efficacy of these treatments across experimental models.

**Conclusions:** This study confirms the potential of miR-660-5p and miR-125a-5p antagonists as effective treatments for liver fibrosis, significantly reducing fibrosis markers in both animal and cell models.

**Keywords:** Liver Fibrosis, NASH, Microrna

Saturday, June 29, 2024, 13:40-15:00

## 13. HBV & HCV

### FP-73

# Analysis of a Machine Learning-Based Predictive Model for Hepatocellular Carcinoma in Chronic Hepatitis B Patients

Ye Jun Kim[1], Jae Geun Jang[1], Soon Sun Kim[2], Hyo Jung Cho[2], Ji Eun Han[2], Jae Youn Cheong[2], Charmgil Hong[1]

[1]School of Computer Science and Electrical Engineering, Handong Global University; [2]Department of Gastroenterology, School of Medicine, Ajou University

**Aims:** Accurate early assessment of hepatocellular carcinoma (HCC) risk in chronic hepatitis B (CHB) patients is vital for effective treatment strategies. Current prediction models for HCC in CHB patients predominantly utilize statistical scoring and forecasting methods. In this study, we hypothesize that the application of machine learning (ML) techniques can improve the prediction accuracy of HCC occurrence. Therefore, we aim to develop an ML model to forecast HCC with greater precision than current methods.

**Methods:** This retrospective study analyzes data from 6,148 patients diagnosed with CHB between 2010 and 2021. Variables including gender, age, albumin, bilirubin, platelet count, HBV-DNA, and the presence of liver cirrhosis are standardized through data preprocessing and labeling (Table 1). After preprocessing, the dataset comprises 2,142 patients records with a 27.1% incidence rate of HCC (Figure 1). We develop our predictive model using XGBoost (Chen, T., & Guestrin, C., 2016). For experimental analysis, we optimize our model using 5-fold cross-validation, and hyperparameter tuning is executed via the Optuna framework. For evaluation, benchmarking against existing models, including CU-HCC, PAGE-B, and mPAGE-B, is conducted for predictive performance comparison.

**Results:** Our presented model outperforms the previous models: It shows significantly higher area under the receiver operating characteristic curve (AUROC) and area under the precision-recall curve (AUPRC) scores of 0.852 and 0.712, respectively, compared to CU-HCC (0.739, 0.507), PAGE-B (0.729, 0.504), and mPAGE-B (0.787, 0.587) with statistical significance. Moreover, our model also achieves significantly greater accuracy and balanced accuracy scores (0.801 and 0.771, respectively) than CU-HCC (0.660, 0.679), PAGE-B (0.701, 0.669), and mPAGE-B (0.743, 0.721) (Table 2).

**Conclusions:** The presented model demonstrated its validity and usefulness in predicting HCC for CHB patients. The results strongly support the enhanced predictive precision of our model, reflecting its potential for clinical application in the early detection of HCC in CHB patients.

**Keywords:** Chronic hepatitis B (CHB), Hepatocellular carcinoma (HCC), Machine learning, Artificial intelligence

Table 1. Criteria for calculating scores for existing models

| Score Model | Score calculation criteria and variables |
|---|---|
| PAGE-B | Gender : Male is 6point<br>Age : 16-29 2point, 2 points every 10 years from 30, over 70 is 10point<br>Platelets($/mm^9$) : 100,000-199,999 6point, under 100,000 is 9point |
| mPAGE-B | Gender : Male is 2point<br>Age : 3 point from the 30, 2 points every 10 years, over 70 is 11point<br>Platelets ($x10^9$/L) : 200-250 is 2point, 150-200 is 3point, 100-150 is 4point, under 100 is 5point. |
| CU-HCC | Age : over 50 is 3point<br>Albumin (g/L) : over 35 is 20point<br>Bilirubin (μmol/L) : over 18 is 1.5point<br>HBV-DNA (logcopies/ml) : 4-6 is 1point, over 6 is 4<br>Cirrhosis: 15 points if present |

Fig 1. Data preprocessing process

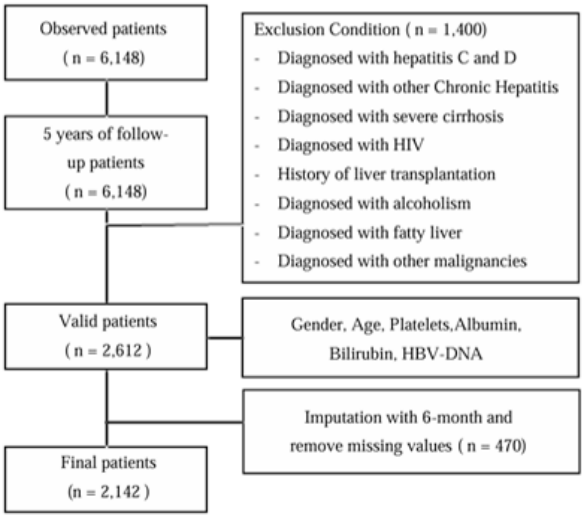


Table 2. Compare results for each model (t-test at $\alpha = 0.05$)

| metrics \ model | CU-HCC | PAGE-B | mPAGE-B | Ours(XGBoost) |
|---|---|---|---|---|
| AUROC | 0.7387 (0.0112) | 0.7287 (0.0273) | 0.7871 (0.0294) | **0.8517** (0.0068) |
| AUPRC | 0.5068 (0.0101) | 0.5040 (0.0435) | 0.5873 (0.0507) | **0.7119** (0.0281) |
| Accuracy | 0.6600 (0.0205) | 0.7007 (0.0725) | 0.7427 (0.0380) | **0.8006** (0.0205) |
| Balanced Accuracy | 0.6791 (0.0094) | 0.6687 (0.0209) | 0.7211 (0.0209) | **0.7706** (0.0124) |
| F1-Score | 0.5364 (0.0230) | 0.5258 (0.0323) | 0.5908 (0.0323) | **0.6661** (0.0192) |

## FP-74

### Association between Viral Replication Activity and Recurrence of HBV-Associated Hepatocellular Carcinoma after Curative Resection

Won-Mook Choi[1], Subin Heo[2], Jiwon Yang[1], Young-In Yoon[3], Jonggi Choi[1], Danbi Lee[1], Ju Hyun Shim[1], Kang Mo Kim[1], Young-Suk Lim[1], Han Chu Lee[1]

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**Aims:** Little is known about the impact of baseline viral replication activity on intrahepatic recurrence in hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) after curative resection.

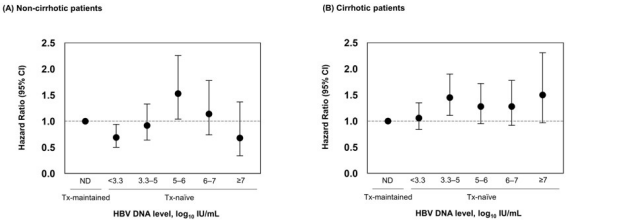
**Methods:** A hospital-based cohort of 1,932 patients with very early or early-stage HBV-associated HCC who consecutively underwent curative resection and received either entecavir or tenofovir between 2010 and 2018 were analyzed. Patients were divided into two groups: those who had previously been on antiviral therapy with viral suppression (Tx-maintained group) and those who initiated antiviral therapy due to detectable HBV DNA (Tx-naïve group) at the time of resection. We compared intrahepatic HCC recurrence between these two groups and based on baseline viral replication activity.

**Results:** During a median follow-up of 4.9 years, 876 (45.3%) patients developed intrahepatic HCC recurrence. In the multivariable analysis, the risk of intrahepatic recurrence was similar between the Tx-maintained and Tx-naïve groups (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.94–1.27; *P*=0.23). However, when stratified by cirrhosis, Tx-naïve group showed a higher risk of intrahepatic recurrence than Tx-maintained group in cirrhotic patients (HR, 1.23; 95% CI, 1.01–1.48; *P*=0.04), but not in non-cirrhotic patients (HR, 0.87; 95% CI, 0.68–1.12; *P*=0.27). Intriguingly, in non-cirrhotic Tx-naïve patients, a parabolic association was observed between baseline HBV DNA levels and the risk of intrahepatic recurrence, with patients having HBV DNA levels between 5–6 $\log_{10}$ IU/mL showing significantly higher intrahepatic recurrence risk compared with the Tx-maintained group (HR, 1.53; 95% CI, 1.04–2.26; *P*=0.03).

**Conclusions:** Association between HBV replication activity and the risk of intrahepatic HCC recurrence varied depending on cirrhosis, providing important insights for optimizing the timing of antiviral treatment and post-operative surveillance strategies.

**Keywords:** Liver cancer, Surgery, Chronic hepatitis B, Antiviral treatment

**Figure. Comparative risk of intrahepatic recurrence between treatment-maintained and treatment-naïve patients with HBV-associated HCC after surgical resection, stratified by baseline HBV DNA levels.** (A) non-cirrhotic patients and (B) cirrhotic patients.
Hazard ratio plot adjusted for age, sex, platelet count, HBeAg-positivity, levels of albumin, bilirubin, AST, AFP, and PIVKA-II, statin use, aspirin use, antiviral type, hypertension, diabetes, BCLC stage, tumor size, and presence of microvascular invasion, capsular invasion, and satellite nodules with the Tx-maintained group as a reference.
AFP, alpha-fetoprotein; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PIVKA-II, prothrombin induced by vitamin K absence-II; Tx, treatment.




## FP-75

### Diagnostic Impact or Circulating Tumor DNA for the Early Stage of HBV Induced HCC with Profiling Fragmentation and DNA Methylation

Tom Ryu[1], Sung Hwan Yoo[2], HyoJu Kim[1], Young Chang[1], Sang Gyune Kim[3], Do Seon Song[4], Young Sun Lee[5], Su Jong Yu[6], Sae Hwan Lee[7], Hyuk Soo Eun[8], Won Kim[9], Jae Young Jang[1], Seongho Ryu[10], So Young Jin[11], Hyun Woong Lee[2], Soung Won Jeong[1]

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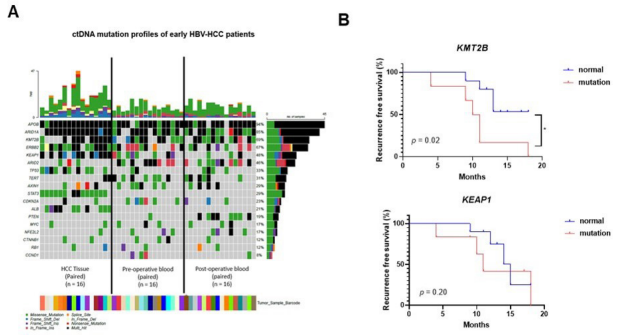
**Aims:** Although there has been a step forward for diagnosis of early stage of hepatocellular carcinoma (HCC) with radiologic findings and tumor markers, it is difficult to detect the early HCC. Here, we suggest that profiling fragmentation and detection of DNA methylation in peripheral blood could be an effective diagnostic tool for finding out the early HCC.

**Methods:** The multicenter prospective study enrolled 36 patients with early hepatitis B virus (HBV) induced HCC (tumor size ≤ 3cm) and 21 paired samples were available for analysis. For variants analysis, we designed a 19 targeted gene, and which were selected based on previous HBV induced HCC studies. Circulating tumor DNA (ctDNA) was extracted from the plasma of patients before and after of HCC resection. Also, genomic DNA (gDNA) was isolated from formalin-fixed paraffin-embedded tumor tissue blocks. Isolated DNA were handled for capture probes utilizing Celemics target enrichment kit.

**Results:** *APOB, ARID1A, ERBB2, KMT2B*, and *KEAP1* were the most frequently mutated genes in pre-operative plasma and cancer tissue of early HBV-HCC derived cancer patients, among the selected genes. Especially, *AXIN1* had been mutated with any types of variation in the ctDNA obtained from pre-operative plasma, while the mutation had disappeared in ctDNA originated from post-operative blood sample. In addition, patients with pre-operative mutation of ctDNA with *KMT2B* had significantly aggravated recurrence free survival of HCC, while presence of the other frequently mutated genes had no alterations for the recurrence and survival rate.

**Conclusions:** For early stage of HBV-HCC, liquid biopsy of ctDNA would be one of the effective method for the easier and the quicker diagnosis and prediction of prognosis. Mutation for ctDNA with *AXIN1* and *KMT2B* would be efficient target for early diagnosis and indicating prognosis, respectively.

**Keywords:** Circulating tumor DNA, Hepatitis B virus, Hepatocellular carcinoma, Liquid biopsy




## FP-76

### The Effect of SRC1 Inhibitors in Hepatitis B-Related Liver Cancer

Agustiningsih Agustiningsih[1], Loraine Kay Cabral[2], Korri Elvanita El Khobar[1], Claudio Tiribelli[3], Caecilia Sukowati[1,3]

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**Aims:** Hepatitis B virus (HBV) infection is the leading cause of chronic hepatitis B, cirrhosis, and hepatocellular carcinoma (HCC). HBV x protein (HBx) interacts with and modulates a variety of signal transduction pathways leading to HCC, including Src family kinases (SFKs). This study aims to investigate the effect Src inhibitor on HBV infection in an *in vitro* model of HBV-related HCC.

**Methods:** Hep3B, a HCC cell line with integrated HBV genome was treated with two SRC1 inhibitors, saracatinib (SAR) and dasatinib (DAS) with concentration raging from 0.02 to 10.00 μM for 24,48, and 72 hours. Lethal concentrations 50 ($LC_{50}$) of all treatments were calculated from cytotoxicity assay using MTT test. mRNA and protein expressions SFKs, including *SRC/ASV1*, *FGR*, *YES*, and *FYN* were assessed by qRT-PCR and Western blot, respectively.

**Results:** Cytotoxicity test showed dose-dependent toxicity of SAR with $LC_{50}$ of 2.0 and 3.1 μM for 48 and 72 hours treatment, respectively. SAR and DAS treatments using concentration of 1.25, 2.5, and 5 μM significantly down-regulated the expressions of SRC1 and FGR ($P<0.05$), while FYN was reduced only by DAS, and YES by SAR. The down-regulation of SRC mRNA was also confirmed by the decrease of protein expression. Interestingly, positive correlations between HBV X gene and SRC1,

**Conclusions:** The inhibition of the SFKs is associated with HBV infection, showing a potential linear correlation between host and pathogen.

**Keywords:** Hepatitis B virus, Hepatocellular carcinoma, SRC inhibitor

## FP-77

### Post-Marketing Surveillance of the Safety and Effectiveness of Glecaprevir/Pibrentasvir in Korean Patients with Chronic Hepatitis C

Jeong Heo[1], Sang Hoon Ahn[2], Jin-Woo Lee[3], Jung Gil Park[4], Jae Youn Cheong[5], Ki Tae Yoon[6], Won Young Tak[7], Yang Hyun Baek[8], Su Jong Yu[9], Youn-Jae Lee[10]

College of Medicine, Pusan National University and Biomedical Research Institute, Pusan National University Hospital,[1] Yonsei University College of Medicine,[2] Inha University School of Medicine,[3] Yeungnam University College of Medicine,[4] Ajou University Hospital,[5] Pusan National University Yangsan Hospital,[6] Kyungpook National University,[7] Dong-A University College of Medicine,[8] Seoul National University College of Medicine,[9] Inje University College of Medicine[10]

**Aims:** Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease. Previous clinical trials demonstrated that glecaprevir/pibrentasvir (G/P) treatment is effective and well-tolerated among patients with chronic hepatitis C (CHC), although there is limited data in real-world clinical settings. This prospective, multi-center post-marketing surveillance study (NCT03740230) evaluated the safety and efficacy of G/P in Korean patients with CHC in real-world settings.

**Methods:** The study included participants aged ≥ 12 years with CHC and received G/P regimen in South Korea (January 2021 to January 2023) for 8, 12 or 16 weeks according to approved local labels.

**Results:** Of the 1,674 participants evaluated for safety, mean (SD) age was 59.54 (±12.17) years, 52.93% were female, 18.58% had liver cirrhosis, and 28.61% had liver impairment.

Adverse events (AEs) occurred in 11.23% of participants, including treatment-related AEs (TRAEs) in 5.91%. Serious AEs occurred in 1.43% of participants, including serious TRAEs in 0.12%. Unexpected TRAEs occurred in 3.05% of participants, including unexpected serious TRAEs in 0.06%. Among 1,304 participants evaluated for efficacy, sustained virological response 12 weeks post-treatment (SVR12) was achieved in 98.77%; 98.36% achieved end-of-treatment response. SVR12 rates were similar regardless of HCV genotype, presence/absence of liver cirrhosis, prior CHC treatment and age group. Treatment breakthrough occurred in 1.07% of participants and post-treatment virologic relapse in 1.00%.

**Conclusions:** G/P was well-tolerated and effective in Korean adults with CHC regardless of HCV genotypes in real-world clinical settings. No new safety signals were observed regardless of age group and presence of hepatic or renal impairment.

**Keywords:** Chronic hepatitis C, Post-marketing surveillance, Glecaprevir, Pibrentasvir

## FP-78

### Epidemiological Insights into Hepatitis C through Blood Samples from the Korea National Health and Nutrition Examination Survey (2016-2020)

Chang Hun Lee[1], Hwa Young Choi[2], Gwang Hyeon Choi[3], Sojung Han[4], Won-Mook Choi[5], Gi-Ae Kim[6], Ji-Hyun Ahn[7], Kyung-Ah Kim[8], Moran Ki[2], Sook-Hyang Jeong[3], In Hee Kim[1]

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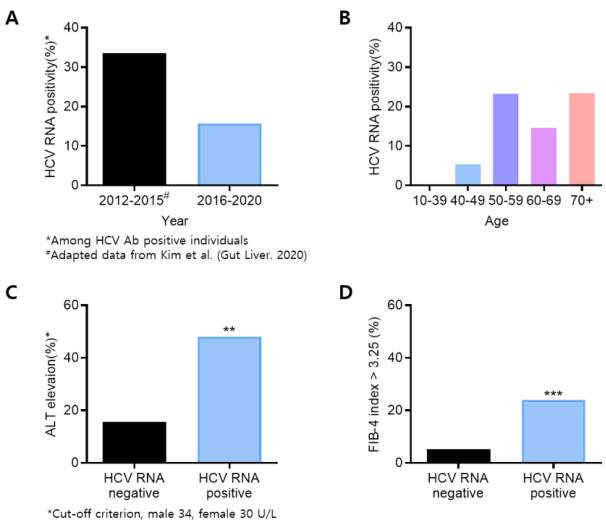
**Aims:** As an indicator for viral hepatitis elimination, the World Health Organization (WHO) defines hepatitis C virus (HCV) infection as the presence of HCV RNA. However, there is limited domestic data available on HCV RNA positivity rates. Our aim was to assess the current status of HCV infection in Korea.

**Methods:** A total of 159 blood samples, which were positive for HCV antibodies from participants of the Korea National Health and Nutrition Examination Survey (KNHANES) and stored at the National Biobank of Korea from 2016 to 2020, were analyzed.

**Results:** The analysis of the blood samples revealed a 15.7% HCV RNA positivity rate. This signifies a notable decline of 52.54% from the 33.5% rate (63/188 individuals) documented in Kim et al.'s research, which analyzed KNHANES data spanning 2012-2015. The positivity rates were similar between genders, with men at 16.5% and women at 15.0%. HCV RNA-positive individuals had an average age of 65.9 years, notably higher than the 56.8 years observed in those testing negative. The age group over 70 showed the highest positivity rate at 23.4%, followed closely by the 50-59 age group at 23.3%, and the 60-69 age group at 14.6%. Among those tested, 56% of individuals with HCV RNA positivity had HCV antibody quantitative values above 10, significantly higher than the 8.2% among those negative for HCV RNA ($P$<0.0001). Clinically, HCV RNA-positive individuals more frequently exhibited elevated AST or ALT levels, indicative of liver damage. Furthermore, 24.0% of those testing positive for HCV RNA showed FIB-4 index above 3.25, indicating a higher likelihood of liver fibrosis, in contrast to only 5.2% in those without detectable HCV RNA.

**Conclusions:** Analysis of KNHANES blood samples collected between 2016 and 2020 indicates a 15.7% HCV RNA positivity rate among individuals with HCV antibodies, reflecting a decline from the rates observed between 2012 and 2015. Additionally, HCV RNA-positive individuals showed elevated levels of AST, ALT, and FIB-4 index.

**Keywords:** Viral hepatitis, Hepatitis C, Elimination, Epidemiology



Saturday, June 29, 2024, 09:10-10:15

## 14. LC, Clinical & Liver Failure

### FP-79

### Inhibition of Sodium-Glucose Cotransporter-2 and Liver-Related Complications in Individuals with Diabetes: A Mendelian Randomization and Population-Based Cohort Study

Sung Won Chung[1,2], Hye-Sung Moon[3], Hyunjae Shin[1], Hyein Han[4], Sehoon Park[5], Heejin Cho[1], Jeayeon Park[1], Moon Haeng Hur[1], Min Kyung Park[1], Sung-Ho Won[3,4,6,7], Yun Bin Lee[1], Eun Ju Cho[1], Su Jong Yu[1], Dong Ki Kim[5], Jung-Hwan Yoon[1], Jeong-Hoon Lee[1,8], Yoon Jun Kim[1]

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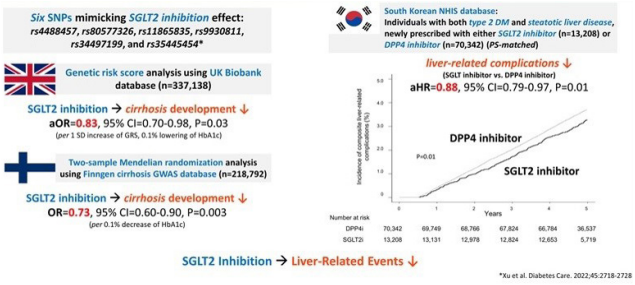
**Aims:** No medication has been found to reduce the liver-related events. We evaluated the effect of sodium-glucose cotransporter-2 inhibitor (SGLT2i) on liver-related outcomes.

**Methods:** Single nucleotide polymorphisms (SNPs) associated with SGLT2 inhibition were identified, and a genetic risk score (GRS) was computed using the UK Biobank (UKB) data (n=337,138). Two-sample Mendelian randomization (MR) was conducted using the FinnGen (n=218,792) database and UKB data. In parallel, a nationwide population-based study using the Korean National Health Insurance Service (NHIS) database was conducted. The development of liver-related complications (i.e., hepatic decompensation, hepatocellular carcinoma, liver transplantation, and death) was compared between individuals with type 2 diabetes mellitus and steatotic liver diseases treated with SGLT2i (n=13,208) and propensity score-matched individuals treated with dipeptidyl peptidase-4 inhibitor (DPP4i) (n=70,342).

**Results:** After computing GRS with six SNPs (rs4488457, rs80577326, rs11865835, rs9930811, rs34497199, and rs35445454), GRS-based MR showed that SGLT2 inhibition (per 1 SD increase of GRS, 0.1% lowering of HbA1c) was negatively associated with cirrhosis development (adjusted odds ratio=0.83, 95% confidence interval [CI]=0.70–0.98, *P*=0.03) and this was consistent in two-sample MR (odds ratio=0.73, 95% CI=0.60–0.90, *P*=0.003). In the Korean NHIS database, the risk of liver-related complications was significantly lower in the SGLT2i group than in the DPP4i group (adjusted hazard ratio [aHR]=0.88, 95% CI=0.79–0.97, *P*=0.01), and this difference remained significant (aHR=0.72–0.89, all *P*<0.05) across various sensitivity analyses.

**Conclusions:** Both Mendelian randomizations using two European cohorts and a Korean nationwide population-based cohort study suggest that SGLT2 inhibition is associated with a lower risk of liver-related events.

**Keywords:** Metabolic dysfunction-associated steatotic liver disease, Hepatocellular carcinoma, Obesity, Polygenic risk score




### FP-80

### Development and External Validation of Global Leadership Initiative on Malnutrition-Dictated Nomograms Predicting Long-Term Mortality in Hospitalized Cirrhosis

Chao Sun, Qing Liu

Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital

**Aims:** Global Leadership Initiative on Malnutrition (GLIM) gradually accounts for the mainstay evaluating nutritional status. Herein, we sought to establish GLIM-dictated nomograms with other prognostic factors influencing long-term mortality and externally validated their predictive performance in decompensated cirrhosis.

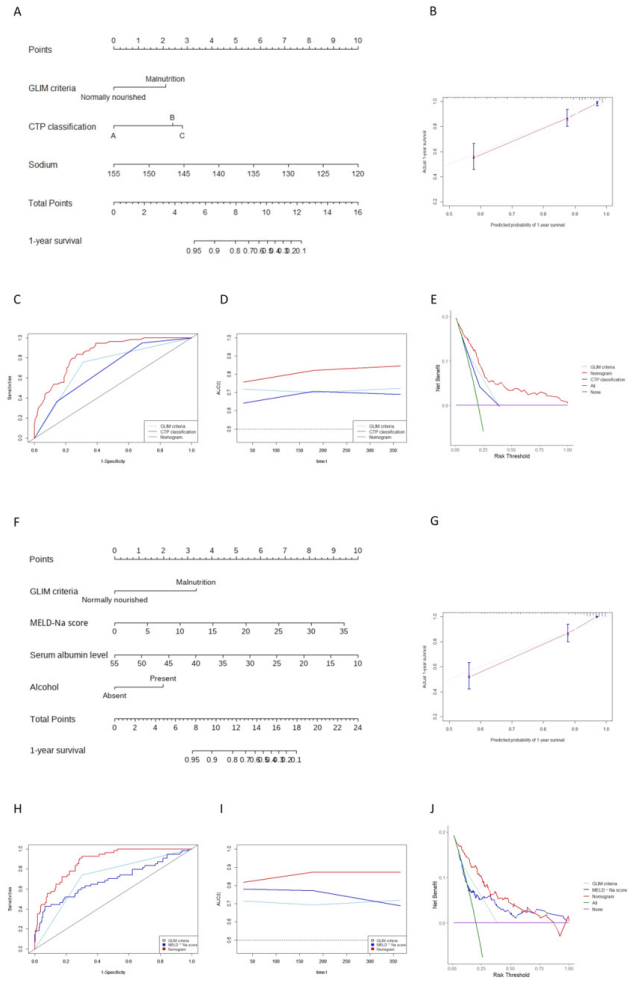
**Methods:** The derivation cohort comprised 301 patients presenting cirrhosis-related acute insults, while the validation cohort encompassed 101 subjects from another tertiary hospital. Two nomograms were constructed to predict the 1-year all-cause mortality by integrating the GLIM criteria. The study population was stratified into low-, moderate- and high-risk mortality groups according to the proposed models.

**Results:** Adjusted for Child-Turcotte-Pugh classification (Nomo#1) or Model for End-stage Liver Disease-Sodium score (Nomo#2) separately, the GLIM criteria were independently associated with 1-year mortality in the multivariate Cox regression analysis (Nomo#1 HR=3.139, *P*<0.001; Nomo#2 HR=3.456, *P*<0.001). The C-index and time AUC for Nomo#1 and Nomo#2 performed significantly better than those of the GLIM criteria

or conventional scoring systems alone. The survival rate of the low-risk group was significantly higher than that of the moderate- or high-risk groups (Nomo#1: 95% *vs* 65.8% *vs* 33.3%, *P*<0.001; Nomo#2: 94.3% *vs* 64.5% *vs* 25%, *P*<0.001). Furthermore, the proposed models exhibited moderate prediction accuracy and could identify malnourished patients with poor survival conditions in the external validation cohort.

**Conclusions:** GLIM criteria-defined malnutrition independently impacted long-term mortality in the context of decompensated cirrhosis. Our established nomograms can predict survival status with sufficient discriminative ability, along with good consistency and clinical benefits, supporting their effectiveness in daily practice.

**Keywords:** GLIM, Liver cirrhosis, Nomogram, Malnutrition, C-index, Mortality




## FP-81

### Impact of Spontaneous Portosystemic Shunts on the Risk of Hepatic Decompensation in Patients with Cirrhosis

**Sung Won Chung**, Kanghee Park, Won-Mook Choi, Danbi Lee, Ju Hyun Shim, Kang Mo Kim, Young-suk Lim, Han Chu Lee, Jonggi Choi

Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

**Aims:** Spontaneous portosystemic shunts (SPSS) are frequently detected through imaging in patients with cirrhosis. While the presence of SPSS is associated with hepatic deterioration, the specific factors of SPSS driving this deterioration are not well-defined. This study aims to identify the clinical characteristics of SPSS that influence hepatic deterioration and clinical outcomes.

**Methods:** This retrospective cohort study included patients with radiologically confirmed SPSS at Asan Medical Center from January 2012 to May 31, 2022. SPSS were categorized based on their location. The total shunt area (TSA) and number of shunts were measured. Primary outcomes were liver-related outcomes, which included gastrointestinal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, development of main portal vein thrombosis, and liver-related death.

**Results:** Out of 450 patients with SPSS, gastrorenal shunt was the most prevalent type (n=215, 47.8%). Throughout a median follow-up period of 79 months, 184 liver-related outcomes occurred. Patients with large TSA significantly increased the risk of liver-related outcomes (per 1 $cm^2$, Hazard Ratio [HR] 1.11; 95% Confidence Interval [CI] 1.01–1.23; *P*=0.039; adjusted HR 1.19; 95% CI 1.05–1.34; *P*=0.008). Among the types of SPSS, esophageal shunts (adjusted HR 2.75; *P*<0.001) and gastrorenal shunts (adjusted HR 1.56; *P*=0.01) significantly elevated the risk of liver-related outcomes.

**Conclusions:** In cirrhotic patients with SPSS, a larger TSA is associated with increased hepatic deterioration, underscoring the need to consider the overall dimensions of SPSS in clinical practice. Esophageal and gastrorenal shunts, in particular, require vigilant monitoring due to their substantial impact on the risk of adverse liver-related outcomes.

**Keywords:** Cirrhosis, Spontaneous portosystemic shunt

## FP-82

### The Effects of Captopril on Portal Vein Thickness and Transforming Growth Factor Beta 1 (TGF-β1) Levels in Patients with Liver Cirrhosis: An Experimental Double-Blind Randomized Controlled Trial

Muhammad Ilham Malda[1,2], Indra Buono[2,3]

[1]KH Hayyung General Hospital; [2]Medical Faculty of Sebelas Maret University; [3]DR Moewardi General Hospital

**Aims:** Cirrhosis is a pathological condition with progressive and lasting deformation of the liver anatomy due to end-stage liver fibrosis. TGF-β1 is a key factor that stimulates fibrogenesis in liver by triggering processes in stellate cells that promote fibrosis. Hyperdynamic circulation and vascular sclerosis were generated by an increase the activity of the renin-angiotensin-aldosterone axis inside the liver, which was regulated by TGF-β1. This study aimed to establish the impact of captopril on the concentrations of TGF-β1 and thickness of the portal vein in patients diagnosed with liver cirrhosis

**Methods:** This study is an experimental double-blind randomized controlled trial. The study followed a total of 27 patients with liver cirrhosis until completed the study. Of these patients, 14 were given captopril and 13 were given placebos. Measurements of TGF-β1 concentrations in serum were conducted using the enzyme-linked immunosorbent assay (ELISA) technique. Pre- and post-test monitoring of SGOT, SGPT, urea, creatinine, Child-Pugh score values, and adverse effects is required. The statistical analysis employed various tests including Mann-Whitney test, t-test, Wilcoxon test, and Pearson correlation. The significance level was set at $P<0.05$

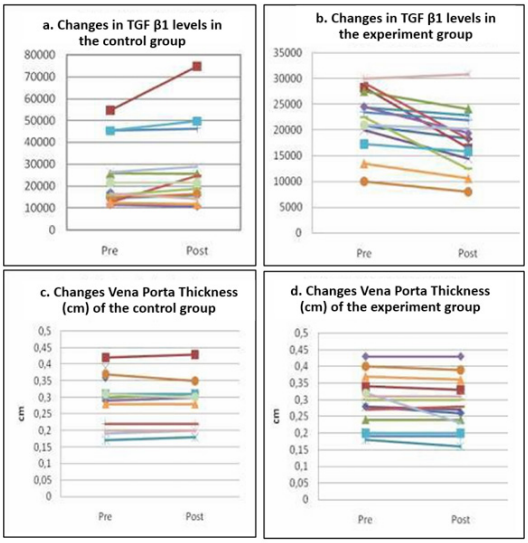



**Figure 1. Changes in TGF-ß1 levels in the placebo-control group (a) and captopril-treated group (b); Changes in portal vein thickness in placebo-control group (c) and captopril-treated group (d)**

**Results:** Captopril significantly decreased the levels of TGF-β1 (-7772±5502.8 pg/ml; $P=0.001$) and reduced the thickness of portal vein (-0,11±0.24 mm; $P=0.022$). Additionally, it improved the velocity of portal venous flow (+8,21±4.25cm/sec; $P=0.001$). However, there was no significant improvement in diameter (0.96±1.39 mm; $P=0.225$). The placebo group did not show any significant improvement levels of TGF-β1 ($P=0.221$), portal vein thickness ($P=0.387$), portal venous flow velocity ($P=0.849$), or diameter ($P=0.164$). Administration of captopril did not yield a substantial improvement the prognosis of liver cirrhosis as measured by the Child-Pugh score. Cough is the predominant adverse reaction

**Conclusions:** Captopril decreased levels of TGF-β1 in patients diagnosed with liver cirrhosis and reduced the thickness of the portal vein

**Keywords:** Captopril, TGF-β1, Child-pugh score, Portal vein thickness

## FP-83

### Development of an Artificial Intelligence-Based Predictive Model and Treatment Decision System Using the Korean Acute-on-Chronic Liver Failure Cohort (KACLiF)

Seong Hee Kang[1], Hyung Joon Yim*[1], Young Kul Jung[1], Seunghak Lee[1], Tae Hyung Kim[2], Do Seon Song[3], Eileen L. Yoon[4], Hee Yeon Kim3, Young Chang[5], Jeong-Ju Yoo[6], Sung Won Lee3, Jung Gil Park[7], Ji Won Park[2], Sung-Eun Kim[2], Soung Won Jeong[5], Ki Tae Suk[8], Moon Young Kim[9], Sang Gyune Kim[6], Won Kim[10], Jae Young Jang[5], Jin Mo Yang[3], Dong Joon Kim[8] on behalf of The Korean Acute-on-Chronic Liver Failure (KACLiF) Study Group

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**Aims:** Acute on Chronic Liver Failure (ACLF) is associated with high mortality due to multisystem organ failure. However, the accurate prediction of mortality is to help guide better the dialysis therapies and wait longer for a liver transplantation. We hypothesized that artificial intelligence models are more precise than standard models for predicting outcomes in ACLF.

**Methods:** A novel deep-learning-based model was developed data collected patients with MELD ≥ 21 prospectively from July 2015 to August 2018 and retrospectively from January 2013 to December 2013 from the Korean Acute-on-Chronic Liver Failure (KACLiF) cohort. The prospective data was split into training and validation sets in a 7:3 ratio and used as a derivation cohort (n=294), while the retrospective data was used as a validation cohort (n=177). We used Decision Tree, Minimum Redundancy Maximum Relevance (MRMR), Elastic

Net and least absolute shrinkage and selection operator were utilized to refine the selection of important features. The selected features were evaluated using Random Forest to assess their ability to predict survival.

**Results:** The 30-day mortality rates of patients in the derivation cohort and the validation cohort were 25.9% and 25.4%, respectively, and the 90-day mortality rates were 33.7% and 36.7%, respectively. For predicting 90-day mortality, the MRMR demonstrated the highest AUC in both derivation (0.745) and validation (0.617) cohorts. Baseline international normalized ratio, previous acute deterioration event, circulatory failure, ascites, hepatic encephalopathy, GI bleeding, body temperature, respiratory rate, cause of liver disease, and albumin were the top features determining the 90-day outcomes. Although it demonstrated low predictive power, this model had the highest AUC among the previously reported models: MELD (0.522), MELD-Na (0.623), MELD 3.0 (0.543), CLIF-ACLF score (0.650), CLIF-C OFs (0.676), and CLIF-SOFA score (0.640).

**Conclusions:** The deep-learning-based model had better performance than the previous models for predicting the mortality in patients with ACLF.

**Keywords:** Acute-on-chronic liver failure, Artificial intelligence, Predictive model

Saturday, June 29, 2024, 13:40-15:00

## 15. Liver Transplantation 2

### FP-84

### Outcomes of 6000 Living Donor Liver Transplantation: A 30-Year Journey in a High-Volume Single Center

**Young-In Yoon,** Sung Gyu Lee, Shin Hwang, Ki-Hun Kim, Chul-Soo Ahn, Deok-Bog Moon, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung, Gil-Chun Park

Division of Hepatobiliary Surgery And Liver Transplantation, Asan Medical Center, Republic of Korea

**Aims:** The objective of this study was to share the outcomes of 6000 LDLTs with center around the world and identified risk factors for in hospital mortalities to optimize outcomes.

**Methods:** We conducted a retrospective review of 6,000 recipients who underwent LDLTs from 6,570 live donors, including 312 children below 18 years old, at Asan Medical Center, Seoul, Korea, from December 1994 to January 2021.

**Results:** Our analysis revealed significant decreases in operative time, intraoperative RBC transfusion, postoperative hospital stay, and in-hospital mortality as the number of cases accumulated. Particularly noteworthy was the decline in hospital mortality from 6.1% in Era I to 3.2% in Era II, and a remarkable 1.2% in Era III ($P$=0.000) for adult-to-adult LDLT using single lobe recipients. Furthermore, multivariate analyses identified several significant and independent risk factors for in-hospital mortality in adult-to-adult LDLT using single lobe recipients, including age above 65 years ($P$=0.019), male gender ($P$=0.0006), MELD score above 30 ($P$=0.0008), re-transplantation ($P$=0.0033), earlier eras of LDLT ($P$=0.000), viral liver disease ($P$=0.0198), pre-LT renal replacement ($P$=0.0471), donor age below 50 years ($P$=0.0047), and GRWR below 0.7 ($P$=0.0211).

**Conclusions:** Our experience demonstrates excellent outcomes based on standardized surgical techniques, protocols for donor/recipient evaluation, and perioperative management. The data derived from Asan Medical Center's extensive experience serves as a valuable resource for the global medical community, contributing significantly to the advancement of the LDLT field.

**Keywords:** Living donor liver transplantation

### FP-85

### Advancing Graft Failure Prediction Post-Liver Transplantation: External Validation of a Model Using Aspartate Aminotransferase, Total Bilirubin, and Coagulation Factors

**Sunghyo An**[1], Jinsoo Rhu[1], Jong Man Kim[1], Gyu-Seong Choi[1], Jae-Won Joh[2]

[1]Department of Surgery, Samsung Medical Center, Republic of Korea, [2]Department of Surgery, Samsung Changwon Hospital, Republic of Korea

**Aims:** Developed from single-institution data, our model predicting early graft failure post-liver transplantation showed high internal validity, warranting external validation for broader applicability.

**Methods:** Our study externally validated a Cox regression model for early graft failure post-liver transplantation, using post-transplant aspartate aminotransferase, total bilirubin, and international normalized ratio. We analyzed data from SMC (Living: 342, Deceased: 114; 2019-2021), SNUH (Living: 716, Deceased: 157; 2015-2021), and Severance Hospital (Living: 967, Deceased: 428; 2005-2021). The model's efficacy was compared with MEAF and EAD benchmarks through C-index and time-dependent AUC.

**Results:** The C-index of the model for SMC living donor (0.96,CI=0.91–1.00) was significantly higher compared to those of both MEAF (0.9, $P$=0.003) and EAD (0.84, $P$=0.04) while C-index for SMC deceased donor (0.96, CI=0.94–0.99) was only significantly higher compared to C-index of EAD. (0.7, CI=0.58-0.81, $P$<0.001) The C-index of the model for SNUH living donor (0.81,CI=0.7–0.93) was significantly higher compared to C-index of EAD (0.65, $P$=0.006) while C-index for SNUH deceased donor (0.89, CI=0.77–1) was significantly higher compared to C-index

of EAD. (0.7, *P*=0.009) The C-index of the model for Severance hospital living donor (0.89,CI=0.8–0.96) was significantly higher compared to those of both MEAF (0.84,*P*=0.03) and EAD (0.77,*P*=0.03) while C-index for Severance hospital deceased donor (0.88, CI=0.82–0.95) was significantly higher compared to those of both MEAF (0.75,*P*=0.007) and EAD (0.67,*P*<0.001)

**Conclusions:** The external validation of our Cox regression model demonstrated its superiority over MEAF and EAD benchmarks in predicting early graft failure post-liver transplantation, indicating its potential for widespread clinical application.

**Keywords:** Early GRAFT failure, Prediction, External validation

## FP-86

### Beyond Transplant Criteria: The Prognostic Impact of Macrotrabecular-Massive Hepatocellular Carcinoma in Liver Transplantation

Eun-Ki Min[1,2], Byungsoo Ahn[3], Deok-Gie Kim[1,2], Mun Chae Choi[1,2], Seung Hyuk Yim[1,2], Hwa-Hee Koh[1,2], Minyu Kang[1,2], Dong Jin Joo[1,2], Myoung Soo Kim[1,2], Jae Hyon Park[4], Young Nyun Park[3], Jae Geun Lee[1,2]

[1]Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]The Research Institute for Transplantation, Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Department of Pathology, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Department of Radiology, Armed Forces Daejeon Hospital, Daejeon, Republic of Korea

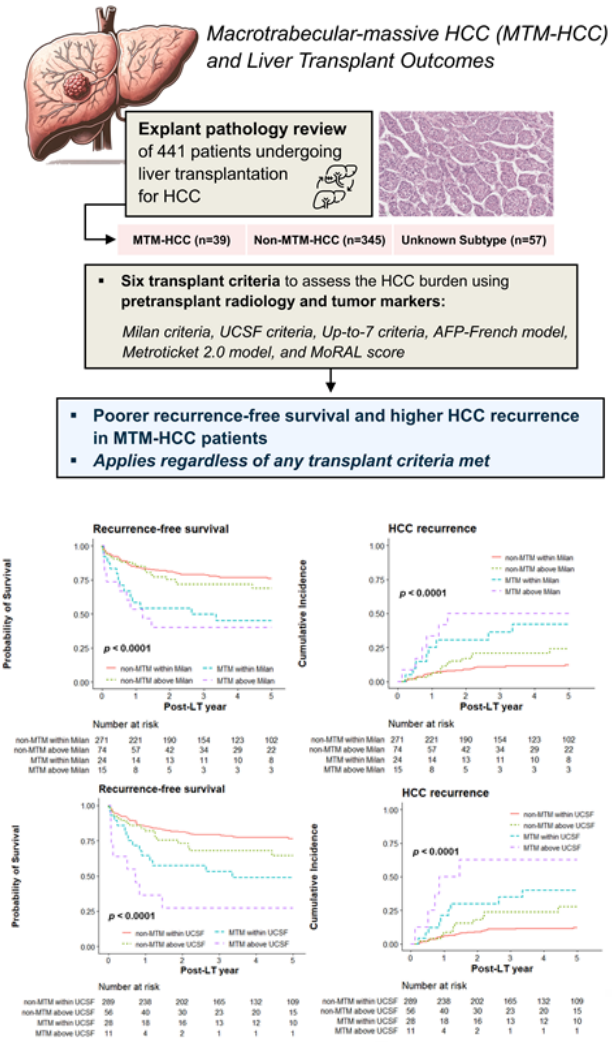
**Aims:** Macrotrabecular-massive hepatocellular carcinoma (MTM-HCC) represents a uniquely aggressive histologic subtype; however, its clinical significance regarding liver transplantation (LT) outcomes remains unknown. This study aimed to assess the impact of the MTM-HCC subtype in the prognostication of oncologic outcomes after LT.

**Methods:** In this single-center retrospective study, we reviewed explant pathology of 441 patients undergoing LT for HCC. Clinical and biological characteristics, as well as adherence to six renowned LT selection criteria were reviewed. Overall survival (OS), recurrence-free survival (RFS), and cumulative recurrence rate were compared and analyzed concerning the MTM-HCC subtype and transplant criteria.

**Results:** MTM-HCC was identified in 39 cases, constituting 8.8% of the total cohort and 10.2% of histopathologically confirmed cases. MTM-HCC was significantly associated with higher levels of alpha-fetoprotein and prothrombin induced by vitamin K absence or antagonist-II, microvascular invasion, poor differentiation, the presence of satellite nodules, and keratin 19 positivity (all *P*<0.001). Patients with MTM-HCC exhibited poorer RFS and higher 5-year cumulative HCC recurrence rate than non-MTM-HCC patients, irrespective of whether they met the Milan criteria or UCSF criteria (all *P*<0.001). This pattern in RFS and HCC recurrence remained statistically significant across the four other established transplant criteria. Multivariate regression analysis confirmed the negative impact of MTM-HCC on OS and RFS, with hazard ratios of 1.88 (95% confidence interval [CI]: 1.01-3.48, *P*=0.046) and 2.06 (95% CI: 1.22-3.47, *P*=0.006), respectively.

**Conclusions:** Our study reveals that the MTM-HCC subtype significantly impacts patient survival and tumor recurrence post-LT, further stratifying established selection criteria. Histopathological information should be incorporated into the LT decision-making through pretransplant diagnosis, enabling a more tailored therapeutic approach for the MTM subtype.

**Keywords:** Hepatocellular carcinoma, Macrotrabecular-massive subtype, Liver transplantation, Transplant criteria



## FP-87

### Survival Benefits in Living-Donor Liver Transplantation: A Nested Case-control Analysis Based on the MELD Score Trajectories from the Waitlist

Seung Hyuk Yim, Deok-Gie Kim, Minyu Kang, Hwa-Hee Koh, Mun Chae Choi, Eun-Ki Min, Jae Geun Lee, Dong Jin Joo, Myoung Soo Kim

Department of Surgery, Severance Hospital, Republic of Korea

**Aims:** The suitability of LDLT for patients with different MELD scores has been a subject of considerable debate. While earlier studies indicated benefits of LDLT predominantly for patients with MELD scores under 15, recent findings suggest LDLT has survival benefits in MELD-Na scores of 11 or greater. Therefore, we aimed to assess the survival advantage of LDLT over waiting for DDLT in a comprehensive range of MELD scores.

**Methods:** This study encompassed patients on the LT waitlist at a single center from June 2005 to December 2021. Patients under 18 and those with malignancies, including HCC, were excluded. A nested case-control analysis with a 1:4 match was implemented, comparing LDLT recipients with MELD trajectory controls (n=25,735). Overall survival rates were compared between the LDLT and the Wait-more groups.

**Results:** From 1954 cases, 344 were in the LDLT and 1610 were in the Wait-more group. Both groups had similar characteristics, except for admission duration within 3 months (6.0 days in LDLT vs. 4.0 in Wait-more, $P$=0.023). In Kaplan-Meier survival analysis, the LDLT group demonstrated higher survival rates (1-year, 89.3% vs. 65.1%; 5-year, 82.2% vs. 46.7%; $P$<0.001). Sub-group analysis of MELD score category showed the LDLT group consistently demonstrating improved survival over the Wait-more group, notable even in the MELD 6-10 (1-year, 95.8% vs. 86.8%; 5-year, 87.4% vs. 60.4%, $P$=0.017) and extending to MELD scores of 36 or higher (1-year, 74.8% vs. 21.9%; 5-year, 65.7% vs. 20.0%; $P$<0.001).

**Conclusions:** LDLT offers a survival benefit across a broad spectrum of MELD scores, highlighting its potential wider applicability.

**Keywords:** Liver transpantation, Live donor, Waiting list

## FP-88

### Impact of Liver Graft Complexity on Long-Term Survival Outcomes in Living Donor Liver Transplantation

Incheon Kang[1], Jae Geun Lee[2], Dai Hoon Han[2], Gi Hong Choi[2], Myoung Soo Kim[2], Jin Sub Choi[2], Dong Jin Joo[2], Deok-Gie Kim[2]

[1]Department of Surgery, Bundang CHA, Republic of Korea; [2]Department of Surgery, Severance Hospital, Republic of Korea

**Aims:** Living donor liver transplantation (LDLT) is a critical solution for organ shortages, but its success is challenged by the variable anatomy of liver grafts. The impact of graft anatomy on post-transplant outcomes remains unclear, highlighting the need for further study.

**Methods:** A retrospective review of LDLT performed at Severance Hospital from July 2005 to December 2022 was conducted, analyzing a cohort of 908 adult patients. The cohort was divided into complex-graft (n=418) and control groups (n=490), based on the presence of multiple anatomical structures in the graft. Kaplan-Meier and Cox proportional hazards regression models assessed the association between graft complexity and long-term survival.

**Results:** Before and after propensity score matching (PSM), graft survival rates between recipients of complex and standard grafts did not significantly differ ($P$=0.162 pre-PSM; $P$=0.274 post-PSM). Complex graft recipients, however, experienced a statistically significant increase in vascular complications (12.8% vs. 7.7%, $P$=0.013) and a higher likelihood of bile duct complications, with a risk ratio of 1.26 ($P$=0.042). In subgroup analysis, grafts with multiple hepatic arteries were associated with a non-significant reduction in survival ($P$=0.059), whereas grafts with two or more hepatic veins significantly improved survival outcomes ($P$=0.016).

**Conclusions:** The anatomical complexity of liver grafts does not significantly alter overall survival outcomes in LDLT. However, it is associated with an increased risk of specific postoperative complications. These findings underscore the importance of considering graft complexity in preoperative planning and risk assessment to optimize LDLT outcomes.

**Keywords:** Liver transplantation, Complex grafts, Graft survival

## FP-89

### Living Donor Liver Transplant (LDLT): Analysis in Asia's case of Liver Transplant

Muhammad Fajrul Aslim[1], Vivi Usmayanti[2], Helena Kartika Utami[3]

[1]Center for Data and Information Technology (PUSDATIN) Ministry of Education, Culture, Research, and Technology, [2]Department of Health Economics, Universitas Sriwijaya, [3]Medical Doctor, Bhayangkara Hospital, Jambi, Indonesia

**Aims:** The recipient of Acute liver failure transplantation has a fragile with a high risk of morbidity and mortality. Living Donor Liver Transplant (LDLT) and Deceased Donor Liver Transplant (DDLT) are the options for timely liver transplantation. However, with limited access from deceased donors, LDLT can be considered as a solid option to increase life expectancy. This study aims to explore one of the methods of liver transplants in Asia and the driving factors.

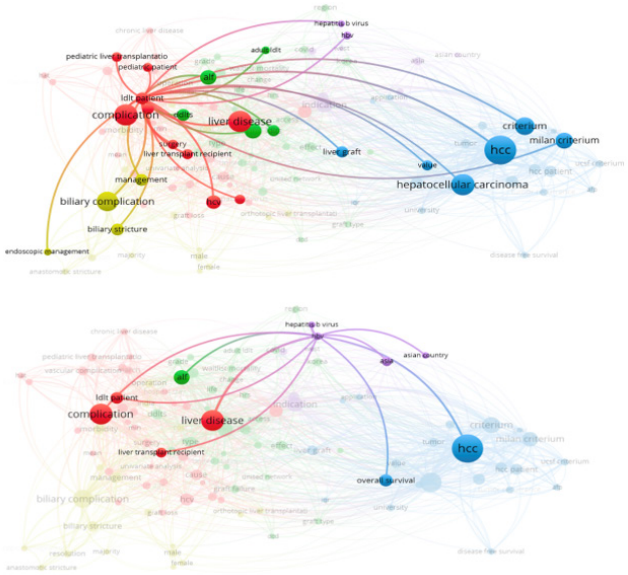
**Methods:** The method used is a descriptive analysis, which

serves to describe or give an overview of the object under study by identifying 21 published papers from 2010-2024. Longitudinal and cross-sectional studies were used to breakdown the analysis.

**Results:** In Asia, LDLT is popular and has spread established procedures representing the standard of care liver transplant, in case of not available grafts from deceased donors, technique. Further, there are socioeconomic factors that determine the method for liver transplantation. One of the factors is religiosity which has a pivotal role as a basic principle and also contributes to the reason for choosing LDLT rather than DDLT. In Malaysia, NAFLD and obesity represent major challenges to an emerging *LDLT* program. Then, in Hong Kong, A 5-year overall and disease-free survival rate of 78.9% and 76.3% were achieved regards the critical organ shortage and high demand for transplantation. Meanwhile, in Japan, *LDLT* has been implemented resulting in limited options for donor availability with biliary atresia. Extensively, in Korea, the technology for LT performs purely laparoscopic and robotic living donor hepatectomies. *LDLT* was an independent protective factor, reducing the risk of overall death by 49% in the pre-IPTW analysis.

**Conclusions:** Living-donor liver transplant (LDLT) offers the advantages of improved intention-to-treat outcomes and management of the shortage of deceased-donor allografts in Asia which is in line with the socioeconomics factors, such as Religiosity in Asia.

**Keywords:** LDLT, DDLT, ASIA, Liver transplantation



# The Liver Week 2024

www.theliverweek.org
June 27-29, 2024 | Walkerhill, Seoul, Korea

THE LIVER WEEK 2024

DAY 2: June 28 (Fri)

# Oral Poster Presentation 1

| | |
|---|---|
| **OP-1~OP-6** | HBV I |
| **OP-7~OP-12** | MASLD, Basic |
| **OP-13~OP-17** | MASLD, Clinical 1 |
| **OP-18~OP-23** | LC Clinical & Liver Failure 1 |
| **OP-24~OP-29** | Liver Transplantation 1 |
| **OP-30~OP-34** | HCC, Basic 1 |
| **OP-35~OP-39** | HCC, Clinical 1 |
| **OP-40~OP-45** | HCC, Clinical 2 |
| **OP-46~OP-50** | Surgery, Technical Issues |
| **OP-51~OP-56** | Autoimmune Disease |
| **OP-57~OP-61** | Others |

Friday, June 28, 2024, 16:30-17:30

# 1. HBV 1

## OP-1

### Effect of Diabetes on the Risk of Fibrosis Progression in Patients with Chronic Hepatitis B

MI Na Kim[1,2], Jae Seung Lee[1,2], Hye Won Lee[1,2], Beom Kyung Kim[1,2], Seung Up Kim[1,2], Jun Yong Park[1,2], Do Young Kim[1,2], Sang Hoon Ahn[1,2]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [2]Yonsei Liver Center, Severance Hospital, Seoul, Republic of Korea

**Aims:** Diabetes is associated with a higher risk of hepatocellular carcinoma in patients with chronic hepatitis B (CHB). However, there are limited data regarding fibrosis progression in CHB patients with diabetes compared with those without diabetes. We investigated the effect of diabetes on the risk of fibrosis progression in patients with CHB.

**Methods:** We recruited 3,450 patients with CHB who performed transient elastography from 2012 through 2020. The primary cross-sectional outcome was the prevalence of advanced fibrosis. The primary longitudinal outcome was fibrosis progression. Advanced fibrosis was defined, according to guidelines, as a liver stiffness measurement greater than 9.0 kilopascals. Fibrosis progression was defined as incident advanced fibrosis at 3-year of follow-up.

**Results:** The prevalence of advanced fibrosis in our cohort was 27.4% at baseline. A higher proportion of patients with diabetes had advanced fibrosis than those without diabetes (37.3 % vs 24.8 %; p < 0.001). In multivariate analysis, diabetes was significantly associated with advanced fibrosis (odds ratio [OR], 1.49; 95% confidence interval [CI], 1.24–1.78). The longitudinal analysis was done in 2,504 patients with fibrosis stage of F0–2 at baseline. Diabetes was significantly associated with a higher risk of fibrosis progression after multivariate-adjustment (OR, 1.98; 95% CI, 1.48–2.65). The independent association of diabetes and the risk of fibrosis progression remained in each cohort of patients without antiviral therapy (OR, 1.83; 95% CI, 1.22–2.75), and those with antiviral therapy (OR, 2.15; 95% CI, 1.42–3.27).

**Conclusions:** In a large, well-characterized cohort study of patients with CHB, diabetes was associated with advanced fibrosis, and a higher risk for progression to advanced fibrosis.

**Keywords:** Chronic hepatitis B, Diabetes, Fibrosis progression

## OP-2

### Lack of Association between Early On-Treatment HBeAg-Seroclearance and Development of Hepatocellular Carcinoma or Decompensated Liver Cirrhosis

Gyung Sun Lim[1], Hyunjae Shin[1], Won-Mook Choi[2], Seung Up Kim[3], Yunmi Ko[1], Youngsu Park[1], Jeayeon Park[1], Moon Haeng Hur[1], Min Kyung Park[1], Yun Bin Lee[1], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Jeong-Hoon Lee[1], Fabien Zoulim[4]

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**Aims:** The association between hepatitis B virus envelope antigen (HBeAg)-seroclearance during long-term nucleos(t)ide analogue (NA) treatment and the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB) remains unclear. Here, we aimed to investigate the association of HBeAg-seroclearance during potent NA treatment with the development of HCC and decompensated liver cirrhosis.

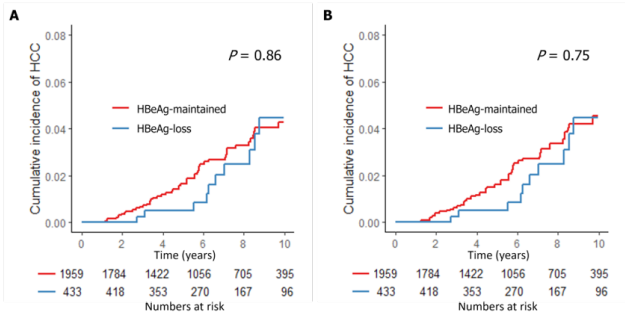
**Methods:** Using a multicenter historical cohort including 2,392 non-cirrhotic adult patients with HBeAg-positive CHB who initiated NA treatment with tenofovir or entecavir, the risk of HCC and decompensated liver cirrhosis was compared between patients who achieved HBeAg-seroclearance within 36 months of NA treatment (the HBeAg-loss group) and those who did not (the HBeAg-maintained group), using inverse probability of treatment weighting.

**Results:** Over a median of 6.6 years of NA treatment, 1,077 patients achieved HBeAg-seroclearance (HBeAg-loss rate=6.0 per 100 person-years), 64 patients developed HCC (HCC incidence rate=0.39 per 100 person-years), and 46 patients developed decompensated liver cirrhosis (decompensation incidence rate=0.28 per 100 person-years). The HBeAg-loss and HBeAg-maintained groups had a similar risk of developing HCC (hazard ratio [HR]=0.89, 95% confidence interval [CI]=0.47–1.68; *P*=0.72), and developing decompensated liver cirrhosis (HR=0.98, 95% CI=0.48–1.81; *P*=0.91). Compared with delayed HBeAg-seroclearance beyond 10 years of NA treatment, the risk of HCC was comparable in those who achieved earlier HBeAg-seroclearance at any time point within 10 years, regardless of baseline age and fibrotic burden.

**Conclusions:** Early HBeAg-seroclearance during NA treatment was not associated with a reduced risk of development of HCC or decompensated liver cirrhosis in non-cirrhotic HBeAg-positive CHB patients.

**Keywords:** Nucleos(t)ide analogue, Entecavir, Tenofovir, Liver

cancer;,Time-varying effects




## OP-3

### Stratification of HBeAg-Negative Chronic Hepatitis B Patients through Longitudinal Monitoring of HBV DNA Levels

Hae Lim Lee[1,2], Soon Kyu Lee[1,2], Ji Won Han[1,2], Hyun Yang[1,2], Heechul Nam[1,2], Pil Soo Sung[1,2], Hee Yeon Kim[1,2], Sung Won Lee[1,2], Do Seon Song[1,2], Jung Hyun Kwon[1,2], Chang Wook Kim[1,2], Si Hyun Bae[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Jeong Won Jang[1,2]

[1]Division of Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [2]The Catholic University Liver Research Center, Seoul, Republic of Korea

**Aims:** The international guideline states that the disease phase of chronic hepatitis B(CHB) cannot be determined by a single assessment due to the continuous interaction between viral activity and the host immune response. In this study, we longitudinally monitored HBV DNA levels over a 2-year period in HBeAg-negative patients not initially indicated for antiviral treatment(AVT), with the aim of allocating them to a more precise disease phase and differentiating prognoses.

**Methods:** A total of 2,032 patients diagnosed with CHB between 2008 and 2019 were enrolled from the medical centers of The Catholic University of Korea. Clinical prognoses were compared among patient groups categorized based on their HBV DNA level patterns during the 2-year period.

**Results:** During the 2-year period, HBV DNA level was persistently low in 53.0% of the patients (<2,000 IU/mL, low-level viremia(LLV) group), elevated in 15.2% (≥ 2,000 IU/mL during > 75% of tests, high-level viremia(HLV) group), and fluctuated in 31.8% (remaining patients, intermittently high-level viremia(IHV) group). Alanine aminotransferase level remained <40 IU/L in 65.3%, 51.7%, and 32.4% of the patients in the LLV, IHV, and HLV groups, respectively. AVT was initiated in 5.2% of the LLV group, 24.1% of the IHV group, and 55.7% of the HLV group, indicating a transition to a chronic hepatitis phase during the follow-up period. The estimated annual incidence rate of HBsAg seroclearance, stratified by HBV DNA group, revealed rates of 3.2%, 1.8%, and 0.6% in the LLV, IHV, and HLV groups, respectively ($P$<0.001). When censoring patients at the initiation of AVT, the estimated annual incidence rate of hepatocellular carcinoma development, also stratified by HBV DNA group, showed rates of 0.39%, 0.37%, and 0.79% in the LLV, IHV, and HLV groups, respectively ($P$=0.03).

**Conclusions:** Precise stratification of HBeAg-negative CHB patients holds significant promise in guiding clinicians to establish personalized treatment approaches using current potent AVT, as well as forthcoming novel therapeutic strategies.

**Keywords:** Chronic hepatitis B, Hbv dna, Phase, Prognosis

## OP-4

### Comparison of Denosumab and Bisphosphonates for Tenofovir-Induced Osteoporosis in Patients with Chronic Hepatitis B

Yunmi Ko[1], Byeong Geun Song[2], Youngsu Park[1], Jaeyeon Park[1], Hyunjae Shin[1], Min Kyung Park[1], Yun Bin Lee[1], Su Jong Yu[1], Dong Hyun Sinn[2], Yoon Jun Kim[1], Jung-Hwan Yoon[1], Seung-Shin Park[3], Moon Haeng Hur[1], Jeong-Hoon Lee[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [2]Department of Internal Medicine and Liver Research Institute, Samsung Medical Center, Seoul, Korea; [3]Department of Internal Medicine and Endocrinology and metabolism, Seoul National University College of Medicine, Seoul, Korea

**Aims:** Tenofovir disoproxil fumarate (TDF), a first-line antiviral drug for chronic hepatitis B (CHB), is a risk factor for osteoporosis. This study aimed to compare the effectiveness of denosumab and bisphosphonates for TDF-induced osteoporosis in CHB patients.

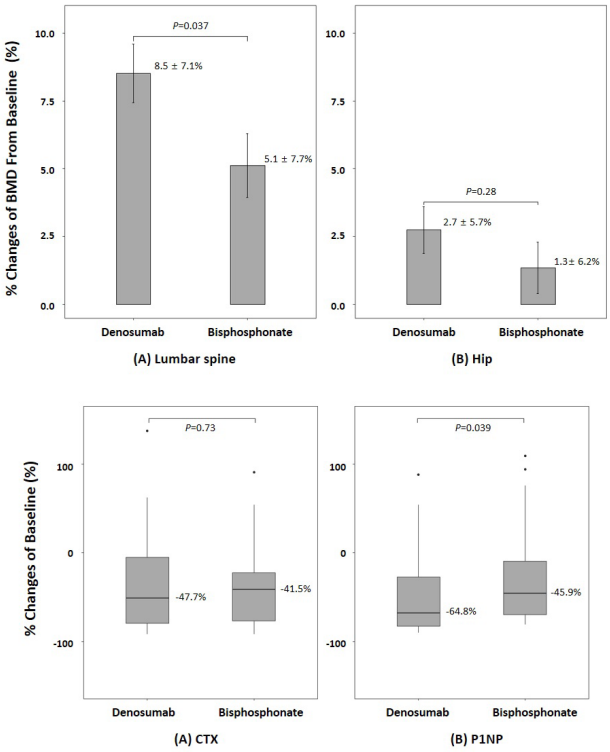
**Methods:** CHB patients who were treated with either denosumab or bisphosphonates for newly diagnosed osteoporosis during > 1 year of TDF treatment between 2010 and 2022 were included from two tertiary centers in Korea. The primary outcome was bone mineral density (BMD) change at year 1. Secondary outcomes included changes in two bone turnover markers, procollagen type 1 N-terminal propeptide (P1NP) and C-telopeptide of type 1 collagen (CTX).

**Results:** A total of 125 patients were included: 50 received denosumab and 75 received bisphosphonates. The median time to the diagnosis of osteoporosis from the TDF initiation was 4.6 (interquartile range=2.9–6.5) years. After balancing baseline characteristics using propensity score matching, the denosumab group showed a significantly greater increase in the lumbar spine BMD (denosumab vs. bisphosphonate: 8.5% vs. 5.1%, $P$=0.037), but comparable change in the hip (2.7% vs. 1.3%, $P$=0.28) at year 1. The denosumab group showed a significantly greater reduction in P1NP levels at year 1 (-64.8%

vs. -45.9%, *P*=0.039), with no significant difference in CTX changes (-47.7% vs. -41.5%, *P*=0.73) compared to the bisphosphonates group.

**Conclusions:** In CHB patients with TDF-induced osteoporosis, denosumab outperformed bisphosphonates in the lumbar spine BMD recovery but was comparable in the hip at year 1. The reduction in P1NP level was also more prominent in the denosumab group.

**Keywords:** Chronic hepatitis B, Tenofovir disoproxil fumarate, Osteoporosis, Antiresorptive agents




## OP-5

### Cost-Effectiveness of Antiviral Therapy in Patients with Chronic Hepatitis B in the High Viremic Gray Zone

**Won-Mook Choi**[1], Suk-Chan Jang[2], Gi-Ae Kim[3], Gwang Hyeon Choi[4], Yun Bin Lee[5], Dong Hyun Sinn[6], Hye-Lin Kim[7], Young-Suk Lim[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]School of Pharmacy, Sungkyunkwan University, Suwon, Gyeonggi-do, Republic of Korea; [3]Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Republic of Korea; [4]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam-si, Gyeonggi-do, Republic of Korea; [5]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [6]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [7]College of Pharmacy, Sahmyook University, Seoul, Republic of Korea

**Aims:** Growing evidence suggests that individuals in the high viremic gray zone with low ALT levels face a higher risk of hepatocellular carcinoma (HCC) with a non-linear, parabolic pattern between HBV DNA levels and HCC risk. This study aimed to evaluate the cost-effectiveness of initiating antiviral therapy in the high viremic gray zone.

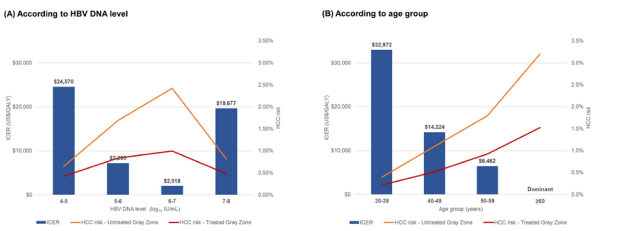
**Methods:** A cost-utility analysis was conducted using a Markov model to compare the cost-effective ratio (ICER) using QALY of initiating antiviral therapy at the gray zone phase ('treat-GZ') versus delaying treatment until the immune-active phase ('untreat-GZ'). A hypothetical cohort of 10,000 patients with chronic hepatitis B (CHB) in the gray zone phase (60% male, HBV DNA levels 4–8 log10 IU/mL, ALT levels <40 IU/L, 50% HBeAg-positivity) was simulated over a 10-year horizon. Input parameters were obtained from a multicenter historical cohort, Korea.

**Results:** From a healthcare system perspective, the ICER of the treat-GZ strategy was US$ 12,050/QALY, indicating cost-effectiveness under the willingness-to-pay threshold of US$ 25,000/QALY. From a societal perspective, the ICER of the treat-GZ strategy was less than 0, indicating lower costs compared with the untreat-GZ strategy, thus representing a dominant strategy. Stratified analyses by HBV DNA levels showed a U-shaped pattern between baseline HBV DNA levels and the ICERs, with the highest cost-effectiveness observed for levels of 6–7 $\log_{10}$ IU/mL, exhibiting an ICER of US$ 2,018/QALY, followed by 5–6 (US$ 7,233/QALY), 7–8 (US$ 19,677/QALY), and 4–5 (US$ 24,570/QALY) $\log_{10}$ IU/mL, in accordance with the order of HCC risk.

**Conclusions:** Initiating antiviral therapy in the high viremic gray zone was identified to be cost-effective compared with delaying treatment to the immune-active phase, thus supporting the commencement of antiviral therapy during the high viremic gray zone phase.

**Keywords:** HBV DNA, Liver cancer, Indeterminate phase, Nucleos(t)ide analogues

**Figure. Incremental cost-effectiveness ratio and hepatocellular carcinoma risk stratified by HBV DNA levels from the healthcare system perspective. (A) According to HBV DNA level and (B) according to age group.**



## OP-6

### Comparable Outcomes between Besifovir and Other Antiviral Therapies in Hepatocellular Carcinoma Development among Patients with Chronic Hepatitis B

Jae Seung Lee[1,2,3], Sung Won Lee[4], Sang Gyune Kim[5], Yeon Seok Seo[6], Su Jong Yu[7], Hyung Joon Yim[8], Hye Won Lee[1,2,3], Mi Na Kim[1,2,3], Beom Kyung Kim[1,2,3], Jun Yong Park[1,2,3], Do Young Kim[1,2,3], Sang Hoon Ahn[1,2,3], Seung Up Kim[1,2,3]

[1]Department of Internal Medicine, Yonsei University College of Medicine, Seoul 03722, South Korea; [2]Division of Gastroenterology, Yonsei University College of Medicine, Seoul 03722, South Korea; [3]Yonsei Liver Center, Severance Hospital, Seoul 03722, South Korea; [4]Department of Internal Medicine, Bucheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon 14647, South Korea; [5]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University School of Medicine, Bucheon 14584, South Korea; [6]Department of Internal Medicine, Korea University Medical Center, Seoul 02841, Republic of Korea; [7]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [8]Department of Internal Medicine, Division of Gastroenterology and Hepatology, Korea University Ansan Hospital, Korea University Ansan Hospital, Ansan 15355, South Korea

**Aims:** Besifovir dipivoxil maleate (BSV), an acyclic nucleotide phosphonate, has potent antiviral efficacy against chronic hepatitis B (CHB), similar to other antiviral agents, such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). This study compares outcomes between BSV and the other antiviral agents in hepatocellular carcinoma (HCC) development among patients with CHB.

**Methods:** We conducted a retrospective cohort of 2,684 treatment-naïve patients with CHB who started their first-line antiviral therapy (AVT) between May 2017 and April 2022 with ETV (n=840), TAF (n=706), TDF (n=666), or BSV (n=472) at six tertiary medical institutions in South Korea. The incidence and hazard ratio (HR) were calculated using Kaplan-Meier and Cox regression analyses, respectively. Selection bias was minimized using inverse probability of treatment weighting (IPTW) and propensity score matching (PSM).

**Results:** Compared to the patients with other antiviral agents, BSV users showed a higher proportion of male patients (61.2% vs. 50.1–56.2%), alcohol intake > 20g/day (12.1% vs. 5.5–11.2%), and cirrhosis (37.9% vs. 30.5–34.3%). The incidence of HCC in BSV users (n=6, 4.4 per 1000 person-years [PYs]) was similar to that in TAF users (8.5 per 1000 PYs, log-rank *P*=0.111, HR 2.098, 95% confidence interval [CI] 0.827–5.324), however, significantly lower than those in ETV (n=38, 12.7 per 1000 PYs, log-rank *P*=0.026, HR 2.603, 95% CI 1.087–6.233) and TDF users (12.7 per 1000PYs, log-rank *P*=0.035, HR 2.539, 95% CI 1.034–6.234). After applying 1:1:1:1 IPTW, the incidence of HCC in BSV users (n=7 of 591, 3.8 per 1000 PYs) was similar to that in TAF users (n=17 of 713, 8.6 per 1000 PYs, adjusted HR [aHR] 2.324, 95% CI 0.894–6.043), however, significantly lower than in ETV (n=32 of 706, 12.4 per 1000 PYs, aHR 2.795 (95% CI 1.138–6.866, E-value 5.035) and TDF users (n=34 of 674, 14.6 per 1000 PYs, aHR 3.322 (95% CI 1.334–8.274, E- value 6.099). Following separated 1:1 PSM (all 472 pairs), the incidence of HCC in BSV users (n=6, 4.4 per 1000 PYs) was similar to that in TAF users (n=12, 8.6 per 1000 PYs, log-rank *P*=0.782, aHR 1.167, 95% CI 0.392–3.471), however, significantly lower than in ETV (n=27, 15.2 per 1000 PYs, log-rank *P*=0.025, aHR 2.978, 95% CI 1.024-8.659, E-value 5.404), and TDF users (n=27, 16.6 per 1000 PYs, log-rank *P*=0.025, aHR 3.000, 95% CI 1.090–8.254, E-value 5.449).

**Conclusions:** BSV showed comparable outcomes in HCC development among patients with CHB compared to TAF, ETV, and TDF. Given the small number of events and the relatively short follow-up duration observed in BSV users, further long-term analysis is warranted.

**Keywords:** Besifovir, Hepatocellular carcinoma, Antiviral therapy, Hepatitis B

Friday, June 28, 2024, 16:30-17:30

# 2. MASLD, Basic

## OP-7

### Quercetin and Resveratrol Ameliorates Diabetic Induced NAFLD by Inhibiting Proprotein Convertase Subtilisin/Kexin Type 9 and Dipeptidyl Peptidase-IV

Anand Krishna, Purnima Tripathi

Department of Life Science, Shri Vaishna Vidyapeeth Vishwavdyalaya, Indore

**Aims:** Non-alcoholic fatty liver disease (NAFLD) has become a prevalent complication of diabetes mellitus, characterized by hepatic lipid accumulation and inflammation. Proprotein convertase subtilisin/kexin type 9 (PCSK9) and dipeptidyl peptidase-IV (DPP-IV) are emerging therapeutic targets implicated in the pathogenesis of NAFLD and diabetes. In this study, we investigated the synergistic effects of quercetin and resveratrol on diabetic-induced NAFLD and explored their modulation of PCSK9 and DPP-IV activity.

**Methods:** Diabetic rat model induced by streptozotocin and high-fat diet. Utilizing *in-vivo* in rat models of NAFLD, co-administration of quercetin (50 mg/kg/day) and resveratrol (30 mg/kg/day) exerted a potent synergistic effect. DPP-IV inhibition, PCSK9 inhibition activity was measured in serum and hepatic tissue along with the lipid profiling. We have also evaluated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), Insulin resistance, HOMA-IR, and Histology of liver tissue.

**Results:** The combination treatment effectively suppressed

PCSK9 and DPP-IV activity by 40.3±3.1% and 43.6±2.4% for PCSK9, and 61.2±5.3% and 65.3±3.6% for DPP-IV, in liver tissue and serum, respectively. Hepatic TG content decreased by 39%, with a 22% reduction in VLDL levels and increased HDL levels. Serum AST, ALT, and γ-GT declined, indicating improved liver function, alongside reduced HOMA-IR, suggesting enhanced insulin sensitivity. Histological analysis showed improved liver tissue architecture post-treatment, indicating alleviated liver damage and inflammation.

**Conclusions:** Our findings demonstrate that quercetin and resveratrol synergistically ameliorate diabetic-induced NAFLD by targeting key regulators of lipid metabolism and glucose homeostasis. The inhibition of PCSK9 and DPP-IV represents a novel therapeutic strategy for managing NAFLD in diabetic individuals. quercetin and resveratrol inhibited hepatic PCSK9 production, leading to enhanced hepatic LDL receptor-mediated cholesterol uptake and clearance. Additionally, the compounds exerted inhibitory effects on DPP-IV activity, thereby improving glucose homeostasis and insulin sensitivity.

**Keywords:** Non-alcoholic fatty liver disease, Dipeptidyl peptidase-IV, Proprotein convertase subtilisin/kexin type 9, Diabetes

## OP-8

### Translational Investigation of Non-Alcoholic Fatty Liver Disease in a Rat Model for Hepatocyte Transplantation

Cheng-Maw Ho[1,2], Shih-Jer Hsu[3], Ya-Hui Chen[4], Hung-Yen Chen[1,2], Chun-Hsien Yu[5], Hui-Ling Chen[2], Rey-Heng Hu[1], Po-Huang Lee[1]

[1]Department of Surgery, [2]Hepatitis Research Center, [3]Department of Internal Medicine, National Taiwan University Hospital, [4]Department of Pediatrics, National Taiwan University Children Hospital, Taipei, [5]Department of Pediatrics, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan

**Aims:** Non-alcoholic fatty liver disease is a major issue of clinical concern in liver or hepatocyte donation. The aims of this study are to established a spectrum of rat model of NAFLD, including non-alcoholic steatohepatitis (NASH) and to assess the soundness and functional characteristics of fatty rat hepatocytes.

**Methods:** Livers from male Sprague Dawley (SD) rats fed with a high-fat, high-cholesterol (HFC) diet (chow diet supplemented with 12% lard, 12% soybean oil, and 1% cholesterol) or additionally treated with temporary bile duct ligation (reversible BDL, rBDL) mimicking NASH were characterized *in vivo* and *in vitro*. Donor cells isolated from rat fatty liver were transplanted into rat model of acute liver failure through portal vein.

**Results:** Degrees of fatty liver increased progressively from 1 week to 8 weeks after HFC diet in gross appearance, liver size, and intracellular fat content, and maximal triglyceride (TG) amount was reached above 35 mg/g liver at 4 weeks. No fibrosis was observed till week 8. Weight of rat and livers increased slowly after rBDL under HFC diet, maximal TG concentration can be reached (but with a large variation) at 4 weeks, and fibrosis with activated stellated cells developed early since week 1 and subsided after 4 weeks. Geographic difference of macrophage distribution was noted with relative sparing of central vein at 2 weeks and 4 weeks after HFC diet or rBDL+HFC diet. CD163+ cells were dominant in HFC groups and CD68+ cells were in rBDL+HFC group. After culture for 1 day, fatty liver cells expressed hepatocyte nuclear factor 4 alpha and exhibit fat droplets. WST-1 readings of liver cells were increased in the order of conditions (HFC 2w, HFC 4w, HFC 4w with rBDL). Notably, clusters of progenitor cell were noted early (since day 5) in culture of liver cells using a 25% percoll gradient protocol. Preliminary results of fatty hepatocyte transplantation in a rat mode of acute liver failure showed good engraftment.

**Conclusions:** For NAFLD model using SD rats, feeding HFC diet for 4 weeks is adequate for further study design for donors using fatty liver organs or cells. Although transient fibrosis developed early, NASH model using strategy of HFC and rBDL may not represent the steatotic inflammation because the ignition of fibrosis did not trigger the event to occur. Fatty hepatocyte transplantation in acute liver failure might be a feasible option.

**Keywords:** Non-alcoholic fatty liver disease, Rat, Donor

## OP-9

### Intrahepatic IgA-Fibroblast Interaction and Its Impact on Inflammation in Steatotic Liver Diseases

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**Aims:** Immunoglobulin A (IgA) is known to facilitate inflammation and dismantle anti-tumor immunity in the inflamed liver. In this study, we aimed to elucidate the role of intrahepatic IgA complex on the fibroblast activation in the inflamed livers with steatotic liver diseases (SLDs).

**Methods:** Intrahepatic fibroblasts were isolated from SLD livers. Patient-derived fibroblasts were treated with mock or IgA complex for some experiments. CD71 and PD-L1 expression levels in patient-derived fibroblasts was analyzed by flow cytometry. A choline deficiency, L-amino acid-defined, high-fat diet (CDAHFD) induced MASH model was used to increase serum IgA level in mouse.

**Results:** *In vitro* treatment of IgA complex to cultured, patient-derived fibroblasts showed increased IgA mean fluorescence intensity (MFI) values, suggesting that the IgA complex-

es were attached to the cell surface. IgA-treated fibroblasts showed increased PD-L1 and FAP expression compared with mock-treated fibroblasts. Serum IgA level was increased in CDAHF diet-fed mice compared with those on a normal carbohydrate diet. Intrahepatic IgA was showed to be increased In CDAHF diet-fed mice with elevated serum IgA levels. Upon examining $IgA^{+}FAP^{+}$ cell numbers per gram of liver weight, we observed increased numbers in the livers of CDAHF diet-fed mice. These results indicate that the binding of IgA to hepatic fibroblasts may increase FAP expression and induces inflammation within the liver.

**Conclusions:** The interaction between intrahepatic IgA and fibroblasts appears to play a significant role in the activation of fibroblasts and the induction of inflammation in steatotic liver diseases.

**Keywords:** Fibroblast, Mash, IGA, Mafild

## OP-10

### Bacteroides Eggerthii as a Potential Treatment Strategy for NAFLD and Obesity

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**Aims:** The gut microbiome is known to play a crucial role in NAFLD pathogenesis, but a microbiome-based treatment effective for NAFLD in humans remains unclear. Our study aimed to identify the configuration of the gut microbiome that is helpful in the treatment or prevention of NAFLD and subsequently validate its efficacy in suppressing fatty liver and obesity through animal experiments.

**Methods:** We identified *Bacteroides eggerthii* as significantly decreased in patients with NAFLD by analyzing the gut microbiome using 16S rRNA sequencing from the fecal samples of human subjects with and without NAFLD. Male C57BL/6 mice were orally administered with a normal diet (ND), western diet + PBS (WD), or western diet + *Bacteroides eggerthii* for 12 weeks. Subsequently, a comprehensive analysis encompassing serum biochemical profiling and liver histopathology was performed to assess the validity of the identified strains. To identify metabolites altered by the strain, we performed non-targeted metabolites analysis using mouse feces.

**Results:** In the WD group, body weight, liver weight, fat content, and levels of AST, ALT, total cholesterol, and glucose were statistically significantly increased compared to those of the ND group. These metrics statistically significantly decreased in the WD+ *Bacteroides eggerthii* group relative to the WD group. Microscopic evaluation of liver sections using H&E staining and Masson's trichrome showed macrovesicular fatty accumulation and moderate inflammation in the WD group. Impressively, the WD+ *Bacteroides eggerthii* group displayed notable histopathological improvement in NAFLD activity score. The multivariate statistical analysis of fecal metabolites obtained using UHPLC-orbitrap-MS revealed 10 bile acids that showed statistically significant differences among the 3 groups.

**Conclusions:** Considering the *Bacteroides eggerthii*'s efficacy in treating NAFLD, our study offers the potential for microbiome-centered strategies to prevent and treat NAFLD and obesity.

**Keywords:** Gut microbiome, NAFLD, 16S RRNA sequencing, Obesity

## OP-11

### Laminarin Ameliorates Hepatic Steatosis and Upregulates Hepatic SMP-30 Expression in High-Fat Diet Mouse Models of Non-Alcoholic Fatty Liver Disease

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**Aims:** SMP-30 (senescence marker protein-30) is a calcium (Ca2+)-binding protein known as regucalcin, abundantly expressed in hepatocytes. SMP-30 plays a crucial role in intracellular calcium homeostasis and protects cells from apoptosis. In this study, we investigated the changes in hepatic SMP-30 expression in high-fat diet mouse models of non-alcoholic fatty liver disease (NAFLD). Additionally, we investigated the effect of laminarin, a polysaccharide obtained from brown algae, in mouse models of NAFLD.

**Methods:** To induce NAFLD, a high-fat diet with or without fructose water was administered to 8-week-old male C57BL/6J mice for 20 weeks. We evaluated the changes in hepatic SMP-30 expression using western blot, quantitative real-time reverse transcription polymerase chain reaction analysis and histological staining in three groups: 1) control diet, 2) high-fat diet, and 3) high-fat diet with fructose water (42 g/L). To investigate the effect of laminarin in NAFLD, the mice were divided into four groups: 1) control diet, 2) high-fat diet, 3) high-fat diet with 1% laminarin water, and 4) high-fat diet with laminarin intraperitoneal injection (50mg/kg/5ml).

**Results:** Compared with the control diet group, hepatic SMP-30 expression significantly decreased in the high-fat diet

groups with or without fructose water supplementation. Among the groups treated with laminarin, only the intraperitoneal injection group showed improved hepatic steatosis and maintained hepatic SMP-30 expression. In an *in vitro* model using Huh7 cells treated with palmic acid, lipid accumulation and decreased SMP-30 expression were observed, however the treatment with laminarin significantly increased SMP-30 expression in a dose-dependent manner. In our *in vitro* and *in vivo* model of NAFLD, levels of reactive oxygen species and phase II detoxification enzymes, such as NQO1 and HO-1, were increased, while SMP-30 was downregulated. Laminarin significantly ameliorated hepatic steatosis and restored SMP-30 expression in the livers of NAFLD mice.

**Conclusions:** These findings demonstrate that hepatic SMP-30 expression decreases during the progression of NAFLD. Laminarin can be a potential therapeutic option for NAFLD by regulating lipid metabolism and upregulating SMP-30.

**Keywords:** Senescence Marker Protein-30, Laminarin, Non-alcoholic fatty liver disease

## OP-12

### sQTL Analysis Reveals Splicing-Mediated Regulation of MASLD Pathogenesis

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**Aims:** Metabolic associated steatohepatitis liver disease (MASLD) is caused by a complex interplay of genetic and environmental factors. Although genome-wide association studies (GWAS) have repeatedly identified MASLD-associated loci across various populations, most of these loci are located in non-coding regions, and the mechanisms linking them to MAFLD remain unclear. Hypothesizing that some loci may affect MASLD pathogenesis by altering alternative splicing of downstream genes, we conducted splicing quantitative trait loci (sQTL) analysis.

**Methods:** Liver tissues from 122 patients (81 with MASLD, 41 without MASLD) underwent high-throughput RNA sequencing, and their blood samples were used for single nucleotide polymorphisms (SNP) arrays. To explore the impact of genotype on alternative splicing, we analyzed 163,094 isoform transcripts of 15,165 genes and 5,071,736 genotyped and imputed SNPs to identify sQTLs. The sQTLs were subjected to subsequent downstream analysis.

**Results:** We identified 32,461 liver-sQTLs and 1,225 associated genes, and 26,851 MASLD-specific sQTLs and 800 associated genes. Compared to sQTLs from the control group, liver-sQTLs and MASLD-specific sQTLs were more likely to be protein-altering. These sQTLs were enriched in splicing sites, intronic regions, and stop-gain loci compared to expression QTLs (eQTLs). The implicated genes (i.e., sGenes) were enriched in biological pathways related to MASLD, such as lipoprotein biosynthetic process and fatty acid metabolism. Among these genes, sQTLs associated with *CBS, CPS1, ACSM5*, and *LRRC31* genes were also located in the LD region of the MASLD GWAS, linking changes in transcript isoform distribution along with genetic implication to MASLD.

**Conclusions:** We have profiled sQTLs involved in MASLD pathogenesis and identified four genes where genotype-dependent alternative splicing changes occur in MASLD. This study highlights the potential for applying personalized medicine to patients with MASLD who carry these genotypes.

**Keywords:** MASLD, sQTL, Alternative splicing

Friday, June 28, 2024, 16:30-17:20

# 3. MASLD, Clinical 1

## OP-13

### Analysis for the Association between Body Weight, Waist Circumference Change and Cardio-Cerebrovascular Risk among Nonalcoholic Fatty Liver Disease Patients

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**Aims:** We investigated whether changes in body mass index (BMI) and waist circumference (WC) are associated with cardiovascular risk in patients with NAFLD using a nationwide dataset.

**Methods:** Using the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) data in Korea, a total of 19,057 subjects who underwent two consecutive medical check-ups (2009–2010 and 2011–2012) and who had a fatty-liver index (FLI) value of ≥ 60 were included in the analysis. Cardiovascular events were defined as the occurrence of stroke or transient ischemic attack, coronary heart disease, and cardiovascular death.

**Results:** After multivariable adjustment, the risk of cardiovascular events was significantly lower in subjects with decreases in both BMI and WC (HR, 0.83; 95% CI, 0.69–0.99) and those with

increased BMI and decreased WC (HR, 0.74; 95% CI, 0.59–0.94) when compared with those who showed increases in both BMI and WC. The effect of cardiovascular risk reduction among the group with increased BMI but decreased WC was particularly pronounced among those who had metabolic syndrome during the second check-up (HR, 0.63; 95% CI 0.43–0.93, p for interaction 0.02).

**Conclusions:** Changes in BMI and WC were significantly associated with cardiovascular risk in NAFLD patients. NAFLD patients with increased BMI and decreased WC had the lowest cardiometabolic risk.

**Keywords:** Body mass index, Cardiovascular diseases, Non-alcoholic fatty liver disease, Waist circumference

## OP-14

### A Novel Point-of-Care Prediction Model for Steatotic Liver Disease: Based on Bioimpedance Analysis with Machine Learning Algorithms

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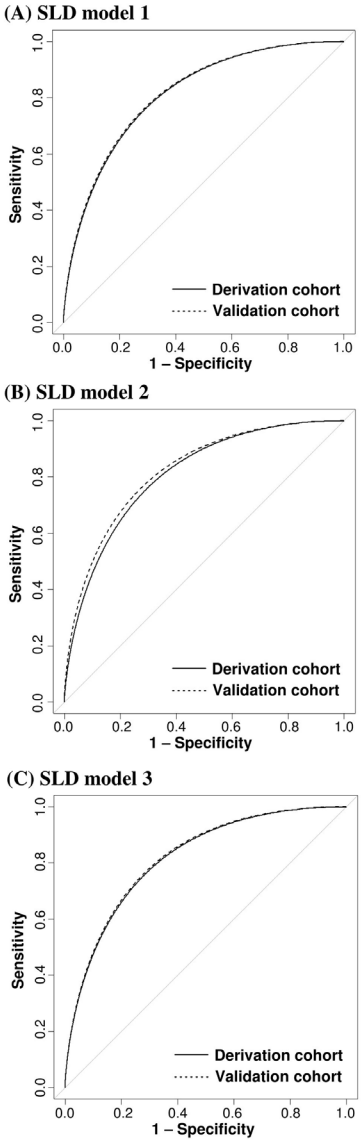
**Aims:** Globally, steatotic liver disease (SLD) incidence is rising across all age groups. Existing non-invasive biomarkers and prediction models for SLD require laboratory tests or imaging, missing early diagnoses in under-screened groups such as young adults and those with healthcare disparities. We aimed to develop a machine learning-based point-of-care prediction model for SLD that is readily accessible to the broader population, facilitating early detection, timely intervention, and ultimately reducing the disease burden.

**Methods:** We retrospectively analyzed 28,506 adults who had routine health check-ups in South Korea from January to December 2022. For external validation, 229,162 subjects were included who visited another healthcare center. All participants underwent abdominal ultrasound and bioelectrical impedance analysis. Data was analyzed and predictions made using a logistic regression model with machine learning algorithms.

**Figure 2**




**Results:** A total of 20,094 subjects were categorized into non-SLD and SLD groups based on the presence of fatty liver. We developed three prediction models: SLD model 1 used age and body mass index (BMI); SLD model 2 included age, BMI, and body fat per muscle mass; SLD model 3 comprised age, BMI, and visceral fat per muscle mass. In the derivation cohort, the area under the receiver operating characteristic curve (AUROC) was 0.817 for model 1, 0.821 for model 2, and 0.820 for model 3. In internal validation, 86.8%, 86.9%, and 87.1% of subjects were correctly classified by SLD model 1, 2, and 3, respectively. External validation showed all models had an AUROC above 0.84, with similar predictive accuracy.

**Conclusions:** The three derived SLD prediction models, charac-

terized by cost-effectiveness, non-invasiveness, and accessibility in settings outside of hospitals, could serve as novel validated clinical tools for SLD mass screening.

**Keywords:** SLD, Non-invasive, Machine learning, Prediction model

## OP-15

### The Number of Meeting Cardiometabolic Criteria in Metabolic-Dysfunction Associated Steatotic Liver Disease Is Associated with Prognosis of Hepatocellular Carcinoma

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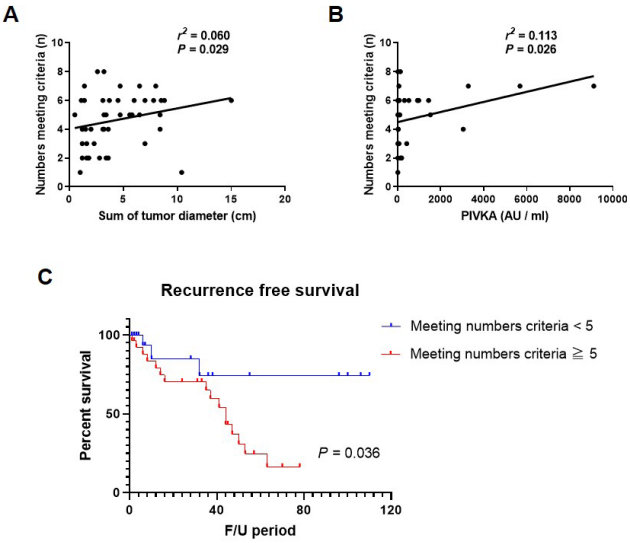
**Aims:** Metabolic-dysfunction associated steatotic liver disease (MASLD) is a nomenclature which encompasses patients with liver steatosis and at least one of cardiometabolic criteria. Here, we suggest that the numbers of meeting criteria of MASLD is correlated with features and prognosis of hepatocellular carcinoma (HCC).

**Methods:** Among the patients diagnosed with HCC for 10 years retrospectively analyzed (n=453), HCC derived from viral hepatitis or alcohol associated liver disease (n=406) were excluded and cardiometabolic criteria of MASLD were applied for inclusion. The number of meeting total seven specified criteria of body mass index, serum fasting glucose, HbA1c, Presence of diabetes mellitus and hypertension, serum triglyceride and high-density lipoprotein level were calculated for each patients. Spearman's rank correlation analysis and Kaplan-Meier survival analysis were conducted for investigation of MASLD related HCC.

**Results:** 47 HCC patients with MASLD in a training hospital were analyzed and followed up for the recurrence and death. The number of meeting cardiometabolic criteria in MASLD at diagnosis was positively correlated with the sum of tumor diameter and Protein induced by vitamin. K absence or antagonist-II level (PIVKA-II), not with alpha-fetoprotein level of blood. Furthermore, patients corhort meeting cardiometabolic criteria by five factors or above significantly had decreased recurrence free survival within 10 year follow up period.

**Conclusions:** Collectively, we suggest that the number of meeting cardiometabolic criteria of MASLD could be one of the important prognostic factors and crucial indicators for the tumor progression at diagnosis and recurrence free survival of HCC induced by MASLD. Further study for larger cohort and prospective method would be requested for the concrete explanation of hypothesis.

**Keywords:** MASLD, Cardiometabolic criteria, Hepatocellular carcinoma




## OP-16

### Association of the Duration of Comorbidities on the Development of Steatotic Liver Disease and Patient Survival

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**Aims:** Steatotic liver disease (SLD) interacts with various comorbidities, impacting outcomes, yet little is known about the duration of comorbidities in SLD development and mortality. We investigated this relationship, focusing on disease predictors and mortality rates.

**Methods:** Analyzing 2010 and 2015 Korea National Health and Nutrition Examination Survey data for patients aged ≥ 20, we categorized ten comorbidities (hypertension [HTN], diabetes mellitus [DM], dyslipidemia, stroke, myocardial infarction [MI], angina pectoris, asthma, chronic obstructive lung disease [COPD], chronic kidney disease [CKD], and depression) by duration. Association rule mining and logistic regression analyzed the association between SLD presence and comorbidity duration, while Cox regression assessed survival.

**Results:** The analysis included 2,757 SLD and 9,505 non-SLD cases. Association rule mining showed that the shorter duration of DM and dyslipidemia and the longer duration of HTN comprised the top-ranked component for SLD. DM with a duration ≤ 1 year showed higher risk of SLD than longer periods (odds ratio, 11.53), while the duration of cardiovascular disease, lung disease, or CKD was not significantly associated with the presence of SLD. Multivariate Cox regression showed that longer HTN and DM durations were significantly associated with increased hazard ratio (HR) beyond 10 years (HR, 2.22 and 2.11, respectively). Cardiovascular disease duration ≤ 5 years and lung disease duration > 5 years showed statistical significance (HR 2.49and 2.38, respectively)

**Conclusions:** Duration of comorbidities should be considered for comprehensive SLD risk stratification, for both the identification of SLD and the assessment of their prognosis after detection.

**Keywords:** Comorbidity duration, Steatotic liver disease, Association, Survival

## OP-17

### Differential Risk of Hepatocellular Carcinoma Based on Antidiabetics in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease

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**Aims:** Coexistence of type 2 diabetes is a significant risk factor for hepatocellular carcinoma (HCC) in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). Nevertheless, the effect of antidiabetics on the risk of HCC in these individuals remains elusive. We investigated the effects of antidiabetics on the risk of the HCC development, using a retrospective study cohort of patients with MASLD who were concurrently diagnosed with diabetes.

**Methods:** Patients with MASLD and diabetes diagnosed at 3 tertiary hospitals between January 1, 2004 and December 31, 2018 were included. Patients were followed from the date of MASLD diagnosis until the diagnosis of HCC, death, or December 31, 2023. The effects of antidiabetics, glycemic control (percent of follow-up time with hemoglobin A1c <7%) and other metabolic disorders on the risk of HCC were investigated using landmark Cox proportional hazard models.

**Results:** A total of 5,878 patients with MASLD and diabetes were identified. During a median follow-up of 4.7 years, 284 (4.8%) patients developed HCC. The median age was 56.0 years, and 3,331 (56.7%) were male. Among patients, 4,116 (70.0%) were treated with antidiabetics, 3,242 (55.2%) had oral antidiabetic drug (OAD), and 874 (14.9%) had insulin-based therapy. OAD therapy had comparable risk of HCC compared with no antidiabetic therapy (HR=1.376, $P$=0.374). Insulin-based therapy was associated with a higher risk of HCC compared to no antidiabetic therapy (HR=4.481, $P$<0.001) or OAD therapy (HR=2.289, $P$<0.001). Among patients treated with OAD, use of sodium-glucose cotransporter 2 (SGLT2) inhibitors was associated with a lower risk of HCC (cause-specific HR=0.632, standard error=0.104, $P$=0.045). Use of metformin was not associated with the risk of HCC development (cause-specific HR=0.830, standard error=0.091, $P$=0.286).

**Conclusions:** SGLT2 inhibitor has a preventive effect on the development of HCC in patients with MASLD and diabetes. While OAD therapy showed neutral effects compared with no antidiabetic therapy, careful consideration of the choice of antidiabetics may play a crucial role in HCC prevention.

**Keywords:** Metabolic dysfunction-associated steatotic liver disease, Hepatocellular carcinoma, Type 2 diabetes, Sodium-glucose cotransporter 2

Friday, June 28, 2024, 16:30-17:30

# 4. LC Clinical & Liver Failure 1

## OP-18

### Development and Validation of an Explainable Machine Learning Model for Predicting Multidimensional Frailty in Hospitalized Patients with Cirrhosis

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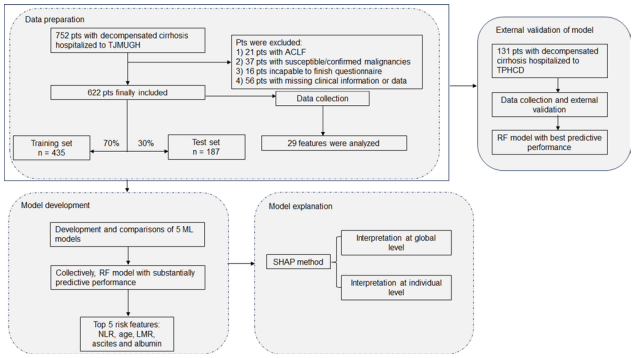
**Aims:** Frailty is linked to a spectrum of inferior outcomes in cirrhosis, thus early prediction is crucial for resulting effective management. We sought to develop and validate a machine learning (ML) model for predicting multidimensional frailty based on clinical and laboratory data. Moreover, explainable ML model utilizing SHapley Additive exPlanations (SHAP) was constructed.

**Methods:** This study enrolled 622 patients hospitalized due to decompensating episode at a tertiary hospital. The cohort data were randomly divided into training and test sets. External validation was carried out using 131 patients from other tertiary

hospital. Frail phenotype was defined according to a self-reported questionnaire (Frailty Index). Area under the receiver operating characteristics curve (AUC) was adopted to compare the performance of five ML models. The importance of the features and interpretation of the ML models were determined using SHAP method.

**Results:** The median age of study population was 62 years with 50.2% female. The proportions of cirrhotic patients with non-frail and frail phenotypes in combined training and test sets were 87.8% and 12.2%, respectively, while 88.5% and 11.5% in the external validation dataset. Five ML algorithms were used, and the random forest (RF) model exhibited substantially predictive performance. Regarding the external validation, the RF algorithm outperformed other ML models. Moreover, SHAP method demonstrated that neutrophil-to-lymphocyte ratio, age, lymphocyte-to-monocyte ratio, ascites and albumin served as the most important predictors for frailty. At the patient level, SHAP force plot and decision plot exhibited clinically meaningful explanation of the RF algorithm.




**Conclusions:** We constructed an ML model (RF) providing accurate prediction of frail phenotype in decompensated cirrhosis. The explainability and generalizability may foster clinicians to understand contributors to this physiologically vulnerable situation and tailor interventions.

**Keywords:** Machine learning, Frailty, Random forest algorithm, Liver cirrhosis, Shapley additive explanations

## OP-19

### Does Senescent Change in Spleen Affect Splenomegaly in Elderly Patients with Liver Cirrhosis?

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Seoul National University Bundang Hospital

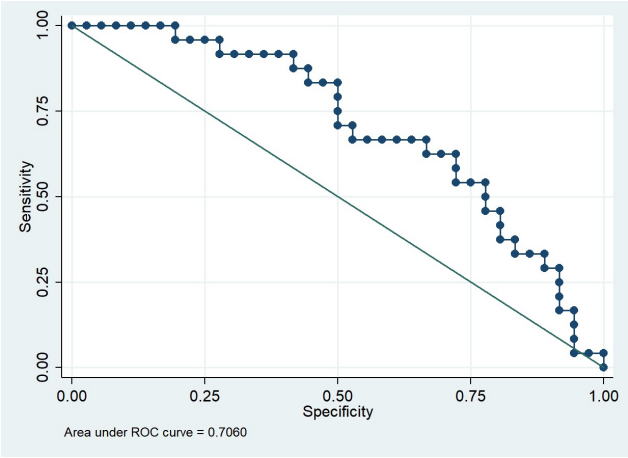
**Aims:** Splenomegaly has been considered a classic hallmark of portalhypertension and frequently used as a diagnostic criterion for liver cirrhosis.Meanwhile, it is also known that the size of spleen shrinks gradually over the laterdecades of life because of ageing-related changes to spleen architecture. However, thechange in spleen volume has not been thoroughly evaluated in elderly patients withadvanced hepatic fibrosis. This study aimed to elucidate the pattern and diagnosticsignificance of splenomegaly in elderly patients with hepatic fibrosis by measuringspleen volume and liver-to-spleen volume ratio (LSVR) from computed tomography (CT) images.

**Methods:** In this observational cohort study, all patients were identified who receivedboth liver biopsy and liver CT studies in our institute between July 2004 and December2022 and classified into two groups: control and geriatric group (≥ 75 years). Propensityscore matching was used to balance the two groups. Whole spleen and liver volumeswere measured on abdominal CT scan images using Inobitec DICOM Viewer.Comparison between the two groups was done using a two-sample t-test with equalvariances in Stata/SE 14.0. ROC analysis was used to assess the diagnostic performanceof each parameter.

**Results:** Both groups included all histologic grades of fibrosis (F0 8.1%, F1 23.7%, F223.7%, F3 12.6%, F4 31.9% in geriatric group and F0 9.3%, F1 22.0%, F2 20.1%, F3 6.9%, F4 41.7% in control group). In control group, patients with advanced fibrosis (METAVIRF3 and F4) had significantly larger spleen volume (277 cm) compared to F0-F2 (163 cm) ($P$<0.001). However, in geriatric group, patients with F3-F4 showed no statisticallysignificant difference in spleen volumes compared to those with stage F0-F2 (174 vs 129cm, respectively; $P$=0.051). Whereas, the area under the ROC curve of spleen showedthat the same cut-off volume for F3-F4 was similar between control and geriatric group(0.691 vs 0.692; cut-off, 158 vs 128 cm for sensitivity of 70%, respectively; $P$=0.991). Also, the ROC curve analysis generated a similar result when comparing spleen volumesin patients with liver cirrhosis (F4) and the others (F0-F3) between control and geriatricgroup (0.677 vs 0.706 (Fig.); cut-off, 159 vs 128 cm, respectively; $P$=0.696). For LSVR,the area under the ROC curve showed no significant differences when comparing thevolumes not only for F0-F2 vs. F3-F4(0.282 vs 0.301; cut-off, 4.165 vs. 5.317 forsensitivity of 70%, respectively; $P$=0.802) but also for F0-F3 vs. F4 (0.308 vs 0.284; cut-off, 4.303 vs. 5.317; $P$=0.74) as well.

**Conclusions:** In elderly patients, splenomegaly may not seem as evident with advancedhepatic fibrosis as younger patients, however, the cutoff values from ROC curveanalysis was not different from those in younger population. Spleen volume may still beused for the prediction of advanced fibrosis since our ROC analysis showed similar AUC values between control and geriatric groups.

**Keywords:** Liver cirrhosis, Splenomegaly, Geriatrics, Portal hypertension




## OP-20

### Prediction of Liver Cirrhosis Using Regular Health Check-up Data: Development of Machine Learning Model and Cross-Country Validation

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**Aims:** This study aims to develop and validate an artificial intelligence (AI) model for predicting liver cirrhosis within five years using regular health checkup data, employing machine learning (ML) techniques.

**Methods:** We utilized data from two extensive cohorts: the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC; 973,303 participants) and the Japanese Medical Data Center Cohort (JMDC; 12,143,715 participants). The NHIS-NSC dataset was divided for training and testing, and JMDC data was used for external validation. We applied six ML algorithms (XGBoost, RF, GBM, LGBM, AdaBoost, and LR) and four ensemble models for prediction. The models' performances were evaluated using sensitivity, specificity, accuracy, balanced accuracy, and AUROC.

**Results:** The ensemble model combining GBM, LR, and LGBM showed superior performance, achieving a balanced accuracy of 78.3% and AUROC of 0.862 in NHIS-NSC testing data. The model maintained high performance in the external validation with JMDC data, indicating robustness and generalizability. Feature importance analysis revealed aspartate transaminase, age, alanine transaminase, and γ-glutamyl transpeptidase as significant predictors of cirrhosis.

**Conclusions:** Our study demonstrates the feasibility of using AI models for early prediction of liver cirrhosis using routine health checkup data. The high performance of our model across diverse datasets suggests its potential utility in clinical settings for early cirrhosis detection and intervention strategies.

**Keywords:** Machine learning, Liver cirrhosis, Prediction

## OP-21

### Evaluation and Comparative Study of Machine Learning-Based Models to Determine the Seropositivity of Hepatitis B Virus (HBV)

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**Aims:** Clinicians and public health experts struggle to identify patients who are at risk of contracting the hepatitis B virus. Traditional hepatitis screening methods can be more effective when used in conjunction with artificial intelligence and machine learning techniques, which can also be used to analyze big datasets and provide a complete picture of regional epidemiological profiles. In this research, four machine learning-based models for predicting the presence of hepatitis B were evaluated and their predictive abilities were compared.

**Methods:** Approaches Adults from the central region of India who experienced viral hepatitis screening in their primary care physicians' offices were evaluated as part of this prospective cohort screening study between March 2022 and October 2022. Four machine learning-based models, -naive bayes (NB), and random forest (RF) K nearest neighbors (KNN), support vector machine (SVM) were used, and their predictive abilities were evaluated, using the clinical characteristics of the patients that were taken from a structured poll.

**Results:** When used to forecast Hepatitis B virus status, all models that were tested outperformed each other. KNN algorithm had the best forecast performance (accuracy: 97.4%), followed by support vector machine and random forest, which both had 96.5% accuracy, and naive bayes, which had 94.3% accuracy. With accuracy levels varying from 77.3% to 95.46%, the predictive performance of these models for Hepatitis B virus status was modest.

**Conclusions:** The machine learning-based models might be helpful resources for predicting Hepatitis B Virus infection and risk stratification for adult patients who participate in a programme for viral hepatitis monitoring.

**Keywords:** Hepatitis V, Machine learning, Models

## OP-22

### A Deep Learning Approach to Predict Liver Fibrosis from Laparoscopic Videos: Intraoperative Liver Resection Decision Support

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**Aims:** In hepatocellular carcinoma (HCC), the background liver status is crucial in determining treatment strategy. Especially for liver resection, the extent of resection can vary depending on the degree of fibrosis or cirrhosis. However, there has been no method to evaluate fibrosis grade quantitatively during surgery before histologic confirmation.

**Methods:** This study included patients who underwent laparoscopic liver resection for HCC at Samsung Medical Center from December 2019 to March 2022. All patients had histologic evaluation of the background liver tissue and their surgical videos were archived. From the surgical videos, frames were extracted at 3 frames per second (FPS) during the inspection of the entire liver before resection. Liver fibrosis was categorized into five stages: no fibrosis (F0), periportal fibrosis (F1), septal fibrosis (F2), incomplete cirrhosis (F3), cirrhosis (F4). To extract features related to fibrosis from surgical scene, the pre-trained DenseNet-121 model was utilized. Training and validation were performed using 5-fold cross-validation, and the model's performance was evaluated based on ROCAUC.

**Results:** A total of 103 patients were included in this study. The prediction of fibrosis was conducted as binary classification between no cirrhosis (F0-2) and cirrhosis (F-3-4). There were 36 patients with cirrhosis and 67 with no cirrhosis. The developed model predicted cirrhosis with a mean AUCROC (SD) of 0.927 (0.039).

**Conclusions:** This study showed that predicting liver fibrosis using laparoscopically captured liver image is feasible with deep learning. This approach may be applied into intraoperative decision making to determine the extent of liver resection for the safety of cirrhotic patients.

**Keywords:** Artificial intelligence, Fibrosis, Deep learning

## OP-23

### An Approach Using Non-Invasive Parameters of Machine Learning Techniques for Predicting Portal Hypertension

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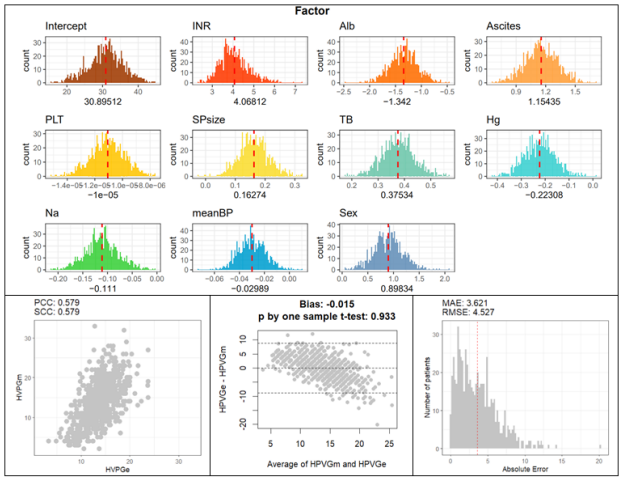
**Aims:** Prediction of portal pressure is crucial role in management of cirrhosis. Increased portal pressure drives poor outcomes in cirrhosis. Non-invasive methods for liver fibrosis for cirrhosis are widely investigated. Measurement of hepatic venous pressure gradient is the gold standard for the presence of portal hypertension. However, patients should undergo invasive measurement for pressure gradient measurement. We designed the model to predict portal pressure using the non-invasive parameters based on 670 pressure gradient data.

**Methods:** We analyzed 670 patients' data who undergo hepatic vein pressure gradient (HVPG) measurement (2000. January-2014. April). The variable was categorized into continuous or categorical variables using class function in R Base package. HVPG and candidate features were entered into univariate linear regression (LiR) as independent and dependent variables. Next, specific cut-offs, including actual *p*-value or top ranking based on its ascending ordering, were applied to select the HVPG-related variables. The dataset was randomly divided into training and testing datasets with ratio of 0.7 to 0.3. The feature selection and establishment of HVPG estimation model was conducted exclusively using the training dataset. Performance measurement was conducted using the testing dataset. The tasks, including the random dataset split, feature selection, and establishment of HVPG prediction model were iterated at 50 times, yielding fifty lists of the candidate predictors and estimated HVPG values of testing dataset.




**Results:** The performance of the HVPG estimation model was measured by three metrics, including bias (–0.011), RMSE (4.257), and correlation (PCC: 0.579; SCC: 0.578). And we also constructed the CSPH prediction model to using feature selection model. Based on the statistical criteria calculated by univariate LR, following 10 clinical variables were finally selected for the CSPH prediction model: INR, Alb, Plt, SPsize, Hb, Ascites, TB, Na, mean BP, and Alcohol intake. And the final formula for predicting CSPH is presented, and the model performance on the CSPH of training dataset is 0.820 of AUC.

**Conclusions:** Increased portal pressure can be predicted by non-invasive parameters.

**Keywords:** Portal hypertension, Machinr learning

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## 5. Liver Transplantation 1

### OP-24

### Metformin Modulates Regulatory T and B Cells and Suppresses Th17 Cells through Various Pathways, Including Gut Microbiome, in Liver Transplantation

Soon Kyu Lee[1], Joo Yeon Jhun[2], Ho Joong Choi[3], Young Kyoung You[3], Jeong Won Jang[4], Pil Soo Sung[4], Seung Kew Yoon[4], Mi-La Cho[2], Jong Young Choi[4]

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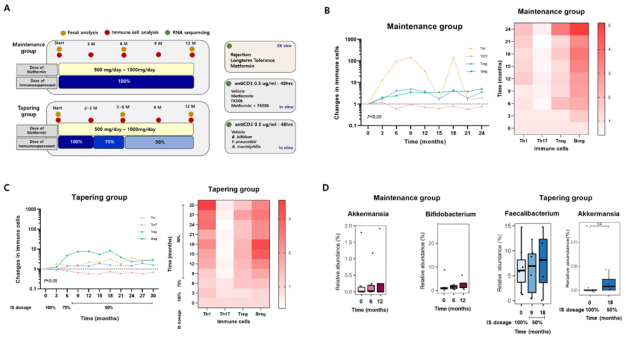
**Aims:** Our previous research demonstrated that a combination of metformin and tacrolimus can enhance immune homeostasis, specifically by modulating regulatory T cells (Tregs) and T helper 17 cells (Th17). This study aims to document serial immune cell changes, including Tregs, regulatory B cells (Bregs), and Th17 cells, following metformin addition in liver transplant (LT) patients. We also explore the underlying pathways of these immunological adjustments, with a specific focus on gut microbial dynamics.

**Methods:** We prospectively enrolled 23 liver transplant (LT) patients diagnosed with diabetes or pre-diabetes, administering metformin at doses ranging from 500 to 1000 mg/day. Initially, 11 patients continued their usual immunosuppressant (IS) regimen (maintenance group) to assess immune cell and microbial changes post-metformin addition. The remaining 12 patients gradually tapered their IS dosage by half (tapering group) following metformin administration, aiming to monitor and validate changes in immune cells and the microbiome, comparing these with the maintenance group.

**Results:** The mean age of included patients was 62.3 years, and the mean duration from underwent LT was 12.5 years. After administering metformin, the proportions of Tregs, Bregs, Th1 cells gradually increased, while Th17 cells decreased over time in the maintenance group (Figure B). These trends were consistently observed in the tapering group, further supporting the immunomodulatory effects of metformin (Figure C). In RNA-seq analysis, compared to tacrolimus monotherapy, the combination of metformin with tacrolimus reduced responses to oxidative stress and inflammation. Microbiome analysis showed a marginal increase in *Akkermansia* and *Bifidobacterium* in the maintenance group, and *Akkermansia* and *Faecalibacterium* in the tapering group post-metformin (Figure D). Additionally, RNA sequencing analysis revealed that these microbiomes were associated with an increase in the expression of the IL-10 gene and a decrease in chemokine-mediated signalling pathways.

**Conclusions:** This study demonstrated that metformin administration in LT patients leads to a gradual increase in Tregs and Breg cells and a concurrent suppression of Th17 cells. These effects are mediated through multiple pathways, including the enhancement of functional microbiomes.

**Keywords:** Liver transplantation, Metformin, Regulatory B cell, Gut microbiome




### OP-25

### Performance of the LI-RADS-Based Milan Criteria and Its Prognostic Implication in Potential Transplant Candidates with Hepatocellular Carcinoma

Yeong Seok Hwang[1], Soo Bin Heo[2], Ji Hyun Ahn[4], Han Joo Lee[1], Kee Won Song[3], Sang Hyun Choi[2], Ju Hyun Sim[1]

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**Aims:** Given the limited availability and feasibility for pathologic confirmation of every hepatic lesion, imaging diagnosis is primarily used to assess Milan criteria in candidates for liver transplantation (LT) with hepatocellular carcinoma (HCC). There is little data on the correlation between explant pathology and radiologic measurement based on LI-RADS in determining LT eligibility in HCC patients. This study aimed to investigate the

radio-pathologic correlation of Milan criteria using LI-RADS-based diagnosis, and also to identify factors affecting discordance and its prognostic impact.

**Methods:** This retrospective study included 267 patients who had any hepatic lesion identified on dynamic liver CT within 3 months prior to LT and/or in the explant livers at Asan Medical Center. Two radiologists reviewed CT examinations, evaluating nodules and the Milan criteria based on LI-RADS v2018. Analyses were performed on a per-lesion and per-patient basis, comparing radiologic lesions with their matched pathology. LR-5 or LR-TR-V nodules were regarded as HCC to determine LI-RADS Milan criteria (MC). Overall survival (OS) and recurrence-free survival (RFS) were measured according to LI-RADS MC and pathologic MC, applying a competing risk analysis to 259 patients, excluding cases of in-hospital mortality.

**Results:** In per-lesion analysis, among 79 LR-5 lesions and 48 LR-3/LR-4 lesions, 72 lesions (91.1%) and 37 (77.1%) were identified as HCCs, respectively. The 189 LR-TR-V lesions were matched with 176 HCCs (93.1%) in pathology. According to per-patient analysis, an overall concordance rate of 87.3% was presented between LI-RADS MC and pathologic MC. These concordances were not affected by pre-LT chemoembolization and type of LT. The 5-year OS and RFS were significantly greater for patients meeting the MC, compared to the counterparts: 96% vs. 86% and 90% vs. 62% for pathologic MC; and 96% vs. 76% and 90% vs. 45% for LI-RADS MC, respectively (Ps<0.003). When cases meeting LI-RADS MC and pathologic MC were compared, there were no significant differences in OS and RFS. Multivariate Cox-proportional hazard models indicated that being outside LI-RADS MC independently predicted OS and RFS (hazard ratios, 6.51 and 6.34; 95% confidence intervals: 2.37- 17.86 and 3.38-11.88, respectively). The presence of nodules other than LR-5/LR-TR-V did not affect survivals.

**Conclusions:** The LI-RADS-based radiology presented high concordance and comparable prognostic performance with explant pathology in determining the MC. LT eligibility could likely be judged by CT LI-RADS in patients with HCC.

**Keywords:** Li-rads V2018, LI-RADS Treatment response algorithm, Liver transplantation, Hepatocellular carcinoma

## OP-26

### Impact of Pre-Liver Transplant Treatments on Imaging Accuracy of HCC Staging and Their Influence on Outcome

Eloisa Franchi[1], Daniele Eliseo Dondossola[1], Giulia Marini[1], Massimo Iavarone[2], Luca Del Prete[1], Clara Di Benedetto[2], Francesca Donato[2], Barbara Antonelli[1], Pietro Lampertico[2], Lucio Caccamo[1]

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**Aims:** The outcome of liver transplantation (LT) for hepatocarcinoma (HCC) is strongly influenced by HCC staging, which is based on radiological examinations in pre-LT setting; concordance be-tween pre-LT radiological and definitive pathological staging remains controversial. To address this issue, we retrospectively analyzed our LT series to assess concordance between radiology and pathology, and to explore factors associated with poor concordance and outcome

**Methods:** This was a retrospective single-center study of all consecutive patients who underwent LT between 2013 and 2018 at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy. We included all LT with an HCC diagnosis performed between the study period. Concordance (Co group) was defined as a comparable tumor burden on preoperative imaging and post-transplant pathology; otherwise, non-concordance was diagnosed (nCo group). Concordance between radiology and pathology was observed in 32/134 patients (Co group, 24%). The number and diameter of the nodules were higher when nCo was diagnosed, as was the number of pre-LT treatments.

**Results:** Although concordance did not affect survival, more than three pre-LT treatments led to lower disease-free survival at 1-3-5 years (83%, 72%, 67% vs. 95%, 72%, and 67%, $P$=0.019). Milan-in patients were more likely to receive ≥ 3 prior treatments, leading to lower survival in multitreated Milan-in patients than in other Milan-in patients.

**Conclusions:** In conclusion, concordance rate between the pre-LT imaging and histopathological results was low in patients with a high number of nodules. Multiple bridging therapies reduce the accuracy of pre-LT imaging in predicting HCC stages and negatively affect outcomes after LT.

**Keywords:** HCC, Downstaging, Bridge treatment

## OP-27

### Validation of Sundaram ACLF-LT-Mortality (SALT-M) Score in Korean Patients with Acute-on-Chronic Liver Failure

Deok-Gie Kim[1], Kunhee Kim[2], Seung Hyuk Yim[1], Jae Geun Lee[1], Dong Jin Joo[1], Myoung Soo Kim[1], Jun Yong Park[2], Sang Hoon Ahn[2], Hye Won Lee[2]

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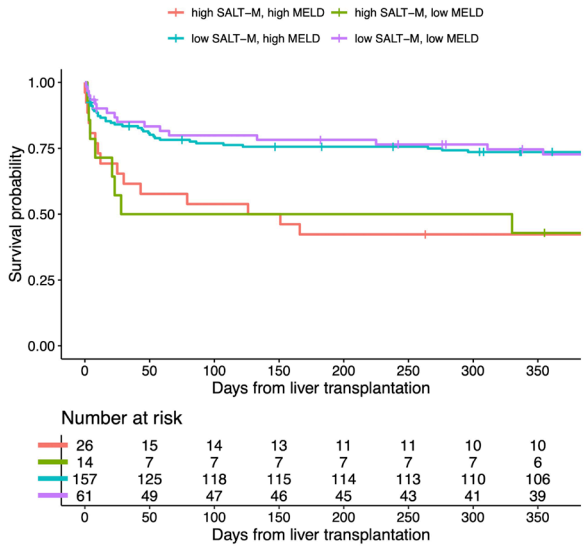
**Aims:** Recently, SALT-M score has been developed for predicting 1-year post-liver transplantation mortality in patients with severe Acute-on-Chronic Liver Failure (ACLF). We validated the SALT-M score in Asian large-volume single center cohort.

**Methods:** We analyzed 224 patients with ACLF grade 2 or 3. Area under the receiver operating characteristic curve (AUROC)

and concordance index (c-index) were used to assess and compare the predictability for post-transplant mortality between SALT-M and other scores. Moreover, we compared the survival between patients with high SALT-M and low SALT-M, in patients categorized by MELD score or ACLF grade.

**Results:** The AUROC for predicting 1-year post-LT survival was higher in SALT-M (0.691) compared to MELD, MELD-Na, MELD 3.0, and delta MELD. Similarly, c-index of the SALT-M (0.650) was also higher than aforementioned MELD systems. When categorized by the cutoff for SALT-M (≥ 20) and MELD (≥ 30), patients with high SALT-M showed lower post-LT survival than those with low SALT-M regardless of high or low MELD (40.0% for high SALT-M/high MELD vs. 42.9% for high SALT-M/low MELD vs. 73.8% for low SALT-M/high MELD vs. 63.7% for low SALT-M/low MELD, $P$<0.001). In subgroup only with ACLF grade 3, post-transplant mortality was also effectively stratified by the SALT-M score (39.4% for high SALT-M vs. 63.1% for low SALT-M, $P$=0.02).




**Conclusions:** SALT-M outperformed previous MELD systems for post-transplant mortality in Asian LT cohort with severe ACLF, which showed lower BMI and higher LDLT rate. Transplantability for the patients with severe ACLF could be determined based on SALT-M.

**Keywords:** SALTM, Liver transplantation, Acute on chronic

## OP-28

### Selection of Safe Donors for Living Donor Liver Transplant Using Extended Right Lobe Graft

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**Aims:** Extended right lobectomy (ERL) for living donor liver transplant (LDLT) is selectively performed in many transplant centers and has shown excellent recipient outcomes as reported in previous studies. Yet, there is no universally accepted indication for ERL in respect to donor safety. Current study was designed to stratify risk factors of adverse donor outcome after ERL.

**Methods:** A total of 79 living donors who underwent ERL for LDLT were included in analysis. Donors were classified as safety and hazard donor groups according to postoperative findings relevant to posthepatectomy liver failure classification by the International Study Group for Liver Surgery.

**Results:** On multivariable analysis, left lateral section volume < 20% of total liver volume and nonpreservation of segment 4a venous drainage were the independent risk factors impairing postoperative outcomes. Despite the short-term impairment of liver function in hazard donor groups, all donors recovered and showed satisfactory remnant liver regeneration. However, these findings have implications in establishing selection criteria of donors eligible for ERL donation.

**Conclusions:** In conclusion, LDLT using ERL graft can be safely performed provided so that left lateral section volume/total donor liver is ≥ 20% besides conventional donor selection criteria. Also, efforts to preserve segment 4a vein must be made in performing ERL graft procurement in LDLT donors.

**Keywords:** Liver transplantation, Extended right lobe, Donor safety

## OP-29

### Adult-to-Adult Right Lobe Graft Living Donor Liver Transplantation for Acute-on-Chronic Liver Failure: An Initial Single-Center Experience in Vietnam

Thang Tran Manh

Vin University, Vietnam

**Aims:** Liver transplants are considered a last resort for individuals with acute-on-chronic liver failure (ACLF), an illness with a very high mortality rate. Although liver transplants from deceased donors have been extensively researched for treating ACLF, little is known about the outcomes of liver transplants from living donors. This study aims to evaluate the outcomes of living donor liver transplantation (LDLT) on ACLF patients.

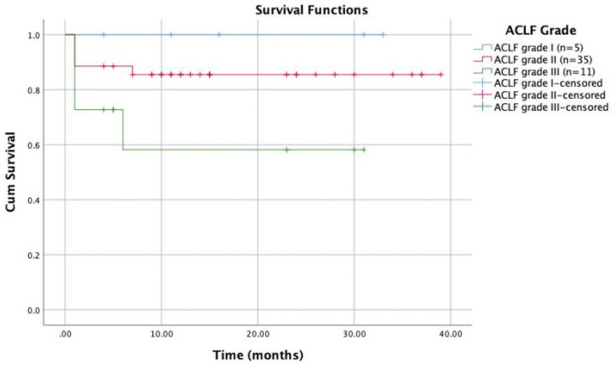
**Methods:** A retrospective study at the 108 Military Central Hospital of 51 patients with ACLF (based on APASL diagnostic criteria) who received treatment with LDLT from December 2019 to December 2022. We utilize the MELD and AARC scores to evaluate and stratify the severity of ACLF.

**Results:** The average age was 47.27±13.61 years, 88.24% of the patients were male, and the average BMI was 22.78±2.61. The most common cause of chronic liver disease is chronic viral hepatitis B (88.2%); the average MELD score is 34.90±5.61, with the majority having high MELD scores, MELD 30-39 accounts for 49.02%, MELD >=40 accounts for 33.33%. In terms

of ACLF severity, five patients had grade I ACLF, accounting for 9.8%; 35 patients had grade II ACLF, accounting for 68.6%; 11 patients had grade III ACLF, accounting for 21.6%, the average AARC score was 9.43±1.68. The most common postoperative complication is biliary complication (19.61%). The duration of treatment at the ICU was 8.59±7.27 days, and the hospital stay was 28.02±13.45 days. The hospital mortality rate was 7/51 (13.7%), and the survival rates at six months, one year, and three years were 84±5.2%, 81.7±5.5%, and 81.7%±5.5%, respectively.

**Conclusions:** Living donor liver transplantation (LDLT) is an effective treatment for the ACLF group of patients with a high post-transplant survival rate. Comprehensive care before, during, and after surgery, along with deciding the proper time to do LDLT plays an important role in saving the lives of ACLF patients.

**Keywords :** Acute on chronic liver failure, Living donor liver transplantation

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## 6. HCC, Basic 1

### OP-30

### Lipophilic Statin Increases Sensitivity for Lenvatinib by Suppressing YAP/TAZ in Hepatocellular Carcinoma Cell Lines and Patient-Derived Organoids

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**Aims:** Elevated expression of the transcription factors Yes-associated protein (YAP) and its paralogue, transcriptional co-activator with PDZ-binding motif (TAZ), contributes to drug resistance and adverse prognosis in patients with hepatocellular carcinoma (HCC). Recent studies have highlighted the potential of statin use in reducing the incidence of diverse cancers, potentially achieved through YAP/TAZ suppression via the mevalonate pathway inhibition *in vitro*. Accordingly, this study aimed to assess the effect of statins on YAP/TAZ inhibition in HCC cell lines and drug-resistant organoid models.

**Methods:** We established cell lines with increased YAP/TAZ expression and evaluated their sensitivity to lenvatinib, with or without the concurrent administration of lipophilic atorvastatin. Additionally, we cultured HCC organoids derived from patient tissues and selected those that exhibited elevated YAP/TAZ levels. Lenvatinib was administered along with varying atorvastatin doses to assess changes in lenvatinib sensitivity by analyzing half-maximal inhibitory concentration ($IC_{50}$) values.

**Results:** Hep3B and YAP-transfected SNU449 cells exhibited elevated $IC_{50}$ values for lenvatinib (9.14 and 16.93 $\mu$M, respectively), which reduced to 4.89 and 5.25 $\mu$M, respectively, with 2 $\mu$M atorvastatin co-administration. Among ten established HCC organoids, six with elevated YAP/TAZ expression displayed higher lenvatinib $IC_{50}$ values than their low-YAP/TAZ counterparts. Dose-dependent atorvastatin administration decreased lenvatinib $IC_{50}$ values in organoids. Co-administration of lenvatinib and atorvastatin suppressed the YAP/TAZ target genes, an effect that was not observed with lenvatinib alone. Lenvatinib inhibited cell proliferation and apoptosis in an organoid model with low YAP/TAZ expression, and co-administration of atorvastatin restored the inhibitory effect of lenvatinib on cell proliferation and apoptosis by suppressing YAP/TAZ expression in an organoid model with high YAP/TAZ expression.

**Conclusions:** Increased protein expression of YAP/TAZ in HCC cell lines and organoid models is correlated with lenvatinib resistance. Atorvastatin enhances the anticancer efficacy of lenvatinib by interfering with YAP/TAZ expression in HCC cell lines and organoids.

**Keywords:** Hepatocellular carcinoma, Organoid, Statin, YAP-TAZ

### OP-31

### Dynamic Peripheral T-Cell Analysis Identifies On-Treatment Prognostic Biomarkers of Atezolizumab plus Bevacizumab in Hepatocellular Carcinoma

Ji Won Han[1,2,3], Min Woo Kang[1,3], Jae-Sung Yoo[1,2], Hee Sun Cho[1,2], Eun Ji Jang[1,3], Soon Kyu Lee[1,4], Jung Hyun Kwon[1,4], Soon Woo Nam[1,4], Hyun Yang[1,5], Si Hyun Bae[1,5], Ji Hoon Kim[1,6], Jeong Won Jang[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2], Pil Soo Sung[1,2,3]

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**Aims:** Variability in response to atezolizumab plus bevacizumab (AB) treatment of hepatocellular carcinoma (HCC) underscores the critical need for the development of effective biomarkers. We sought to identify peripheral blood biomarkers reflecting response to AB treatment.

**Methods:** We analyzed dynamic changes in peripheral blood mononuclear cells from a prospective, multicenter cohort of 36 patients with HCC, using flow cytometry to evaluate the T-cell population before and 3 weeks after the first AB treatment.

**Results:** We found a unique response of the $CD8^+$ T cells in terms of both frequency and phenotype, in contrast to $CD4^+$ T cells and regulatory T cells. Notably, $CD8^+$ T cells showed significant changes in expression of Ki-67 and T-cell immunoreceptors with Ig and ITIM domains (TIGIT). These distinct responses were observed particularly in the programmed cell death receptor-1 $(PD\text{-}1)^+$ subpopulation of $CD8^+$ T cells. Interestingly, the baseline differentiation status of $PD\text{-}1^+CD8^+$ T cells, particularly the central memory T-cell subset, correlated positively with greater proliferation (higher Ki-67 expression) of $CD8^+$ T cells after treatment. Moreover, effector memory cells expressing CD45RA correlated negatively with the increase in $TIGIT^+/PD\text{-}1^+CD8^+$ T cells. Although not associated with the objective response or disease control rates, the dynamic increase in $TIGIT^+/CD8^+$ T cells was greater in patients who developed immune-related adverse events. Importantly, dynamic shifts in Ki-67- and TIGIT-positivity within $CD8^+$ T cells significantly predicted progression-free survival and overall survival, as confirmed by multivariate analysis.

**Conclusions:** These findings highlight the potential of dynamic changes in $CD8^+$ T cells as an on-treatment prognostic biomarker. Our study underscores the value of peripheral blood profiling as a noninvasive and practical method for predicting the clinical outcomes of AB treatment in patients with HCC.

**Keywords:** HCC, Atezolizumab and bevacizumab, T cell, Biomarker

## OP-32

### A Platinum Complex of 2-Benzoylpyridine Induce Mitochondria-Mediated Apoptosis via ROS-Dependent and p53-Independent Pathway in HepG2 Cells

**Yuntao Bao**, Guandou Yuan, Songqing He, Yu-Lan Li

Guangxi Key Laboratory of Immunology and Metabolism for Liver Diseases, Guangxi Medical University, Nanning, China

**Aims:** Liver cancer is now the major diseases that seriously endangering human lives and health. Liver cancer patients who have lost the opportunity for surgery, non-surgical treatment is extremely important. However, chemotherapy is an important treatment method. Cisplatin, as a first-line anticancer drug, has serious side effects. The search for new platinum drugs with higher activity towards liver cancer, less toxic side effects and no cross-resistance has been one of the hot spots of scientists. Therefore, the present study was the antitumor activity of the novel platinum complex of 2-benzoylpyridine (PtC, Figure 1).

**Methods:** The potential therapeutic effects of PtC toward HepG2 were investigated by MTT, western blot and flow cytometry.

**Results:** PtC has potent antitumor effects on HepG2, the $IC_{50}$ value is 2 $\mu$M, PtC caused significantly increase the expression of p53, cytochrome c, apaf-1 and activation of caspase-9 and caspase-3, while for Bcl-2 and Bcl-xL decreased the expression in the HepG2 cells (Figure 2). As shown in Figure 3, comparing with the control, the populations of early apoptosis were 15.00% treatment with PtC, which showed the significantly increase of the percentage of the apoptosis. While pretreatment of 5 mM NAC (an inhibitor of ROS) for 2 h significantly abolished the apoptosis of PtC, but pretreatment of 10 $\mu$M pifithrin-$\alpha$ (an inhibitor of p53 protein) for 2 h did not impair the apoptosis of PtC.

**Conclusions:** It is demonstrating that induction of apoptosis by PtC via ROS-dependent and p53-independent mitochondrial pathway in HepG2 cells.

**Keywords:** Platinum complex, Liver cancer, Antitumor, Apoptosis

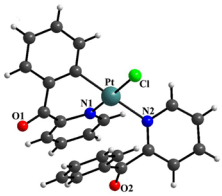


Figure 1. Crystal structure of PtC

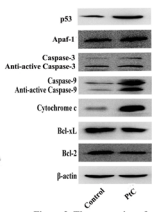


Figure 2. The expression of apoptosis related protein on HepG2 by PtC (2 μM) for 24 h.

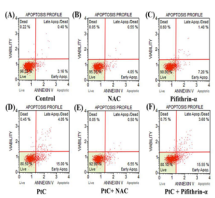


Figure 3. PtC (2 μM) induced cell apoptosis on HepG2 by flow cytometry.

## OP-33

### Circulating Small Extracellular Vesicle-Derived Splicing Factor 3B Subunit 4 as a Non-Invasive Diagnostic Biomarker of Early Hepatocellular Carcinoma

Ju A Son[1,2], Ji Hyang Weon[1,2], Geum Ok Baek[1], Hye Ri Ahn[1,2], Ji Yi Choi[1,2], Moon Gyeong Yoon[1], Hyo Jung Cho[1], Jae Youn Cheong[1], Jung Woo Eun[1], **Soon Sun Kim**[1]

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**Aims:** Hepatocellular carcinoma (HCC) accounts for a majority of primary liver cancer cases and related deaths. The purpose of this study was to assess the diagnostic value of splicing factor 3b subunit 4 (SF3B4) as a novel non-invasive biomarker for HCC and determine the association between SF3B4 expression and immune cell infiltration.

**Methods:** An enzyme-linked immunosorbent assay (ELISA) was used to detect SF3B4 levels in plasma samples obtained from healthy controls (HCs) and patients with chronic hepatitis, liver cirrhosis, and HCC. The expression levels of autoantibodies that detect SF3B4 in the plasma samples of each group of patients were measured. Small extracellular vesicles (EVs) were isolated from patient sera, and the expression levels of EV-SF3B4 were measured using quantitative reverse transcription PCR.

**Results:** ELISA results confirmed that the expression levels of SF3B4 proteins and autoantibodies in the plasma of patients with HCC were higher than those in HCs. However, their diagnostic performance was not better than that of alpha-fetoprotein (AFP). The mRNA expression of SF3B4 in serum EV increased but not in the buffy coat or serum of patients with HCC. Serum EV-SF3B4 displayed better diagnostic power than AFP for all stages of HCC (AUC=0.968 vs. 0.816), including early-stage HCC (AUC=0.960 vs. 0.842), and this was consistent in the external cohort. Single-cell RNA sequencing indicated that SF3B4 expression was correlated with myeloid-derived suppressor cells. The Tumor Immune Estimation Resource database reconfirmed the correlation between SF3B4 expression and immune cell infiltration in HCC.

**Conclusions:** SF3B4 may be associated with tumor immune infiltration in HCC, and EV-SF3B4 shows potential as a novel non-invasive diagnostic biomarker of HCC.

**Keywords:** Biomarker, Liquid biopsy, Liver neoplasms, Myeloid-derived suppressor cell

## OP-34

### Telomere Length and Liver Inflammation: Implications for Disease Progression and Hepatocarcinogenesis

Jung Eun Jang[2], Jin Seoub Kim[2], Hye Seon Kim[2], Jaemo Han[2], Jung Hyun Kwon[1], Ji Won Han[1], Pil Soo Sung[1], Si Hyun Bae[1], Jong Young Choi[1], Seung Kew Yoon[1], Jeong Won Jang[1]

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**Aims:** Telomere shortening has been implicated in the progression of chronic liver diseases, including cirrhosis, which can ultimately lead to hepatocellular carcinoma (HCC) development. However, the relationship between telomere maintenance, inflammation, and liver disease progression remains incompletely understood. This study aimed to investigate the association between telomere length and liver inflammation and subsequent disease progression.

**Methods:** A total of 126 non-tumor liver disease patients and 256 HCC patients were recruited for this study. Telomere length was assessed using quantitative real-time PCR, and inflammatory markers were measured via enzyme-linked immunosorbent assay (ELISA). Correlation analyses were performed to evaluate the relationship between telomere length and multiple cytokines and inflammatory indicators across various stages of liver disease progression and HCC.

**Results:** Telomere length in non-tumor liver tissues exhibited a significant decrease with increasing severity of fibrosis ($P$=0.022*) Furthermore, telomere length in non-cancerous liver tissues showed negative correlations with markers of liver injury, such as AST ($P$=0.015*) and ALT ($P$=0.041*), as well as various cytokine levels including IFN-$\alpha$ ($P$=0.142), IL-10($P$=0.190), IL-12($P$=0.073), and IL-2 ($P$=0.486). Additionally, HCC tissues demonstrated significantly shorter telomeres compared to their matched noncancerous liver tissues ($P$=0.033*).

**Conclusions:** These findings suggest that telomere shortening is associated with liver disease progression and may contribute to hepatocarcinogenesis. Furthermore, the observed correlations between telomere length and inflammatory markers highlight the potential interplay between telomere maintenance and liver inflammation in the pathogenesis of liver diseases, including HCC. Further investigation into these relationships may offer insights into potential therapeutic targets for the management of liver diseases and HCC.

**Keywords:** Telomere, HCC, Inflammation, Progression

Friday, June 28, 2024, 16:30-17:20

# 7. HCC, Clinical 1

## OP-35

### The Prognostic Effect of Regular Surveillance for Recurrence Following Curative Resection for Hepatocellular Carcinoma: A Large Multicentre Analysis

Lan-Qing Yao[1], Han Liu[2], Yong-Kang Diao[1], Yi-Fan Wu[3], Chao Li[2], Ying-Jian Liang[4], Yong-Yi Zeng[5], Ming-Da Wang[1], Guo-Yue Lv[2], Tian Yang[1]

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**Aims:** Surgical resection, the primary curative treatment for hepatocellular carcinoma (HCC), is often overshadowed by the significant risk of recurrence. This study aimed to evaluate the effect of adherence to regular recurrence surveillance on long-term prognosis among patients undergoing curative resection for HCC.

**Methods:** This multicentre observational study involved those patients undergoing curative-intent surgical resection for early-stage (BCLC stage 0/A) HCC. They were stratified into two groups: those with adherence to a protocol of regular surveillance (check-ups every 2-3 months for the first two years and every 6 months thereafter), and those without, i.e., receiving irregular/no recurrence surveillance. The overall survival (OS), time-to-recurrence (TTR), and post-recurrence survival (PRS) were compared between the two groups.

**Results:** Among 1,544 patients, 786 (50.9%) received regular surveillance for recurrence during follow-up. Compared to patients receiving irregular/no recurrence surveillance, patients receiving regular recurrence surveillance presented comparable TTR (median: 61.4 vs. 66.2 months, *P*=0.161) but better OS (median: 113.4 vs. 94.5 months, *P*=0.010), as well as better PRS among those patients who recurred (median: 37.9 vs. 16.3 months, *P*<0.001). Multivariable Cox-regression analyses revealed adherence to regular recurrence surveillance as an independent protective factor for enhanced OS (HR: 0.777; 95% CI: 0.663-0.910; *P*=0.002) and PRS (HR: 0.523; 95% CI: 0.428-0.638; *P*<0.001).

**Conclusions:** Adherence to regular recurrence surveillance significantly improved OS and PRS following surgical resection for HCC. It highlights the crucial role of adherence to regular recurrence surveillance in postoperative HCC management, offering a promising avenue to increase opportunities for subsequent curative treatments and improve long-term survival.

**Keywords:** Hepatocellular carcinoma, Curative resection, Prognostic

## OP-36

### Survival Comparison of Patients with BCLC Stage B Hepatocellular Carcinoma Initially Treated by Surgical Resection and TACE: A Nationwide Multicenter Study

**Yung Kil Kim**, Hyeyoung Kim, Sang Ho Bae, Hae Il Jung

Department of Surgery, Soon Chun Hyang University Cheonan Hospital, Republic of Korea

**Aims:** Although the recent evidence supporting the survival benefit of surgical resection is increasing, transarterial chemoembolization (TACE) is still recommended as the main standard treatment for Barcelona Clinic Liver Cancer B hepatocellular carcinoma (BCLC-B HCC). This study aims to compare the survival benefit of surgical resection and TACE.

**Methods:** The nationwide multicenter database of the Korean Liver Cancer Association was reviewed. Patients with BCLC-B HCC who underwent liver resection (LR) or TACE as a first treatment after initial diagnosis between 2008 and 2018 were selected randomly. Survival outcomes of propensity score matched groups (1:1) were compared.

**Results:** Among 1,596 randomly selected patients with BCLC-B HCC, 217 underwent LR as a first treatment while 978 underwent TACE. After propensity score matching, the two groups were well balanced (n=200, each). HCC-specific median survival in the LR group was better than in the TACE group (56.5 versus 33.0 months, *P*<0.001). The 1-, 2-, 3-, and 5-year HCC-specific survival in the LR group were 89.6%, 79.9%, 71.7%, and 62.6%, and 84.3%, 63.4%, 45.8%, and 30.1% in the TACE group, respectively (*P*<0.001). In multivariate analysis, PIVKA-II ≥ 100mAU/mL (hazard ratio (HR), 2.64; 95% confidence interval (CI, 1.76 to 3.94; *P*<0.001), TACE (HR, 2.28; 95% CI, 1.64 to 3.18; *P*<0.001), preoperative ascites (HR, 1.87; 95% CI, 1.14 to 3.05; *P*=0.013), and tumor number ≥ 4 (HR, 1.56; 95% CI, 1.09 to 2.24; *P*=0.016) were independent predictors for worse HCC-specific survival.

**Conclusions:** Surgical resection provide a significant survival benefit compared with TACE for potentially resectable the BCLC-B HCC.

## OP-37

### Korean Multicenter Prospective Observational Study on Efficacy of Y90 for HCC (KURE-YTT-HCC): Interim Results

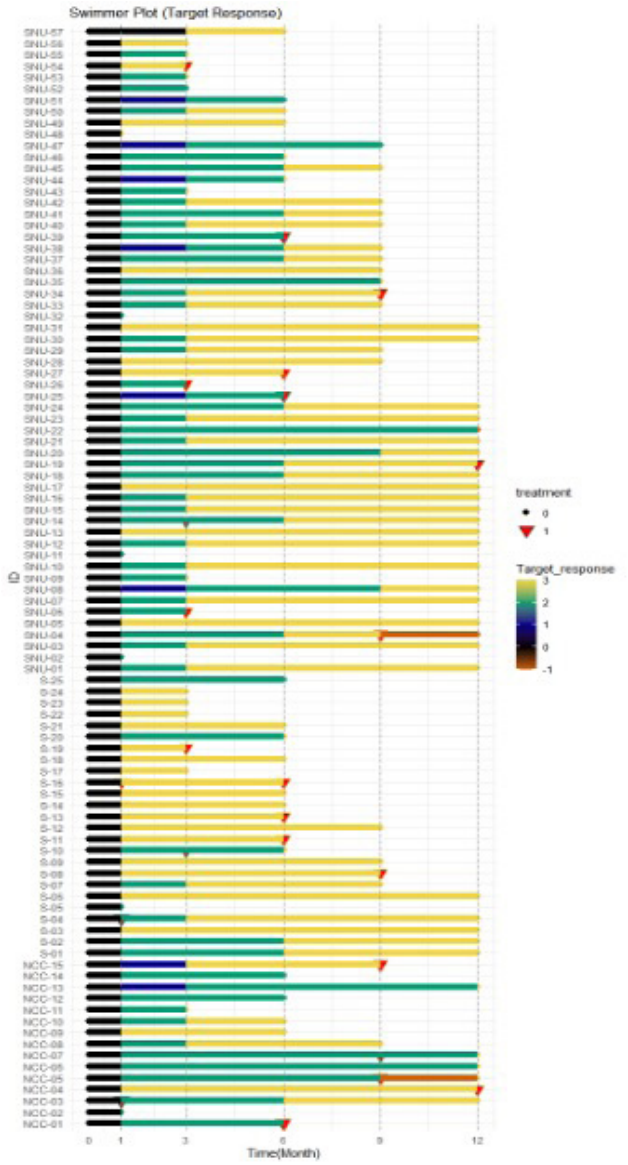
Yoon Jun Kim[1], Do Young Kim[2], Hyo Cheol Kim[3], Dong Hyun Sinn[4], **Dongho Hyun**[5], Yuri Cho[6], Korean Radioembolization Association (KOREA) group

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine; [2]Department of Internal Medicine, Severance Hospital; [3]Department of Radiology, Seoul National University Hospital; [4]Department of Internal Medicine, Samsung Medical Center; [5]Department of Radiology, Samsung Medical Center; [6]Center for Liver and Pancreatobiliary Cancer, Research Institute and Hospital, National Cancer Center

**Aims:** $^{90}$Y radioembolization for very early or early stages HCCs are supported by a retrospective LEGACY and a small prospective studies. To get it more generalized, the current study was planned, and haven been being performed from five Korean institutions (Seoul National University Hospital, Severance Hospital, Samsung Medical Center, and National Cancer Center in Korea) to evaluate best target lesion response, overall survival, time to target lesion progression, time to liver progression, and treatment-related adverse event.

**Methods:** A ninety-seven patient underwent $^{90}$Y glass microsphere radioembolization for very early- or early- stage HCC from January 2022 to May 2023 and followed up to 19 months (mean, 9 months). Mean age was 69.9 years±00 years (range, 40~87). Etiology of liver disease was HBV (59.8%), HCV (10.3%),

alcohol (7.2%), NAFLD (4.1%), and others (18.6%). Child Pugh score was 5 (87.6%) and 6 (12.4%). Median tumor size was 4.1 cm: < 3 cm (23.7%), 3-5 cm (46.4%), and 5-8 cm (29.9%). Mean lung shunt (available in 63 patients) was 3.4% and mean lung dose was 6.03 Gy. Mean absorbed dose was 482.6 Gy (range, 150 ~ 1958 Gy). Radioembolization was performed in a manner of radiation segmentectomy (85.6%), lobar approach (10.3%), and others (4.1%). Treatment response was assessed with mRECIST. Complications were evaluated using CTCAE.




**Results:** Initial objective response rate was 100%; complete response in 76.3% and partial response in 23.7%. Progression occurred in six patients, and conventional TACE, proton beam therapy, radioembolization was performed. Median overall survival did not achieve. Treatment-related adverse events (Grade ≥ 3) occurred in one patient with radioembolization induced liver disease. Asymptomatic bile duct dilatation occurred. Neither radiation pneumonitis nor mortality occurred.

**Conclusions:** $^{90}$Y glass microsphere radioembolization for early- or very early- stage HCC is effective and safety in HBV-related, intermediate size HCCs. Final outcomes of the current study seem to be promising.

**Keywords:** Radioembolization, Hepatocellular carcinoma

## OP-38

### Higher Risk of Proteinuria in Atezolizumab plus Bevacizumab Than Lenvatinib as a First-Line Systemic Treatment in Unresectable Hepatocellular Carcinoma

Jiwon Yang[1], Won-Mook Choi[1,*], Hyung-Don Kim[2], Jonggi Choi[1], Changhoon Yoo[2], Danbi Lee[1], Ju Hyun Shim[1], Kang Mo Kim[1], Young-Suk Lim[1], Han Chu Lee[1]

[1]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

**Aims:** Proteinuria presents a challenging complication during systemic therapy for hepatocellular carcinoma (HCC). This study aims to identify risk factors for proteinuria in patients with HCC treated with atezolizumab plus bevacizumab (Atezo/Bev) or lenvatinib (LEN) as first-line systemic treatment.

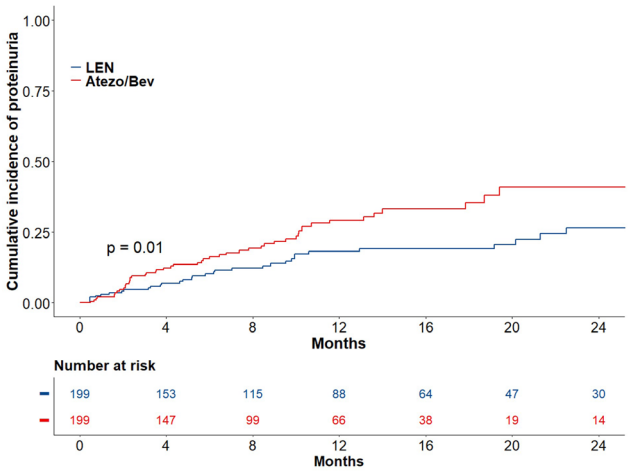
**Methods:** A retrospective analysis was conducted of 604 consecutive patients with unresectable HCC who received Atezo/Bev or LEN as first-line systemic treatment between October 2013 and October 2022. Cumulative incidence of proteinuria was estimated using Kaplan–Meier curves and compared using log-rank tests. Risk factors for proteinuria were identified using Cox proportional hazard models, along with propensity score-matched and subgroup analyses.

**Results:** Among 349 patients treated with Atezo/Bev and 255 with LEN, the cumulative incidence of proteinuria at 12 months was 25.4%. In the multivariable analysis, Atezo/Bev treatment (hazard ratio [HR], 1.73; 95% confidence interval [CI], 1.21–2.47; $P$=0.003), diabetes (HR, 1.52; 95% CI, 1.04–2.24; $P$=0.03), Child–Pugh class B (HR, 3.56; 95% CI, 1.46–8.72; $P$=0.01), macrovascular invasion (MVI; HR, 1.51; 95% CI, 1.06–2.14; $P$=0.02), and an estimated glomerular filtration rate ≤ 60 mL/min/1.73 m$^2$ (HR, 3.31; 95% CI, 2.02–5.41; $P$<0.001) were identified as risk factors for proteinuria. A higher risk of proteinuria in Atezo/Bev patients compared with LEN was consistently observed in the PS-matched cohort, particularly pronounced in subgroups with MVI (HR, 3.15; 95% CI, 1.52–6.52; $P$=0.002) compared with those without MVI (HR, 1.25; 95% CI, 0.73–2.15; $P$=0.42).

**Conclusions:** Patients treated with Atezo/Bev as first-line systemic treatment for HCC exhibited a higher risk of proteinuria

compared with those with LEN, particularly when accompanied by MVI.

**Keywords:** Liver cancer, Adverse events, Systemic treatment, Vascular endothelial growth factor




## OP-39

### Synergistic Effects of Transarterial Chemoembolization and Lenvatinib on HIF-1α Ubiquitination and Prognosis Improvement in Hepatocellular Carcinoma

**Sung Won Chung**, Jin Sun Kim, Won-Mook Choi, Jonggi Choi, Danbi Lee, Ju Hyun Shim, Young-Suk Lim, Han Chu Lee, Kang Mo Kim

Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

**Aims:** A recent trial has shown that adding transarterial chemoembolization (TACE) to lenvatinib therapy results in enhanced therapeutic efficacy in hepatocellular carcinoma (HCC). We aimed to assess the effectiveness of the lenvatinib and TACE combination in a real-world clinical context for managing HCC and to elucidate the molecular pathways involved.

**Methods:** This retrospective analysis included 199 patients who were diagnosed with hepatocellular carcinoma (HCC) and had intrahepatic lesions between 2018 and 2021. The cohort was divided into those who received lenvatinib plus transcatheter arterial chemoembolization (TACE) (n=62, combination group) and those who received lenvatinib monotherapy (n=137, monotherapy group). To further explore the underlying mechanisms, Huh-7 cells were exposed to lenvatinib or a vehicle for 48 hours under normoxic or hypoxic conditions.

**Results:** Propensity score-matched analysis revealed a significant improvement in both overall survival (adjusted hazard ratio [aHR] 0.38; 95% CI, 0.24–0.59; *P*<0.001) and progression-free survival (aHR 0.41; 95% CI, 0.26–0.64; *P*<0.001) in the combination group compared to the monotherapy group. In the laboratory experiments, under hypoxic conditions, lenvatinib notably attenuated hypoxia-inducible factor 1 alpha (HIF-1 $\alpha$) protein levels in Huh-7 cells without altering its mRNA levels. Intriguingly, lenvatinib facilitated the MDM2-mediated ubiquitination and subsequent degradation of HIF-1 $\alpha$. Additionally, cell viability assays confirmed a significant decrease in Huh-7 cell survival following lenvatinib treatment under hypoxic conditions.

**Conclusions:** The combination of lenvatinib and TACE was associated with significant survival benefits for patients with HCC. The mechanistic foundation appears to be the lenvatinib-triggered degradation of HIF-1 $\alpha$ via the MDM2-dependent ubiquitination pathway, highlighting a potential therapeutic target in HCC treatment.

**Keywords:** Liver cancer, Overall survival, Progress-free survival, Hypoxia

Friday, June 28, 2024, 16:30-17:30

# 8. HCC, Clinical 2

## OP-40

### SGLT2i Impact on HCC Incidence in Patients with Fatty Liver Disease and Diabetes: A Nation-Wide Cohort Study in South Korea

**Hyo Jung Cho**, Eunyoung Lee, Ji Eun Han, Soon Sun Kim, Jae Youn Cheong

Department of Gastroenterology, Ajou University School of Medicine, Suwon, South Korea

**Aims:** This study evaluated the effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on cancer development, particularly in hepatocellular carcinoma (HCC), in individuals with concomitant fatty liver disease (FLD) and type 2 diabetes mellitus (T2DM).

**Methods:** Using data from Korea's Health Insurance Review and Assessment Service, we performed Kaplan-Meier and Cox regression analyses in patients with non-alcoholic fatty liver disease (NAFLD) and T2DM (NAFLD-T2DM cohort) and those with chronic viral hepatitis (CVH) alongside FLD and T2DM (FLD-T2DM-CVH cohort).

**Results:** In the propensity score (PS) matched NAFLD-T2DM cohort (N=107,972), SGLT2i use was not significantly associated with the occurrence of overall cancer, including HCC. However, old age, male sex, liver cirrhosis, and hypothyroidism were identified as independent risk factors for HCC occurrence, whereas statin and fibrate usage were associated with reduced HCC risk in this cohort in multivariate Cox regression

analysis. In the PS-matched FLD-T2DM-CVH cohort (N=2,798), a significant decrease in HCC occurrence was observed among SGLT2i users in the Kaplan-Meier analysis (*P*=0.03). This finding remained consistent even after adjusting for various variables using the multivariate Cox regression analysis. (Hazard ratio=2.21, 95% confidence interval=1.01-4.85, *P*=0.048)

**Conclusions:** The study suggested that SGLT2i may be a beneficial option for diabetes management in patients with concomitant T2DM, FLD, and CVH while affirming the overall safety of SGLT2i in other types of cancer.

**Keywords:** Hepatocellular carcinoma, Sodium-glucose cotransporter-2 inhibitors, Fatty liver, Type 2 diabetes mellitus

## OP-41

### To Combine Local or Systemic Therapy? That Is the Question in HCC with MVI

Hyunki Park[1], Jeong Il Yu[1], Hee Chul Park[1], Myung Ji Goh[2], Wonseok Kang[2], Geum-Youn Gwak[2], Yong-Han Paik[2], Joon Hyeok Lee[2], Kwang Cheol Koh[2], Seung Woon Paik[2], Dong Hyun Sinn[2], Moon Seok Choi[2], Jung Yong Hong[2], Ho Yeong Lim[2], Sung Wook Shin[3], Sung Ki Cho[3], Dongho Hyun[3]

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**Aims:** Systemic therapy is the standard treatment for hepatocellular carcinoma (HCC) with macroscopic vascular invasion (MVI). This study was aimed to evaluate the efficacy and safety of tyrosine kinase inhibitor (TKI) plus liver directed external beam radiotherapy (RT) compared with transarterial chemoembolization (TACE) plus RT as a first-line treatment for HCC patients with MVI using subclassification model.

**Methods:** A total of 506 patients who received TKI plus RT (n=68) or TACE plus RT (n=438) for HCC with MVI as a first-line treatment between January 2005 and December 2018 were analyzed. Patients were classified into low and high risk groups by using subclassification system. Classification was done by system proposed in 2019 by Kim et al., assigning points to Child-Pugh class, extrahepatic metastasis, tumor type (nodular or infiltrative), and PVI. The overall survival (OS), progression free survival (PFS) and pattern of failure were compared between the treatment groups according to the subclassification.

**Results:** Patients were classified into two risk groups: low (n=306, 60.2%) and high (n=200, 39.8%). The median PFS and OS for low risk group patients were 6.8 (range, 0.6 to 126.6) and 17.5 months (range, 1.1 to 153.1), 3.1 (range, 0.3 to 122.1) and 7 months (range, 0.8 to 134.4) for high risk group patients. In the low risk group, 162 (52.9%) intrahepatic progression and 42 (13.7%) extrahepatic progression was observed. In the high risk group 104 (52.0%) intrahepatic progression and 108 (54.0%) extrahepatic progression was observed. In terms of local progression 44 (14.4%) in low risk group and 25 (12.5%) in high risk group were observed. Intrahepatic progression was the most common patterns of progression, but in high risk group, extrahepatic progression was more common (*P*<0.001). Patients treated with TACE plus RT showed significantly better local and extrahepatic PFS in low risk group (1-, 5-year local PFS: 88.8%, 83.4 vs. 80.3%, 61.8%, *P*=0.046) and 1-,5-year extrahepatic PFS: 92.0%, 820.% vs. 51.9%, 51.9%, *P*<0.001). However, in high risk group, patients treated with TKI plus RT showed better intrahepatic and extrahepatic PFS (1-,5-year intrahepatic PFS: 36.5%, 34.8 vs. 61.0%, 61.0%, *P*=0.006 and 1-,5-year extrahepatic PFS: 39.8%, 13.0% vs. 50.0%, 50.0%, *P*=0.133).

**Conclusions:** TACE plus RT showed excellent local tumor control, but in the high risk group, TKI plus RT showed better PFS. Combining systemic therapy may be considered as a first-line treatment option for high risk group patients.

**Keywords:** HCC, MVI, Local therapy, Radiotherapy

## OP-42

### Beneficial Effect of Combined Radiation Therapy in Atezolizumab plus Bevacizumab Treatment of Hepatocellular Carcinoma Patients with Main Portal Vein tumor Thrombosis

Sangyoun Hwang[1], Hyun Young Woo[2], Jeong Heo[2], Hyung Jun Kim[1], Young Joo Park[2], Kiyoun Yi[2], Yu Rim Lee[3], Soo Young Park[4], Woo Jin Chung[5], Byoung Kuk Jang[5], Won Young Tak[4]

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**Aims:** Atezolizumab (ATE) plus bevacizumab (BEV) was established as the firstline therapy for patients with advanced hepatocellular carcinoma (HCC) through phase 3 clinical trial. However, survival is still poor in HCC patients with main portal vein tumor thrombosis.

**Methods:** This is a multicenter retrospective study. Between January 2020 to June 2022, 215 patients treated for advanced HCC with at ATE+BEV from four tertiary hospital was analyzed. Among them, 70 patients had vp4 portal vein tumor thrombosis. Tumor response was evaluated with the Response Evaluation Criteria in Solid Tumors (version 1.1.).

**Results:** Among 70 patients with Vp4 portal vein tumor thrombosis, Child-Pugh class was A in 57 (81.5%) and B in 13 (18.5%). 45 (64.3%) received neoadjuvant or concomitant radiation treatment. Baseline characteristics did not differ significantly with or without radiation. In overall, objective response rate was 24.3%. disease control rate was 75.7%. The median progression free survival (PFS) was 7.75 months (95% CI, 5.71-9.79) and median overall survival (OS) was 9.25 months (95% CI, 7.76-10.74). In multivariate analysis, bile duct invasion, preemptive or concomitant radiation therapy and Hb level was significant prognostic factor for survival and progression free survival. Median OS was 10 months (95% CI, 7.85-12.15) in patients with radiation and 7.75 months (95% CI, 3.47-12.03) in patients without radiation. Median PFS was 9.25 months (95% CI, 7.91-10.59) in patients with radiation and 5.00 months (95% CI, 2.23-7.77) in patients without radiation. A total of 58 (82.9%) patients experienced any grade of adverse events (AEs). The most common AEs was proteinuria (14.8%). The rate of grade 3 or higher AE is similar in patients with or without radiation (18.2% vs. 16.7%).

**Conclusions:** ATE+BEV treatment was tolerable in patients with Vp4 portal vein tumor thrombus. Furthermore, radiation therapy could improve the OS and PFS in these patients.

**Keywords:** Atezolizumab, Bevacizumab, Hepatocellular carcinoma, Radiation therapy

## OP-43

### A Risk Prediction Model for Hepatocellular Carcinoma in General Population without Traditional Risk Factors for Liver Disease

Byeong Geun Song[1], Go Eun Park[2], Aryoung Kim[1], Myung Ji Goh[1], Wonseok Kang[1], Geum-Youn Gwak[1], Yong-Han Paik[1], Moon Seok Choi[1], Joon Hyeok Lee[1], Dong Hyun Sinn[1]

[1]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [2]Samsung Advanced Institute for Health Science and Technology, Sunkyunkwan University, Seoul

**Aims:** The available hepatocellular carcinoma (HCC) prediction model for general population without risk factors for chronic liver disease is limited. In this study, we aimed to develop HCC prediction model for individuals without traditional risk factors for HCC.

**Methods:** The total of 138,452 adult participants without chronic viral hepatitis or significant alcohol intake who underwent regular health checkup at a tertiary hospital in South Korea were followed up for the development of HCC. Risk factors for HCC development were analyzed using Cox regression analysis and prediction model was developed using the risk factors.

**Results:** We developed the HCC prediction model among general population without risk factors for chronic liver disease. The predictors were age, sex, body mass index, the presence of type 2 diabetes mellitus, aspartate aminotransferase, alanine aminotransferase, total cholesterol, and platelet count. The Harrell's C-index and Heagerty's integrated area under the receiver operating characteristics (AUROC) curve of the model were 0.88 (95% confidence interval [CI] 0.85-0.91) and 0.89 (95% CI 0.86-0.91), respectively. The AUROC were 0.89 (95% CI 0.88-0.89) at 5 years and 0.87 (95% CI 0.87-0.88) at 10 years, and the model was well calibrated.

**Conclusions:** The new model using clinical parameters is a useful tool for clinicians to stratify HCC risk in general population without risk factors for chronic liver disease.

**Keywords:** Hepatocellular carcinoma, Risk factor, Liver disease

## OP-44

### Temporal Trends and Long-Term Outcomes of Radiofrequency Ablation for Hepatocellular Carcinoma within the Milan Criteria

Se Young Jang[1], Soo Young Park[1], Young Oh Kweon[1], Yu Rim Lee[1], Hun Kyu Ryeom[2], Jung Guen Cha[2], Sungmin Kim[3], Won Kee Lee[4], Won Young Tak[1]

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**Aims:** No study has analysed the temporal trends of the long-term results and clinical characteristics of patients with hepatocellular carcinoma (HCC) treated using radiofrequency ablation (RFA). Therefore, we examined temporal trends of characteristics of patients and treatment-naïve HCCs within the Milan criteria treated by RFA for 20 years.

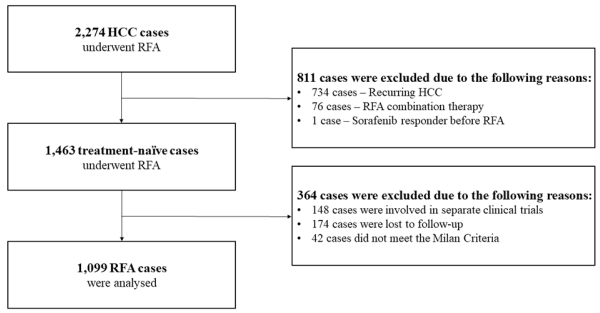
**Methods:** We retrospectively analysed 1,099 patients with HCC within the Milan criteria treated with percutaneous RFA from January 2000 to December 2019. The overall survival (OS), recurrence-free survival (RFS), and factors affecting survival and local tumor progression were analysed using the Kaplan–Meier method and Cox proportional hazards model. A trend test was performed to analyse the changing trends in participants and treatment outcomes.

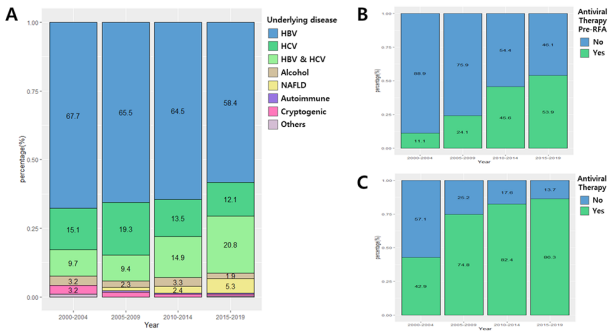
**Results:** The overall and RFS of patients improved during the later period. In addition, viral hepatitis-related HCC incidence decreased, whereas that of alcohol- or non-alcoholic fatty liver disease-related HCC increased from the earlier to the later period ($P$ for trend < 0.001). HBV antiviral therapy was increased and improved OS and RFS in patients treated using RFA.

**Conclusions:** The outcomes after RFA over a 20-year period

improved due to changes over time in target tumors and patients. The results could be useful for selecting patients who will benefit from RFA.

**Keywords:** Radiofrequency ablation, Hepatocellular carcinoma, Hepatitis B virus, Survival




## OP-45

## A Machine Learning Algorithm Facilitates Prognosis Prediction and Treatment Selection for Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma

Ji Won Han[1,2], Soon Kyu Lee[1,3], Jung Hyun Kwon[1,3], Soon Woo Nam[1,3], Hyun Yang[1,4], Si Hyun Bae[1,4], Ji Hoon Kim[1,5], Heechul Nam[1,5], Chang Wook Kim[1,5], Hae Lim Lee[1,6], Hee Yeon Kim[1,6], Sung Won Lee[1,6], Ahlim Lee[1,7], U Im Chang[1,7], Do Seon Song[1,7], Seok-Hwan Kim[1,8], Myeong Jun Song[1,8], Pil Soo Sung[1,2], Jong Young Choi[1,2], Seung Kew Yoon[1,2,9], Jeong Won Jang[1,2*]

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**Aims:** Given its heterogeneity and diverse clinical outcomes, precise subclassification of BCLC-C hepatocellular carcinoma (HCC) is required for appropriately determining patient prognosis and selecting treatment.

**Methods:** We recruited 2,626 patients with BCLC-C stage HCC from multiple centers, comprising training/test (n=1,693) and validation cohorts (n=933). The XGBoost was chosen for maximum performance among the machine learning (ML) models. Patients were categorized into low-/intermediate-/high-/very high-risk subgroups which were based on the estimated prognosis, and this subclassification was named the CLAssification via Machine learning of BCLC-C (CLAM-C).

**Results:** The areas under the receiver operating characteristic curve of the CLAM-C for predicting the 6-/12-/24-month survival of patients with BCLC-C were 0.800/0.831/0.715, respectively—significantly higher than those of the conventional models, which was consistent in the validation cohort. The four subgroups had significantly different median overall survivals, and this difference was maintained among various patient subgroups and treatment modalities. Immune-checkpoint inhibitors and transarterial therapies were associated with significantly better survival than tyrosine kinase inhibitors (TKIs) in the low- and intermediate-risk subgroups. In cases with first-line systemic therapy, the CLAM-C identified atezolizumab-bevacizumab as the best therapy particularly in the high-risk group. In cases with later-line systemic therapy, nivolumab had better survival than TKIs in the low-to-intermediate-risk subgroup, whereas TKIs had better survival in the high-to-very high-risk subgroup.

**Conclusions:** ML modeling effectively subclassified patients with BCLC-C HCC, potentially aiding treatment allocation. Our study underscores the potential utilization of ML modeling in terms of prognostication and treatment allocation in patients with BCLC-C HCC.

**Keywords:** Machine learning, Subclassification, Barcelona clinic liver cancer stage C, Hepatocellular carcinoma

Friday, June 28, 2024, 16:30-17:20

## 9. Surgery, Technical Issues

### OP-46

### Indocyanine Green Fluorescence Navigation in Laparoscopic Hepatobiliary Surgery from Cholecystectomy to Living Donor Right Hepatectomy: A Retrospective Single-Center Study in Vietnam

Thanh Le Van[1], Quang Vu Van[1], Hieu Le Trung[1], Anh Nguyen Hoang Ngoc[1], Thang Tran Manh[2]

[1]Department of Hepatobiliary And Pancreatic Surgery, Military Central Hospital, Vietnam, [2]Surgical Resident Program, Vin University, Vietnam

**Aims:** Indocyanine green (ICG) is a fluorescent dye that has been extensively employed for fluorescence imaging in the context of hepatobiliary surgery. Indocyanine green (ICG) is administered via intravenous injection, thereafter exhibiting preferential hepatic uptake, and ultimately being excreted into the bile. The catabolic and fluorescent characteristics of indocyanine green (ICG) enable the utilisation of various visualisation techniques in the field of hepatobiliary surgery.

**Methods:** In this study, we utilised indocyanine green (ICG) as a contrast agent in laparoscopic cholecystectomy, hepatectomy for hepatocellular cancer, and living donor hepatectomy procedures. The applications of indocyanine green (ICG) in hepatobiliary surgery have been classified into two categories: 1) liver mapping in hepatectomy for HCC and 2) cholangiography in cholecystectomy and living donor hepatectomy. This is a cross-sectional study of patients from May 2021 to December 2023 in 108 Military Central Hospital.

**Results:** There were 68 patients who underwent LC and 28 living right liver donors using ICG fluorescence for bile duct visualization and 58 HCC hepatectomies for liver mapping. The administration of ICG has demonstrated good visualisation through brilliant green fluorescence in various situations, hence facilitating its use in surgical procedures.

**Conclusions:** The utilisation of intra-operative indocyanine green (ICG) fluorescence imaging is a secure, straightforward, and viable approach that enhances the visualisation of both hepatobiliary anatomy and liver tumours from cholecystectomy to living donor right hepatectomy.

**Keywords:** Indocyanine green fluorescence navigation, Laparoscopic hepatobiliary surgery

### OP-47

### Outcomes of Laparoscopic Choledochotomy Using Cholangioscopy via Percutaneous-Choledochal Tube for Treatment of Hepatolithiasis and Choledocholithiasis: A Preliminary Vietnamese Study

Quang Vu Van[1], Thanh Le Van[1], Hieu Le Trung[1], Anh Nguyen Hoang Ngoc[1], Thang Tran Manh[2], Loi Le Van[1]

[1]Department of HBP Surgery And Liver Transplant, 108 Military Central Hospital, VIETNAM, [2]Department of Surgery, Vin University, VIETNAM

**Aims:** Hepatolithiasis and choledocholithiasis are frequent pathologies; unfortunately, current strategies have high recurrence incidence. This study aimed to assess the outcomes of laparoscopic choledochotomy using cholangioscopy via the percutaneous-choledochal tube for treating hepatolithiasis and choledocholithiasis in Vietnamese patients.

**Methods:** A cross-sectional study of patients with hepatolithiasis and/or choledocholithiasis who underwent laparoscopic choledochotomy using intraoperative cholangioscopy via percutaneous-choledochal tube at Departments of Hepatopancreatobiliary Surgery, 108 Military Central Hospital, from June 2017 to March 2020.

**Results:** A total of 84 patients were analyzed. Most patients were females (56%) with a median age of 55.56. 41.8% of patients had previous abdominal operations, with 33.4% having choledochotomy. All patients underwent successful laparoscopic common bile duct exploration followed by T-tube drainage without needing to convert to open surgery. Most patients (64.3%) have both intrahepatic and extrahepatic stones. Regarding stones' size, the rate of stones ≥ 10mm in diameter was 64.3%. Biliary strictures were observed in 19.1% of patients during cholangioscopy. Complete removal of stones was achieved in 54.8% of patients. The intraoperative complications were encountered in two patients, but no need to change the strategy. The mean operating time was 121.85 ± 30.47 minutes. The early postoperative complication rate was 9.6%, all managed conservatively. The residual stones were removed through the T-tube tract by subsequent choledochoscopy in 34/38 patients, so the total success rate was 95.2%.

**Conclusions:** Laparoscopic choledochotomy combined with cholangioscopy through the percutaneous-choledochal tube was a safe and effective strategy for hepatolithiasis and/or choledocholithiasis, even in patients with previous choledochotomy.

**Keywords:** Laparoscopic choledochotomy, Hepatolithiasis and Choledocholithiasis

## OP-48

### Laparoscopic Liver Resection in Fledgling Medical Center with Novice Surgeon: Comparison with Open Resection

Seoung Yoon Rho, Munseok Choi

Surgery, Yongin Severance Hospital, Republic of Korea

**Aims:** Laparoscopic liver resection is still challenging surgery for novice liver surgeon. Many studies reported minimum require number for overcoming learniing curve of LLS as from 20 to 60 cases. We investigated 2nd generation laparoscopic novice liver surgeon in fledgling medical center.

**Methods:** From Mar 2020 to December 2023, total 149 patients underwent liver resection . Among them, 66 patients received laparoscopic liver resection. We compared perioperative outcomes between laparoscopic and open liver resection groups.

**Results:** In laparoscopic resection groups, extent of resection as segmentectomy and morethan 2 segmentectomy were 33.4% . However, in open resection group, more than 2 segmentectomy extent was 56.6%. There were no significant differences in terms of sex, age, BMI between two groups. Laparoscopic liver resection group showed significant shorter length of hospital stay days (9.3±3.4 vs. 14.1±6.8, *P*=0.004 ) and lower estimated blood loss than open resection group (498.2±680.8 vs. 939.2± 559.0, *P*=0.025) Tumor size in laparoscopic resection group was significantly smaller than open resectio group (1.9±1.5 vs. 3.8 ±2.2, *P*=0.008). In comparison of posteropative complications, there were no siginificant differences betwee two groups.

**Conclusions:** The initial outcomes of laparoscopic liver resection in the fledgling center is mainly resection in minor areas, however there is no significant difference from the open group in terms of perioperative outcome, so it should be attempted actively.

**Keywords:** Laparoscopy, Liver resection

## OP-49

### Learning Curves for Laparoscopic Hepatectomy According to Iwate Difficulty Score Using CUSUM Analysis

Sehyeon Yu, Hye-Sung Jo, Young-Dong Yu, Yoo Jin Choi, Dong-Sik Kim

Korea University College of Medicine, Department of Liver Transplantation And Hepatobiliary Surgery, Korea University Anam Hospita, Republic of Korea

**Aims:** In the era of minimally invasive surgery, it is important to know the learning curve associated with performing a safe and skillful laparoscopic hepatectomy. This study evaluated the learning curve of laparoscopic hepatectomy performed by one surgeon according to Iwate criteria.

**Methods:** Laparoscopic hepatectomy cases were listed in order of operation date from 2009 to 2023. Patients were classified into three groups according to Iwate score (Low[LOW, 0-3], Intermediate[INT, 4-6], and Advanced to Expert[ADV-EXP, 7-12]). Finally, Cusum analysis was performed on the operation time in each group.

**Results:** Of the total 349 cases, there were 97 cases in the LOW group showing the learning curve on the 9th-17th case. In the INT group, there were 134 cases and the learning curve was on the 13th-34th case. In the ADV-EXP group, the learning curve appeared between the 16th and 32nd out of 118 cases. There were 6 cases of unexpected open conversion. Three of those cases were in the INT group and the others were in the ADV-EXP group performed on the initial period or learning phase.

**Conclusions:** The learning curve for laparoscopic hepatectomy according to Iwate difficulty score using Cusum analysis appeared shorter in the LOW group, and was similar in the INT group and ADV-EXP group. Since the cases of ADV-EXP group were not performed very early, it seems that previous experience was reflected to the proficiency in the ADV-EXP group which has similar learning phase to the INT group.

**Keywords:** Laparoscopy, Hepatectomy

## OP-50

### Disposable Bipolar Irrigated Sealer (Aquamantys®) Should Be Used with Caution during Liver Resection

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Surgery, Keimyung University Dongsan Medical Center, Republic of Korea

**Aims:** The disposable bipolar sealer combined radiofrequency (RF) energy and saline (Aquamantys®) has been used to reduce perioperative bleeding during liver resection, especially for cut-surface management. Herein, we analyzed the frequency of cut-surface complications such as bleeding, bile leakage and abscess before and after using the disposable bipolar irrigated sealer.

**Methods:** From Jan 2021 to Oct 2023, 177 patients underwent liver resection by single surgeon. Among these patients, 168 patients who underwent liver resection without biliary reconstruction were included in this study. The patients were categorized into 2 groups according to the era of Aquamantys® use (group1: no use of Aquamantys®, group 2: use of Aquamantys®). The surgical outcomes including cut-surface complications were compared between groups.

**Results:** During study period, overall cut-surface complications occurred in 20 patients (11.9%). Bile leakage and cut-surface abscess occurred in 9.5 and 4.8 % patients, respectively. In comparison between groups, group 2 had a higher rate of cut-surface complications (28.9 vs 5.7 %, *P*<0.001). Incidence

rates of bile leakage and cut-surface abscess were significantly higher in Group 2 (bile leakage, 26.7 vs 3.3 %, *P*<0.001; cut-surface abscess, 11.1 vs 2.4 %, *P*=0.019). Although there was no statistical significance, incidence rate of delayed bile leakage was higher in group 2 (50 vs 25 %, *P*=0.383).

**Conclusions:** Aquamantys® is effective in reducing perioperative bleeding during liver resection but might be associated with an increased rate of cut-surface complications. It should be used with caution during cut-surface management during liver surgery.

**Keywords:** Aquamantys, Bipolar irrigated Sealer, Liver resection

Friday, June 28, 2024, 16:30-17:30

## 10. Autoimmune Disease

### OP-51

### AMPK Activation and Hepatoprotective Effects of 1,5-Benzothiazepine Derivatives in Autoimmune Hepatitis: Docking and ADMET Analysis

Rizki Rachmad Saputra[1], Dwi Hermayantiningsih[1], Raiyan Fairozi[2], Muhammad Priyadi[3]

[1]Department of Chemistry, Universitas Palangka Raya, [2]Department of Polyclinic, Education Quality Assurance of Central Kalimantan, [3]Department of Pharmacy, Universitas Palangka Raya

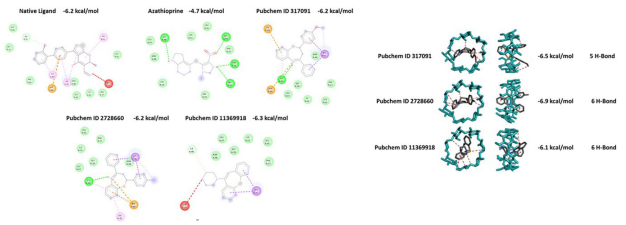
**Aims:** Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease characterized by immune-mediated destruction of hepatocytes. The AMP-activated protein kinase (AMPK) signaling pathway plays a crucial role in regulating hepatic energy metabolism and inflammation. This study delves into the therapeutic potential of 1,5-benzothiazepine derivatives and their inclusion complex with □-cyclodextrin (CD) as AMPK activators for the treatment of AIH using a combined molecular docking and ADMET (absorption, distribution, metabolism, excretion, and toxicity) approach.

**Methods:** Virtual screening of 1,5 benzothiazepine derivatives (10 compounds) and 2 reference compounds were performed using molecular docking simulations toward the AMPK protein (5EZV). The top-ranked hits were further evaluated for their ADMET properties using SwissADME and pkCSM server. In order to maximize targeted distribution, further research concentrated on creating CD inclusion complexes between certain 1,5 benzothiazepine derivatives and carrier molecules. This was done in an effort to increase stability and bioavailability.

**Results:** The compounds with the highest binding affinities were 4 (Pubchem ID 317091), 7 (Pubchem ID 2728660), and 10 (Pubchem ID 11369918), which showed -6.2, -6.2, and -6.3 kcal/mol, respectively. These affinities were superior to Azathioprine's (-4.7 kcal/mol) and very near to the native ligand's (-6.2 kcal/mol). Comparing the native ligand to the AMPK active site, the binding similarity ranged from 64 to 71%. The chosen compound showed better ADMET characteristics. Through CD inclusion complex techniques, intriguing candidates with strong AMPK activator activities, good pharmacokinetics, and increased stability were identified.

**Conclusions:** This study identified novel 1,5 benzothiazepine derivatives with the potential to activate AMPK and act as therapeutic agents for AIH. The combined in silico and ADMET approach provides valuable insights into the drug discovery process for AIH, paving the way for further preclinical and clinical investigations.

**Keywords:** Autoimmune hepatitis, Ampk activators, 1,5-benzothiazepine derivatives, Molecular docking




| Molecules/Pubchem ID | 317091 | 2728660 | 11369918 |
|---|---|---|---|
| ***GENERAL PROPERTIES*** | | | |
| MW | 345.47 | 329.47 | 296.42 |
| #H-bond acceptors | 3 | 2 | 3 |
| #H-bond donors | 0 | 0 | 1 |
| ***LIPOPHILICITY*** | | | |
| Consensus Log P | 6.05 | 6.35 | 2.10 |
| ***WATER SOLUBILITY*** | | | |
| Log solubility (log mol/L) | -6.723 | -6.96 | -3.467 |
| ***PHARMACOKINETICS*** | | | |
| BBB Permeability (log BB) | 0.43 | 0.684 | 0.323 |
| CYP1A2 inhibitor | Yes | Yes | Yes |
| Intestinal Absorption (Human) (% Absorbed) | 95.708 | 94.31 | 97.091 |
| Total Clearance (log ml/min/kg) | 0.245 | 0.155 | 0.825 |
| ***DRUGLIKENESS*** | | | |
| Lipinski #violations | 1 | 1 | 0 |
| Bioavailability Score | 0.55 | 0.55 | 0.55 |
| ***MEDICINAL CHEMISTRY*** | | | |
| Leadlikeness #violations | 1 | 1 | 0 |
| Synthetic Accessibility | 4.07 | 4.14 | 3.43 |
| ***TOXICITY*** | | | |
| Oral Rat Acute Toxicity (LD50) (mol/kg) | 2.689 | 2.425 | 2.723 |

Figure 1. a) 2D Binding Interaction Ligand - Receptor Protein, b) 3D Binding Interaction Ligand - β-cyclodextrin, and c) ADMET Properties

### OP-52

### TNF α 308 G/A Gene Polymorphism with Risk of Autoimmune Liver Disease: An Updated Meta-Analysis

Jin Hee Cha[1], Ardeno Kristianto[2], Franzeska Madeline Chandra[3]

Department of Internal Medicine, St. Carolus Hospital, Indonesia

**Aims:** Autoimmune liver disease (ALD) is a persistent liver inflammation of unknown etiology, with several proinflammatory cytokines thought to play a role in its development. It is believed to have an autoimmune basis in its development, likely involving a complex interplay of genetic and environmental

factors. Tumor necrosis factor alpha (TNF a) is a crucial cytokine with diverse biological effects, mainly involved in enhancing an intense inflammatory reaction. Numerous studies have attempted to investigate the potential association between TNF a gene polymorphisms and ALD; however, the published results have been indeterminate. Therefore, this study aimed to explore the relationship between susceptibility to autoimmune liver disease and the TNF a 308 G/A gene polymorphisms.

**Methods:** This Meta-analysis was in accordance with the PRISMA guidelines. The literature was taken from Pubmed and Google Scholar, with May 2018 as the latest edition that was computed, and it is limited to English only. Total 7 studies were included in this review. A Review Manager 5.4 was utilized to analyze the data.

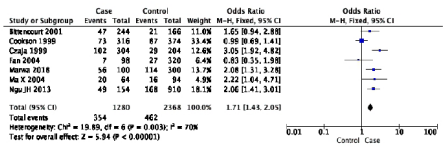



**Fig 1.** Forest plot of association between TNF a 308 G/A and Autoimmune Liver Disease A vs G

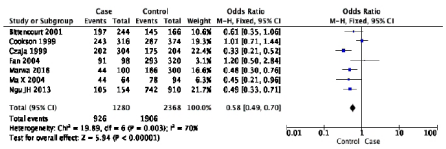



**Fig 2.** Forest plot of association between TNF a 308 G/A and Autoimmune Liver Disease G vs A

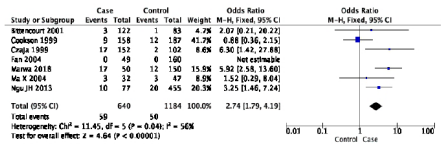



**Fig 3.** Forest plot of association between TNF a 308 G/A and Autoimmune Liver Disease AA vs AG + GG

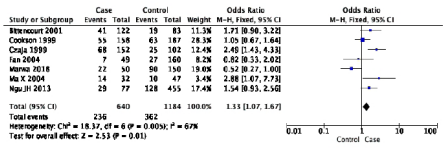



**Fig 4.** Forest plot of association between TNF a 308 G/A and Autoimmune Liver Disease AG vs AA + GG

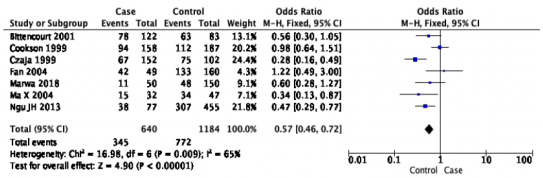



**Fig 5.** Forest plot of association between TNF a 308 G/A and Autoimmune Liver Disease GG vs AA + AG

**Results:** 7 studies were incorporated. From the analysis, TNF a 308 G/A gene polymorphisms was associated with an increased risk of autoimmune liver disease (A vs G, OR 95%CI=1.71 [1.43-2.05] *P*<0.00001; AA vs AG + GG, OR 95%CI=2.74 [1.79-4.19] *P*<0.00001; AG vs AA + GG, OR 95%CI=1.33 [1.07-1.67] *P*=0.01) and a decreased risk of autoimmune liver disease (G vs A, OR 95%CI=0.58 [0.49-0.70] *P*<0.00001; GG vs AA + AG, OR 95% CI=0.57 [0.46-0.72] *P*<0.00001)

**Conclusions:** There was a correlation between gene polymorphisms of TNFa 308 G/A and the risk of autoimmune liver disease.

**Keywords:** Autoimmune liver disease, Gene polymorphisms, TNF a 308 G/A gene

## OP-53

### Advanced Fibrosis and Low Platelet Counts Are Associated with the Development of Liver Cirrhosis in Patients with Autoimmune Hepatitis: A Multicenter Cohort Study

Soon Kyu Lee[1], Sook-Hyang Jeong[2], Gwang Hyeon Choi[2], U IM Chang[3], Ahlim Lee[3], Jeong-Ju Yoo[4], Ja Kyung Kim[5], Hye Yeon Chon[5], Hyung Joon Yim[6], Seung Kak Shin[7], Kyung-Ah Kim[8], Hae Lim Lee[9], Ji-Won Park[10], Young-Joo Jin[11], Heechul Nam[12], Jung Hee Kim[13], Bo Hyun Kim[14], Jung Hyun Kwon[1]

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**Aims:** Although autoimmune hepatitis (AIH) is a rare chronic liver disease, its prevalence has been increasing across all age groups. Given that some AIH patients can progress to liver cirrhosis (LC)—a significant risk factor for mortality—the identification of risk factors for LC development is crucial.

**Methods:** This study included 1,401 newly diagnosed AIH patients from 14 Korean centers, collected between January 2010 and December 2021. Of these, 777 patients who did not have LC at baseline were included in the final analysis. The primary outcome was the development of LC, evaluated using the FIB-4 and histologic fibrosis stages. Secondary outcomes involved identifying risk factors for LC development across the entire population and among patients with liver histology. Death or liver transplantation before LC development were considered as competing factors for LC development.

**Results:** During a mean follow-up of 58.6 months, a total of 103 patients newly developed LC. Patients with high FIB-4 levels (≥ 3.25) exhibited a significantly higher cumulative incidence rate of LC compared to those with low FIB-4 levels ($P$=0.003). Additionally, among patients with liver histology, those with F3 fibrosis had a significantly higher cumulative incidence rate of LC than those with F0-2 fibrosis ($P$<0.001). In a multivariate competing risk analysis, high FIB-4 levels (HR, 2.50, $P$=0.008) and low platelet counts (<100,000/$\mu$L) (HR, 2.64, $P$=0.027) were identified as significant risk factors for LC development. Among patients with liver histology, F3 fibrosis (HR, 1.87, $P$=0.036) and low platelet counts (HR, 3.23, $P$=0.018) emerged as significant predictors. However, high FIB-4 levels were not statistically significant among patients with liver histology, underscoring the importance of histologic fibrosis stages in predicting LC development.

**Conclusions:** Utilizing a large multicenter cohort study, this research is the first to identify significant risk factors for LC development in patients with AIH, highlighting the critical role of advanced fibrosis and low platelet counts.

**Keywords:** Autoimmune hepatitis, Liver cirrhosis, Platelet count, FIB-4

## OP-54

### The Effectiveness of Fenofibrate Use in the Treatment of Primary Biliary Cholangitis with Incomplete Response to Ursodeoxycholic Acid

**Madina Yerezhepbayeva**[1], Ainur Doszhan[2], Zhanat Kassenov[2], Abduzhappar Gaipov[1]

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**Aims:** Fenofibrates are hypolipidemic drugs, used in patients with PBC who have exhibited inadequate response to ursodeoxycholic acid (UDCA) monotherapy. The objective of this research is to study the laboratory and quality of life outcomes following a six-month course of therapy involving UDCA and fenofibrates.

**Methods:** Twenty patients with PBC exhibiting an incomplete biochemical response to UDCA therapy based on Paris I criteria were enrolled in a prospective nonrandomized observational study. Ten patients continued to receive UDCA at a dosage of 13-15 mg/kg/day. In the experimental group, ten patients received combination therapy with UDCA and Fenofibrate at a dosage 145 mg/day. Serum levels of ALP, GGT, ALT, AST, total and direct bilirubin, albumin, and INR were measured at the beginning and after 6 months. Additionally, the PBC-40 questionnaire was used to evaluate the health related quality of life (HRQOL) of patients. The laboratory and questionnaire results were compared within each group and between groups before and after 6 months of treatment.

**Results:** After 6 months, the ALP level exhibited an almost 2-fold reduction in patients undergoing combination therapy (8.00±3.55 mccat/l vs 4.28±2.35 mccat/l, $P$=0.0140). AST and ALP levels decreased and were lower in patients receiving combination therapy compared to UDCA monotherapy in 6 months ($P$=0.0494 and $P$=0.0343 respectively). However, the albumin level was lower in the experimental group (37.67 ±3.34 g/l vs 40.87±2.47 g/l, $P$=0.0284), although the value remained within the normal range. There was no observed change in HRQOL within or between groups after 6 months.

**Conclusions:** Combination therapy with UDCA and fibrates induced decrease in several biochemical parameters, namely ALP, AST levels after 6 months in patients with PBC. However albumin level was lower in patients receiving combination therapy.

**Keywords:** Primary biliary cholangitis, Fenofibrate, Effectiveness

## OP-55

### In Treatment-Naive Autoimmune Hepatitis, Serum Ferritin Levels Are Linked to Progressive Liver Fibrosis

**Ashok Kumar Sah**[1], Kajal Arora[1], Vikash Gaur[2], Ankur Vashishtha[3]

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**Aims:** It is now widely recognized that liver fibrosis in nonalcoholic fatty liver disease and chronic hepatitis C is associated with factors linked to iron metabolism. In autoimmune hepatitis (AIH), the association hasn't been thoroughly investigated, though. Our goal was to look into the relationship between advanced liver fibrosis and factors related to iron metabolism in AIH patients who were not receiving treatment.

**Methods:** This cross-sectional study involved the enrolment of 194 patients with untreated AIH. Liver biopsies and the iron metabolism index were performed on each individual. The relationship between factors linked to iron metabolism and advanced liver fibrosis was investigated using multiple logistic

regression analysis.

**Results:** 76 (39.2%) and 118 (60.8%) of the 194 AIH patients showed advanced liver fibrosis, respectively. Prothrombin time (OR 1.758; 95% CI 1.143–2.704, *P*=0.010), ferritin (OR 1.002; 95% CI 1.001–1.004, *P*=0.012), immunoglobulin G (odds ratio [OR], 1.123; 95% confidence interval [CI] 1.023–1.232, *P*=0.014), platelet count (OR 0.988; 95% CI 0.979–0.997, *P*=0.013), and prothrombin time (OR 1.758; 95% CI 1.143–2.704, *P*=0.010) were independent risk factors for predicting advanced liver fibrosis in AIH patients.

**Conclusions:** In patients with treatment-naive AIH, elevated serum ferritin was independently linked to progressive liver fibrosis.

**Keywords:** Ferritin, Iron metabolic disorders, Non-fatty liver, Autoimmune hepatitis

## OP-56

### Seropositive versus Seronegative Autoimmune Hepatitis (AIH): Comparative Analyses of Histomorphological Characteristics in Liver Biopsies of AIH Patients

Rimlee Dutta[1], Lalita Mehra[1], Rajni Yadav[1], Shalimar[2], Prasenjit Das[1]

Departments of Pathology[1], Gastroenterology and Human Nutrition[2], All India Institute of Medical Sciences (AIIMS), New Delhi

**Aims:** In this study, we tried to compare and evaluate any plausible difference in histomorphological parameters between seropositive and seronegative cases of AIH.

**Methods:** Cases of AIH were shortlisted by retrospectively searching our computerized database. Stained slides of available cases were then retrieved, reviewed and morphologically graded, based on several histological parameters which included architecture, density of portal tract inflammation(PTI) and composition of inflammatory infiltrate, interface hepatitis, confluent necrosis, lobular inflammation, presence of emperipolesis, acinar transformation, bile ductular proliferation, lymphocytic cholangitis, cholestasis, feathery degeneration, Mallory Denke(MD) bodies, macro-or-microvesicular steatosis, plasma cell or lymphoid cluster, Russell body, endotheliitis, kupffer-cell hyperplasia, hyaline globules, nuclear glycogenisation, P-I-R score of liver fibrosis, nodule size and septal thickness. Pertinent clinical information was collected. These parameters were then compared between seropositive versus seronegative cohort.

**Results:** Out of 65 AIH-cases, 44(67.6%) were found to be seropositive, while the rest were seronegative. Few histological parameters like severity of PTI, lymphocytic cholangitis, endotheleiitis were found to be more profound in the seropositive group. MD bodies though occasional were also found only in this group.

**Conclusions:** In our study, seronegative AIH showed almost similar morphological features as compared to seropositive ones. However, more studies incorporating larger cohort of seronegative AIH cases are warranted for highlighting minuscule difference, if any.

**Keywords:** Autoimmune hepatitis, Seronegative AIH, Treatment responsive AIH, Incomplete response/Treatment failure AIH

Friday, June 28, 2024, 16:30-17:20

# 11. Others

## OP-57

### A Multicenter Study on Hepatocellular Adenomas in Korea: Clinicopathological and Imaging Features

Subin Heo[1*], Bohyun Kim[2*], So Yeon Kim[1], Hyo Jeong Kang[3], In Hye Song[3], Sung Hak Lee[4], Jimi Huh[5], Seokhwi Kim[6], Seunghee Baek[7], Seung Soo Lee[1], Sang Hyun Choi[1], Jong Keon Jang[1], Seong Ho Park[1]

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**Aims:** The clinicopathologic and imaging features of hepatocellular adenomas (HCA) in Asian populations remain unclear. Herein, we aimed to comprehensively analyse clinicopathologic and imaging features of HCAs in Korea, and propose an imaging-based method to differentiate $\beta$-catenin mutated HCA ($\beta$HCA) from other subtypes.

**Methods:** This retrospective multicentre study included pathologically confirmed HCAs from three tertiary institutions in Korea between 2010 and 2023. HCA subtypes were determined according to the current World Health Organisation classification using immunohistochemical staining. Two abdominal radiologists reviewed multiphase computed tomography and gadoxetic acid-enhanced magnetic resonance imaging scans. The clinical characteristics and imaging features of HCA subtypes were compared. A scoring system for $\beta$HCA was developed and validated using development (January 2010–April 2021) and validation (May 2021–March 2023) cohorts.

**Results:** A total of 121 patients (47 men; mean age, 39.0 years $\pm$ 13.5) with 138 HCAs were included in the study. HCAs in

Korea displayed characteristic clinicopathologic features, including a high proportion of male (38.8%) and obese patients (35.5%), with the inflammatory subtype as the most common subtype (38.4%) and a low percentage of patients with oral contraceptive use (5.0%). Each HCA subtype demonstrated distinct clinical and imaging features. The scoring system incorporating tumour heterogeneity and hepatobiliary phase signal intensity on MRI for differentiating β-HCA exhibited high performance in both the development cohort (AUC 0.92, 95% CI: 0.87-0.97) and the validation cohort (AUC 0.91, 95% CI: 0.77-1.00).

**Conclusions:** This comprehensive analysis of clinicopathologic and imaging features of HCAs in Korea contributes to the characterisation of HCAs across different geographical regions. The imaging-based scoring system effectively differentiates β-HCA.

**Keywords:** Hepatocellular adenoma, Diagnostic imaging, Mri, Classification

## OP-58

### Epidemiology and Clinico-Epidemiologic Characteristics of Acute Viral Hepatitis in South Korea: A Prospective, Nationwide Multicenter Study

Chang Hun Lee[1], Hoon Gil Jo[2], Eun Young Cho[2], Ju Yeon Cho[3], Jae Hyun Yoon[4], Sung Bum Cho[5], Ki Tae Suk[6], Seok Hyun Kim[7], Hyuk Soo Eun[7], Byung Seok Lee[7], Jeong-Ju Yoo[8], Young Seok Kim[8], Woo Jin Chung[9], Youn-Jae Lee[10], Jun Sik Yoon[10], Hyun-Jin Cho[11], Neung Hwa Park[12], Moon-Young Kim[13], Seul-Ki Han[13], Dae Hee Choi[14], Tae Suk Kim[14], Kyung-Ah Kim[15], Gwang Hyeon Choi[16], Eun Sun Jang[16], Sook-Hyang Jeong[16], In Hee Kim[1]

[1]Department of Internal Medicine, Research Institute of Clinical Medicine of Jeonbuk National University-Biomedical Research Institute of Jeonbuk National University Hospital, Jeonbuk National University Medical School, Jeonju, Republic of Korea; [2]Department of Internal Medicine, Wonkwang University Hospital, Wonkwang University College of Medicine, Iksan, Republic of Korea; [3]Department of Internal Medicine, School of Medicine, Chosun University, Gwangju, Republic of Korea; [4]Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Republic of Korea; [5]Department of Internal Medicine, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea; [6]Institute for Liver and Digestive Diseases, College of Medicine, Hallym University, Chuncheon, Republic of Korea; [7]Departments of Internal Medicine, Chungnam National University Hospital, Daejeon, Republic of Korea; [8]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea; [9]Departments of Internal Medicine, Keimyung University Dongsan Hospital, Daegu, Republic of Korea; [10]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan, Republic of Korea; [11]Departments of Internal Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea; [12]Department of Internal Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Republic of Korea; [13]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [14]Departments of Internal Medicine, Kangwon National University Hospital, Chunchon, Republic of Korea; [15]Departments of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Republic of Korea; [16]Departments of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Republic of Korea

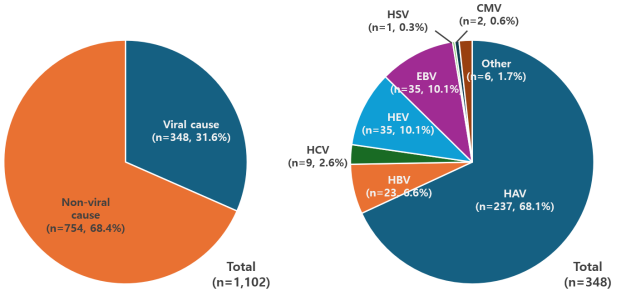
**Aims:** This study aims to examine the epidemiology and clinico-epidemiological characteristics of acute viral hepatitis (AVH) in South Korea, with the objective of informing future public health strategies and clinical management approaches.

**Methods:** From 2020 to March 2024, we recruited participants from 17 centers, specifically targeting patients who met the criteria for acute hepatitis. We conducted analyses on the etiology, clinical characteristics, and progression of acute hepatitis.

**Results:** After excluding patients with non-hepatic causes, we enrolled a total of 1,102 patients. Of these, 348 (31.6%) were diagnosed with acute viral hepatitis (AVH) based on specific serologic markers. The predominant etiology was hepatitis A virus (HAV, 68.1%), followed by hepatitis E virus (HEV, 10.1%), Epstein-Barr virus (EBV, 10.1%), hepatitis B virus (6.6%), hepatitis C virus (2.6%), cytomegalovirus (0.6%), herpes simplex virus (0.3%), and other pathogens (1.7%). When comparing viral and non-viral causes, male predominance was observed among patients with AVH, with an average age of 43.8±12.4 years, significantly younger than those with non-viral causes (50.1±17.6, $P$<0.001). AVH patients also showed higher levels of platelets, alkaline phosphatase, gamma-glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase. However, bilirubin, albumin, and prothrombin time did not differ significantly. Regarding prognosis, there were no significant differences between the viral and non-viral groups in terms of intensive care unit admissions, dialysis, liver transplants, or mortality.

**Conclusions:** AVH accounts for approximately 30% of acute hepatitis cases in South Korea, with HAV, HEV, and EBV infections being the most prevalent, in that order. Through the analysis of the etiology and characteristics of acute hepatitis, our study contributes to the understanding and management of AVH.

**Keywords:** Acute viral hepatitis, Hepatitis, Acute disease, Epidemiology



## OP-59

### Prevalence and Determinants of Depression among Liver Disease Population: A Cross-Sectional Study in Indonesia

Nadyatul Husna, Selmi Winarti

Medical Doctor, Alumnus of Universitas Andalas, dr. Reksodiwiryo Hospital, Padang, Indonesia

**Aims:** Liver Disease often affect the physical and emotional well-being of patients as they are highly influenced by stress. This research aims to assess the prevalence and determinants of depression among liver disease population in Indonesia.

**Methods:** This cross-sectional study involved 22,797 respondents from the Indonesian Family Life Survey 5 (IFLS 5) who met the inclusion and exclusion criteria. Data related to sociodemographic characteristics, lifestyle risk factors, and comorbidities were obtained. Depression was defined using the CES-D-10 scale. Binary logistic regression analysis was performed, and a p-value of less than 0.05 was used as the level of significance.

**Results:** The majority experienced mild depression, while experienced severe depression. Most cases of depression were found in females. Female gender, stress, young adulthood, underweight, lower economic status, smoking, unmarried status, soda consumption, fast food/salty food intake, insufficient physical activity, and comorbidities such as hypertension and dyslipidemia were associated with increased odds of depression in the liver disease.

**Conclusions:** This study highlights a high prevalence of depression among individuals with liver diseases in Indonesia. Various sociodemographic factors, lifestyle choices, and comorbid conditions contribute to the increased risk of depression in this population. Early identification and management of depression in liver disease patients are crucial for improving their overall well-being and quality of life.

**Keywords:** Depression, Determinants, Liver disease, Prevalence

## OP-60

### Potential of a Small Molecule Inhibitor in the Sensitization of Pancreatic Cancer Cells to Gemcitabine

Subash Gupta[1], Anusmita Shekher[2,3], Nikee Awasthee[2], Ankit Srivastava[2]

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**Aims:** Pancreatic cancer (PaCa) manifests as an aggressive tumor due to the late occurrence of early symptoms. The overall five-year survival rate of PaCa is merely 2-9%. Bharangin (BG) is a small molecule diterpenoid quinonemethide with known activities against some cancer types. The activities of this diterpenoid against PaCa and the associated mechanism has not been explored. In this study, we investigated the potential of BG against PaCa. Whether BG can enhance the sensitivity of PaCa cells to gemcitabine (GEM), a standard drug for PaCa patients, was also evaluated.

**Methods:** We used PaCa cell lines such as PANC-1 and MIA-PaCa-2. To assess cell viability, we performed 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay. To examine apoptosis inducing potential of BG, we performed a number of assays such as phosphatidylserine externalization, acridine orange/propidium iodide staining, cell cycle analysis, and DNA laddering. We used western blotting and immunocytochemistry for protein analyses, while quantitative-real time-PCR was used for gene transcription analyses.

**Results:** A dose- and time-dependent suppression in the viability of PaCa cells was observed. BG suppressed the level of tumorigenic proteins in PaCa cells. BG was found to induce apoptosis in PaCa cells. An accumulation in the sub-G1 population was observed by BG. The diterpenoid induced depolarization in the mitochondrial membrane potential. Although GEM is a standard drug for PaCa, patients develop resistance over the course of treatment time. BG enhanced the sensitivity of PaCa cells to GEM. Both BG and GEM modulated the expression of cancer associated lncRNAs such as MEG3, GAS5 and H19. BG also suppressed the translocation of nuclear factor (NF)-$\kappa$B induced by TNF-$\alpha$ in PaCa cells.

**Conclusions:** BG exhibit activities in PaCa cells. The suppression of NF-kB activation and the modulation of lncRNAs expression may provide a basis for further exploration of BG as a therapeutic agent in PaCa.

**Keywords:** Bharangin, Chemosensitization, Diterpenoid, Gemcitabine, Inflammation, Long non-coding RNA, Pancreatic cancer

## OP-61

### The Impact of Portal T-Cell Density on the Outcomes in Chronic Hepatic GVHD and Autoimmune Liver Diseases

Soon Kyu Lee[1,2], Ji Won Han[2,3], Si Hyun Bae[2,4], Jung Hyun Kwon[2,3], Jeong Won Jang[2,3], Jong Young Choi[2,3], Seung Kew Yoon[2,3], Pil Soo Sung[2,3]

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University of Korea, Seoul 06591, Republic of Korea

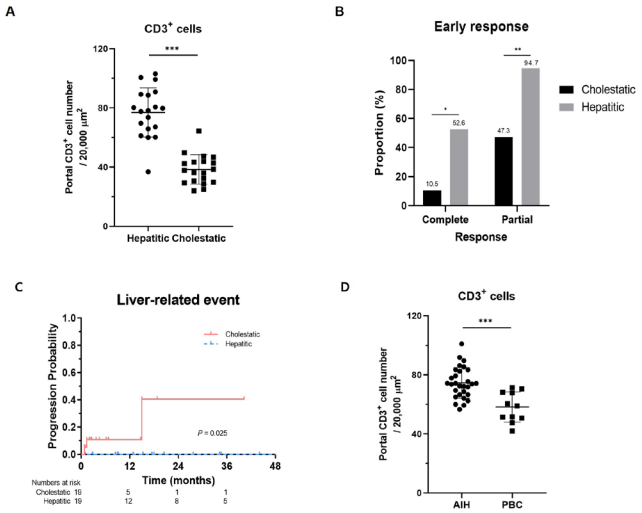
**Aims:** Hepatic graft-versus-host disease (GVHD) affects morbidity and mortality in allogeneic hematopoietic stem cell transplant recipients. We aimed to study the implications of portal T-cell infiltration on the clinical outcomes in hepatic GHVD and its association with autoimmune liver disease.

**Methods:** We enrolled 137 patients with biopsy-confirmed hepatic GVHD (n=49) or autoimmune liver disease (n=88) between 2016 and 2021. Of these, 78 patients with immunohistochemical staining results were included in the analysis (hepatic GVHD, n=38; autoimmune liver disease, n=40). The cholestatic variant was defined by an R-value < 2.0, based on the ratio of alanine aminotransferase to alkaline phosphatase. The primary outcome was the biochemical response at 4 (early) and 8-12 (late) weeks after corticosteroid treatment, with liver-related event-free survival (EFS) as a secondary outcome.

**Results:** In hepatic GVHD patients, the hepatitic variant (n=19) showed greater $CD3^+$ T-cell infiltration than the cholestatic variant (n=19; $P<0.001$; Figure A). No significant differences were observed in the infiltration of $CD20^+$, $CD38^+$, or $CD68^+$ cells. The hepatitic variant had significantly better early (Figure B) and late responses and higher liver-related EFS (Figure C) than the cholestatic variants ($P<0.05$). Concerning autoimmune liver diseases, the autoimmune hepatitis (AIH) group (n=29) had significantly more portal T-cell infiltration (Figure D) and better treatment responses than the primary biliary cholangitis (PBC) group (n=19).

**Conclusions:** Higher portal T-cell infiltration may be associated with better clinical outcomes in patients with hepatic GVHD. Additionally, this study highlights similarities in portal T-cell infiltration and treatment response patterns between AIH and the hepatitic variant, as well as PBC and the cholestatic variant.

**Keywords:** Graft-versus-host diseases, Autoimmune hepatitis, Primary biliary cholangitis, T cell

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DAY 3: June 29 (Sat)

# Oral Poster Presentation 2

| | |
|---|---|
| **OP-62~OP-67** | HBV 2 |
| **OP-68~OP-73** | HCV |
| **OP-74~OP-78** | MASLD, Clinical 2 |
| **OP-79~OP-83** | LC & Others, Basic |
| **OP-84~OP-89** | LC Clinical & Liver Failure 2 |
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| **OP-101~OP-106** | Liver Transplantation 2 |
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Saturday, June 29, 2024, 09:30-10:30

## 12. HBV 2

### OP-62

### Non-Linear Association between Liver Fibrosis Scores and Viral Load in Patients with Chronic Hepatitis B

Gi-Ae Kim[1], Seung Won Choi[2], Seungbong Han[3], Young-Suk Lim[4]

[1]Department of Internal Medicine, Kyung Hee University School of Medicine, [2]University of Ulsan College of Medicine, [3]Department of Biostatistics, Korea University, [4]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine

**Aims:** Serum hepatitis B virus (HBV) DNA levels and non-invasive liver fibrosis scores are significantly associated with hepatocellular carcinoma (HCC) risk in chronic hepatitis B (CHB) patients. Nonetheless, the relationship between HBV DNA levels and liver fibrosis scores is unclear.

**Methods:** A historical cohort comprising 6,949 non-cirrhotic Korean CHB patients without significant alanine aminotransferase elevation was investigated. The association of HBV DNA levels with the aspartate aminotransferase to platelet ratio index (APRI) and fibrosis (FIB)-4 score at baseline was analyzed using general linear models.

**Results:** In HBeAg-negative patients (n=4,868), HBV DNA levels correlated linearly with both APRI and FIB-4 scores. In contrast, in HBeAg-positive patients (n=2,081), HBV DNA levels correlated inversely with both APRI and FIB-4 scores. Across the entire cohort, a significant non-linear parabolic relationship was identified between HBV DNA levels and fibrosis scores, independent of age and other covariates. Notably, moderate viral loads (6–7 $\log_{10}$ IU/mL) corresponded to the highest APRI and FIB-4 scores ($P$<0.001). Over a median 10-year follow-up, 435 patients (6.3%) developed HCC. Higher APRI scores ≥ 0.5 and FIB-4 scores ≥ 1.45 were significantly associated with elevated HCC risk ($P$<0.001 for both). HBV DNA level remained a significant predictive factor for HCC development, even after adjusting for APRI or FIB-4 scores.

**Conclusions:** HBV viral load is significantly correlated with APRI and FIB-4 scores, and is also associated with HCC risk independent of those scores in CHB patients. These findings suggest that HBV DNA level is associated with hepatocarcinogenesis through both direct and indirect pathways.

**Keywords:** Hepatitis B virus, Hepatocellular carcinoma, Liver cancer, Liver fibrosis score

### OP-63

### Seroprevalence of Sexually Transmitted Diseases among Overseas Job Seekers in Nepal

Arun Bahadur Chand[1], Ajaya Basnet[2], Bindu Sen[3], Dev Raj Joshi[4], Shiba Kumar Rai[2]

[1]Department of Microbiology, KIST Medical College and Teaching Hospital, Lalitpur, Nepal; [2]Department of Medical Microbiology, Shi-Gan International College of Science and Technology, Kathmandu, Nepal; [3]Department of Dentistry, Shree Samaj Dental Clinic, Kathmnadu, Nepal; [4]Central Department of Microbiology, Tribhuwan University, Kathmandu, Nepal

**Aims:** Migration is one of the socioeconomic factors that contribute to the acquisition and dissemination of sexually transmitted disease/s (STDs), a long-recognized major global health issue. This study aimed to determine the seroprevalence of STDs among Nepalese overseas job seekers.

**Methods:** Retrospective serological data of Nepalese overseas job seekers (n=14,980), who were tested for Hepatitis B (HB), Hepatitis C (HC) and Acquired Immune Deficiency Syndrome (AIDS) with an enzyme-linked immunosorbent assay, and syphilis with Treponema pallidum hemagglutination assay, were extracted (January and December 2021) from the electronic database of a diagnostic center and analyzed using SPSS version 17.0

**Results:** Syphilis seroprevalence was 0.59% among overseas job seekers, while HB, AIDS, and HC seroprevalences were 0.32%, 0.15%, and 0.11%, respectively. Unlike syphilis, which was predominated in the age group of 31-40 years, viral hepatitis and AIDS were prevalent in the age group of 21-30 years. Males had higher incidences of HB (n=48), HC (n=17), AIDS (n=23), and syphilis (n=86) compared with females. Co-prevalence of HIV-syphilis and HIV-HBV occurred in 0.020% (n=3) and 0.013% (n=2) of individuals, respectively, whereas both HIV-HCV and HBV-HCV co-prevalence was observed in 0.007% (n=1) of individuals.

**Conclusions:** Syphilis is the most common STD among Nepalese overseas job seekers, with the highest co-occurrence with AIDS.

**Keywords:** Overseas job seekers, Seroprevalence, Sexually transmitted diseases, Nepal

### OP-64

### The Impact of Alanine Aminotransferase Fluctuation on the Hepatocellular Carcinoma Risk in Chronic Hepatitis B Patients

Youngsu Park, Hyunjae Shin, Yunmi Ko, Jeayeon Park, Moon Haeng Hur, Min Kyung Park, Yun Bin Lee, Yoon Jun Kim, Jung-Hwan Yoon, Jeong-Hoon Lee

Department of Internal Medicine and Liver Research Institute, Seoul Na-

tional University College of Medicine, Seoul, Republic of Korea

**Aims:** High alanine aminotransferase (ALT) levels are well-established risk factors for hepatocellular carcinoma (HCC) development in chronic hepatitis B (CHB) patients. However, the impact of ALT fluctuation around normal margin on the development of HCC remains unclear.

**Methods:** Patients with CHB, whose ALT levels were measured at least 4 times for the first two years, were enrolled. Based on the tertiles of coefficient of variation (CV, standard deviation divided by mean) of serial ALT levels, patients were divided into low-, intermediate-, or high-fluctuation groups. The primary outcome was HCC occurrence. Baseline characteristics were balanced using the inverse probability of treatment weighting (IPTW).

**Results:** A total of 4,192 patients were enrolled during a median follow-up of 12.6 (interquartile range [IQR]=6.9–18.7) years. The median CV values of the low-, intermediate-, and high-fluctuation groups were 0.15, 0.30, and 0.71, respectively. Owing to notable disparities in baseline characteristics among the high-fluctuation group compared to the other two, the analysis of the primary outcome was focused on the comparison between the low-fluctuation and intermediate-fluctuation groups. Before balancing the baseline characteristics, the risk of HCC was significantly higher in the intermediate-fluctuation group compared to the low-fluctuation group (hazard ratio [HR]=2.18, 95% confidence interval [CI]=1.16–4.12, *P*=0.02). After applying IPTW, the intermediate-fluctuation group maintained a significantly higher risk of HCC than the low-fluctuation group (HR=2.05, 95% CI=1.05–3.99, *P*=0.035). Sensitivity analysis conducted with various definitions of ALT fluctuation reaffirmed the consistent result of the main analysis.

Figure 1. HCC development

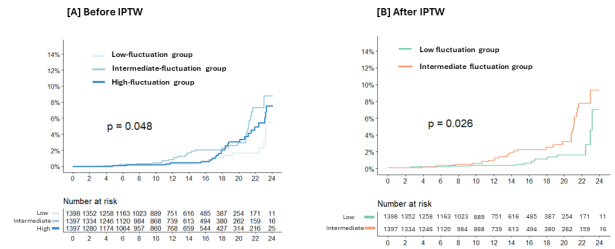
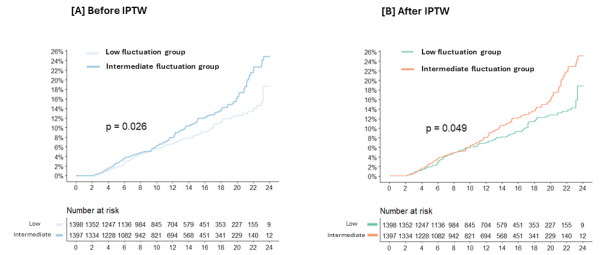



Figure 2. Liver-related outcome




**Conclusions:** In CHB patients without antiviral treatment, fluctuating ALT is associated with an increased risk of HCC. Further studies are warranted to evaluate if antiviral treatment for patients with ALT fluctuation could reduce the HCC risk.

**Keywords:** Fluctuation, Inflammation, Liver cancer, Time series analysis

## OP-65

### Multi-Method Analysis Identifies Genotypes in All Evaluated Participants on-NA, B-Together Study

Jeong Heo[1,2], Maria Buti[3], Leigh Felton[4], Jerome Bouquet[5], Maximilian Lee[6], Thomas Greene[6], Divya Lakshminarayanan[6], Scott D. Speer[6], Helene Plein[4], Dickens Theodore[7], Melanie Paff[6], Susan Dixon[4]

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**Aims:** In B-Together, 9–15% of participants with chronic hepatitis B virus (HBV) infection on background nucleos(t)ide analogs (NAs) receiving sequential bepirovirsen and pegylated interferon-$\alpha$-2a (bepirovirsen+Peg-IFN) therapy achieved the primary outcome of hepatitis B surface antigen (HBsAg) and HBV DNA

**Methods:** HBV GTs in virally suppressed participants were determined using medical history, HBV sequencing, and a serology method (IMMUNIS® HBV Genotype EIA by Institute of Immunology Co.).

**Results:** The three methodologies had a high degree of concordance (75–100%) and determined GT for 101/108 (94%) participants. By contrast, medical history and HBV DNA/RNA sequencing alone were only successful in identifying GT in 50% of participants. GT-C and GT-D were the most common; GT-B the least (Table). GT-B (n=3/4) and GT-C (n=30/37) were predominantly identified in Asia; GT-A (n=14/16) and GT-D (n=30/34) in Europe. Virological response to bepirovirsen was observed across all common HBV GTs. Baseline HBsAg varied markedly by GT. Analysis of the relationship between HBV GT and treatment response is currently ongoing across studies exploring the efficacy of bepirovirsen-containing regimens.

**Conclusions:** This innovative three-tiered approach identified HBV GTs in all tested participants on NAs. GT analysis of participants in trials for novel HBV therapies is an important tool to understanding disease heterogeneity in chronic HBV infection.
Funding: GSK (209348)

**Keywords:** Chronic hepatitis B, HBV Genotypes, Bepirovirsen, Peg-interferon

**Table: Summary of genotype prevalence in the B-Together study**

| Genotype | Genotype Prevalence n (%) (N=108) |
|---|---|
| A | 16 (15%) |
| B | 4 (4%) |
| C | 37 (34%) |
| D | 34 (31%) |
| Other* | 10 (9%) |
| Missing | 7 (6%) |

*Other constituted genotypes E, H, and unclassified. When investigator-reported genotype is missing, genotype was assigned using HBV sequencing data; when HBV sequencing is missing, genotype was assigned using serology data.

## OP-66

### HBV Mother-to-Child Transmission in Infants Born to Chronic HBV Mothers with or without Tenofovir Therapy During Pregnancy

Ha Linh, Le Quoc Tuan, Dinh Cong Tiep, Dinh Cong Dang

103 Cam Khe Clinic, Vinh Phuc Hospital

**Aims:** The rate of Hepatitis B Virus (HBV) infection in Vietnam is about 10-20% of the population, especially in pregnant women and children. Children infected with HBV from their mothers can develop cirrhosis and liver cancer in the future.

**Aims:** To determine the status of HBV infection in infants born to chronic HBV mothers with or without Tenofovir Disoproxil Fumarate (TDF) therapy during the last trimester of pregnancy.

**Methods:** Cohort study on 2 groups of pregnant women with HBV and children born to these pregnant women from May 2019 to January 2024. Group of pregnant women receiving TDF prophylaxis: Pregnant women with HBV (results available) HBsAg (+), 25th week of pregnancy (± 2 weeks). Group of pregnant women who do not have access to TDF prophylaxis: Pregnant women with HBV (with HBsAg (+) results), admitted to the ward to give birth.

**Results:** Percentage of HBV-infected children born to HBV-infected mothers treated with TDF in the last trimester of pregnancy: 2.6% (95% CI: 0.88 - 8.36). Percentage of HBV-infected infants born to HBV-infected mothers not treated with TDF in the last trimester of pregnancy: 5.9% (95% CI: 1.2-15.5). Percentage of HBV-infected infants born to HBV-infected mothers with HBV-DNA levels ≤ $10^6$ copies/mL without treatment with TDF in the last trimester of pregnancy: 0.8% (95% CI: 0.2- 4,8).

**Conclusions:** Access to preventive treatment as well as adherence to TDF prophylaxis in pregnant women reduces the transmission of HBV from mother to child.

**Keywords:** Infants, Tenofovir disoproxil, Fumarate (TDF), Pregnancy, Hepatitis B virus

## OP-67

### Impact of Maternal Hepatitis B Virus Infection on Congenital Heart Disease Risk in Offspring: A National Cohort Study

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**Aims:** Maternal hepatitis B virus (HBV) infection influence both maternal and fetal health. Recent studies reported increased congenital anomalies in offspring of HBV-infected mothers. This study investigated whether maternal HBV infection was associated with higher risk of congenital heart disease (CHD) in children.

**Methods:** With the Korean National Health Insurance Service (K-NHIS) database, this retrospective cohort study included live births from 2005 to 2019, born to women under 40. Propensity score matching with 1:3 ratio was conducted to compare HBV-infected mother's children with HBV-uninfected mother's children while adjusting for various maternal and pregnancy-related factors. Logistic regression models were used to estimate the risk.

**Results:** Of 2,673,059 eligible participants, 263,904 children were born to HBV-infected mothers. Risk estimation in this group showed a modestly increased risk of CHD (OR=1.05, 95% CI=1.02, 1.09). Notably, when pregnant mothers were treated with antiviral medication, there was an indication of reduced CHD risk, although this result was not statistically significant. The highest risk of CHD was observed in children who were themselves infected with HBV.

**Conclusions:** The study indicates an association between maternal HBV infection and an increased CHD risk in offspring. The findings suggest the need to reevaluate the timing of antiviral treatment during pregnancy to align more closely with early stages of fetal cardiac development. Further research is needed to understand the biological mechanisms of this association and to redefine clinical guidelines for managing HBV infection in pregnancy.

**Keywords:** Hepatitis B virus, Congenital heart disease, Antiviral treatment, Pediatric outcome

Saturday, June 29, 2024, 09:30-10:30

## 13. HCV

### OP-68

### Prognosis after Sustained Virologic Response of Chronic Hepatitis C Patients Treated with Sofosbuvir Based Treatment; A Multicenter Prospective Observational Study

Jeong Han Kim[1], Jae Hyun Yoon[2], Sung Eun Kim[3], Ji Won Park[3], Gi-Ae Kim[4], Yewan Park[4], Seong Kyun Na[5], Hyo Young Lee[5], Young-Sun Lee[6]

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**Aims:** Direct-acting antiviral (DAA) therapy can cure chronic hepatitis C (CHC) and sofosbuvir (SOF) and ledipasvir (LDV)/SOF were introduced to Korea in 2016. Good prognosis is expected in patients achieved sustained virologic response (SVR) after DAA treatment. However, information about prognosis of Korean CHC patients achieved SVR after SOF based treatment is still limited. We aimed to investigate prognosis of these patients.

**Methods:** This is a multicenter prospective observational study. The CHC patients achieved SVR after SOF or LDV/SOF treatment were enrolled and final follow up date was December 2023. Primary end-point was hepatocellular carcinoma (HCC) occurrence. At last one time in year, we checked about this end-point.

**Results:** Total 516 patients were included in this analysis and mean follow up duration was 40.5 months. Male was 231 patients (44.8%) and mean age was 61.7 years. Genotypes were 1 (90, 17.4%), 2 (423, 82.0%) and 3 (3, 0.6%). SOF and ribavirin combination was the most common treatment (394, 76.4%). Cirrhosis was 160 patients (31.0%) and mean Child-Pugh score was 5.1. HCC occurrence cases were 21 patients (4.1%) up to 7 years. HCC patients were older (69 years vs. 61 years, $P$=0.013) and had more cirrhosis prevalence (81.0 vs. 28.9%, $P$<0.001), higher AFP (6.0 vs. 3.3, $P$=0.003) and higher APRI (0.8 vs. 0.5, $P$=0.005). Cox regression analysis showed age older than 65 years ($P$=0.016) and cirrhosis ($P$=0.005) were significant risk factors for HCC occurrence.

**Conclusions:** Prognosis of patients achieved SVR after SOF based treatment was generally good. However, HCC risk was not completely removed especially in older and cirrhosis patients. Therefore, regular follow up surveillance is still warranted and early treatment is important.

**Keywords :** Hepatitis C, Direct-Acting antiviral, Hepatocellular Carcinoma, Sofosbuvir

### OP-69

### Treatment Efficacy and Safety Profile of Sofosbuvir and Velpastavir Based Treatment in South Korea: Multi-Institutional Prospective Study

Jae Hyun Yoon[1], Ju Yeon Cho[2], Jin Dong Kim[3], Hun Gil Cho[4], Chang Hun Lee[5]

[1]Department of Gastroenterology and hepatology, Chonnam National University Hospital and Medical School, Gwangju, South Korea; [2]Department of Internal Medicine, College of Medicine, Chosun University, Gwangju, Korea; [3]Department of Internal Medicine, Cheju Halla General Hospital, Jeju, Korea; [4]Department of Gastroenterology and hepatology, Wonkwang University Hospital and Medical School, Iksan, South Korea; [5]Department of Gastroenterology and hepatology, Jeonbuk National University Hospital and Medical School, Jeonju, South Korea

**Aims:** Sofosbuvir and velpatasvir (S/V) based treatment is a combination of direct-acting antiviral agents (DAA) which has strong treatment efficacy on all genotypes of hepatitis C virus (HCV) These two agents have been recently introduced in Korea and we elucidated the real-world treatment efficacy and safety profile in South Korea.

**Methods:** From November 2022 to May 2023, patients diagnosed as chronic HCV infection and underwent S/V based HCV treatment from five hospitals were enrolled.

**Results:** Among 92 patients with S/V, the mean age was 64.23 years, 20 (51.3%) patients were male. Eighteen patients (46.2%) had genotype 2, 21 patients (53.8%) had genotype 1b and only two patients had prior history of interferon treatment. The mean baseline level of HCV RNA was 3,753,531 IU/mL and each 4 and 6 patients had underlying decompensated liver cirrhosis and compensated liver cirrhosis, respectively. Due to lack of observation period, sustained virological response at 12 week (SVR12) was assessable in 83 patients and 78 patients achieved SVR12 (94.0%) while five patient was lost during follow-up. Among 16 patients who underwent S/V/V regimen, the mean age was 61.84 years, 5 (31.3%) patients were male. Among enrolled patients, 11 patients had failed to achieve SVR with previous DAA treatment, 2 patients had achieved SVR and 1 patient had self-stopped the DAA. Four patients had underlying compensated liver cirrhosis. Due to lack of study period, 8 patients were assessable for SVR 12 and all achieved SVR12. Both patients group in S/V and S/V/V had no serious adverse events (≥ grade 3) during DAA treatment period.

**Conclusions:** S/V based treatment demonstrated excellent SVR12 and also showed fair safety profile.

**Keywords:** Hepatitis C virus, Sofosbuvir, Velpatasvir, Efficacy

## OP-70

### Unveiling Potential Antiviral siRNAs Targeting Hepatitis C Virus Genotype 1 for Therapeutic Breakthroughs

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**Aims:** Presently, hepatitis C virus (HCV) infection remains a major factor in conditions like liver cirrhosis, hepatocellular cancer, and liver transplantation. Therefore, there is a pressing need for an efficient antiviral medication to combat HCV infections. This study aimed to design potential antiviral small interfering RNAs (siRNAs) specifically targeting the 3'-untranslated region (3'UTR) of HCV genotype 1.

**Methods:** siRNA molecules were generated using the siDirect platform. A sequential filtering bioinformatics methodology was utilized to identify potential antiviral siRNAs targeting the 3'UTR of HCV genotype 1. The siRNA Scales tool was utilized to sift through siRNA candidates. Subsequently, these candidates underwent additional examination using MaxExpect and DuplexFold to determine the folding free energy of the siRNAs and the binding free energy between the guide strand and the target, respectively. The effectiveness of the siRNAs was forecasted using SMEPred.

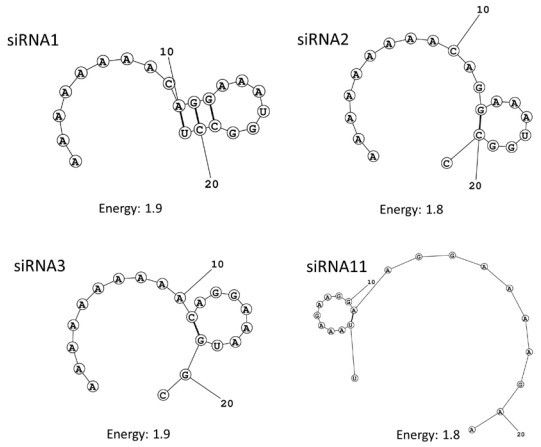


**Figure 1.** Secondary structure of the guide strands of siRNAs and their energy values.

**Results:** A total of 11 siRNAs were successfully designed based on the complete genome of HCV genotype 1 (NC_004102.1). Subsequent analyses using diverse bioinformatics tools identified four siRNAs demonstrating the potential to effectively silence the 3'UTR region of HCV genotype 1, exhibiting the highest efficacy level at 84.5.

**Conclusions:** This study introduces four promising siRNA molecules as potential candidates for antiviral siRNA-based therapy to mitigate HCV genotype 1 infection. Nonetheless, it remains imperative to validate the predicted siRNAs through laboratory experiments.

**Keywords:** 3'UTR region, Hepatitis C virus, SIRNA, Bioinformatics

## OP-71

### Real-World Experience on the Effectiveness and Safety of Sofosbuvir/Velpatasvir/Voxilaprevir in Patients with Chronic Hepatitis C Who Have Failed Previous Treatments with Direct Acting Antivirals in Korea: A Multi-Center Study

Sangdeok Shin[1], Sung Hwan Yoo[2,3], Tae Seop Lim[2,4], Chang Won Ha[1], Byeong Geun Song[1], Myung Ji Goh[1], Dong Hyun Sinn[1], Geum-Youn Gwak[1], Young-Han Paik[1,6], Moon Seok Choi[1], Joon Hyeok Lee[1], Hye Won Lee[2,5], Wonseok Kang[1,6]

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**Aims:** Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) has recently been introduced to Korea for the treatment of patients with chronic hepatitis C virus (HCV) infection who have failed previous treatments with NS5A inhibitors or those who have been treated without NS5A inhibitors in a regimen including sofosbuvir, based on genotype and the degree of cirrhosis. We aimed to evaluate the effectiveness and safety of SOF/VEL/VOX in a real-life clinical practice in Korea.

**Methods:** In this multicenter study, a total of 30 patients with chronic HCV infection who have failed previous treatments with direct acting antivirals (DAAs) were treated with SOF/VEL/VOX between November 2022 and February 2024. Sustained virologic response at 12 weeks after the end of treatment (SVR12) rate, change in noninvasive fibrosis markers (i.e. FIB-4), and treatment-related adverse events of SOF/VEL/VOX treatment were analyzed.

**Results:** The mean age was 61.3 years, and 66.7% were female. Eight patients (26.7%) had cirrhosis. HCV genotype distribution was as follows: 19 patients (63.3%) with genotype 1b, 7 (23.3%) with genotype 2, 3 (10%) with genotype 3, and 1 (3.3%) with genotype 6. All patients had a previous experience of DAA treatment, including daclatasvir/asunaprevir (46.7%), ledipasvir/sofosbuvir (36.7%), elbasvir/grazoprevir (10%), ombitasvir/paritaprevir/ritonavir/dasabuvir (3.3%), and glecaprevir/pibrentasvir (3.3%). Among the patients with cirrhosis, the FIB-4 index decreased from 5.36 (range, 2.61-11.12) to 4.47 (range, 1.83-9.38) after treatment. The end-of-treatment response rate was 100% (27/27) and SVR12 rate was 100% (23/23), with no treatment-related adverse effects observed.

**Conclusions:** The use of SOF/VEL/VOX in patients with chronic hepatitis C who have failed previous DAA treatments demonstrated excellent effectiveness and safety profiles, highlighting SOF/VEL/VOX as a highly effective and safe treatment option for this patient population in a real-world clinical setting in Korea.

**Keywords:** Sofosbuvir/velpatasvie/voxilaprevir, Chronic hepatitis C, Real-world

## OP-72

### Development of Diagnostic/Prognostic Marker and Therapeutic Target for HCV-Mono- and HIV/HCV-Co-Infection-Mediated Liver Diseases

Pankaj Chaudhary, In-Woo Park

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**Aims:** Identification of biomarkers is imperative for accurate diagnosis and prognosis of clinical stages of hepatocellular carcinoma (HCC) and for elucidation of molecular mechanisms of HIV-1-mediated acceleration of liver disease progression toward HCC in HCV-infected patients.

**Methods:** A new high-resolution assay from Affymetrix, GeneChip Human Transcriptome Array (HTA2.0) was performed to identify molecular signatures in each of the early and advanced stages of liver disease from HCV-mono- and HIV/HCV-co-infected liver specimens.

**Results:** The Transcriptome array identified three candidate genes, acyl-CoA synthetase long-chain family number 4 (ACSL4), glycine N-methyltransferase (GNMT), interferon, alpha-inducible protein 27 (IFI27; a.k.a, ISG12), and miR122, which are expressed stage-specifically in HCV mono- and HIV-1/HCV co-infective hepatic disease. Protein products of each gene were detected in the endoplasmic reticulum (ER) where HCV replication takes place, and the genes' expression was found to significantly alter replicability of HCV in the sub-genomic replicon cells. Further, these genes regulated the level of p53, a key tumor suppressor, and several promoter activities of important cellular genes associated with HCV replication and HCC, giving a direction for the mechanistic study of the genes. Since hepatocytes were neither susceptible nor permissive for HIV replication in our experiments, we focused on the impacts of the three well-known transferrable HIV-1 viral elements - Env, Nef, and Tat-on regulation of HCV replicability and hepatocellular biology. Among those three HIV-1 viral proteins, Nef uniquely augmented replicon expression, while Tat, but not the others, substantially modulated expression of the candidate genes in hepatocytic cells. Combinatorial expression of these cellular and viral genes in the replicon cells further altered replicon expression.

**Conclusions:** Not HIV-1 per se, but HIV-1 viral proteins can exacerbate liver pathology in the co-infected patients by disparate molecular mechanisms - directly or indirectly dysregulating HCV replication and modulating stage-specific expression of hepatocellular genes, providing major insights into the development of stage-specific hepatocellular biomarkers for improved diagnosis and prognosis of HCV-mediated liver disease.

**Keywords:** HCC, HCV, Biomarker, Therapy

## OP-73

### Implementation of an Electronic Medical Record-Based Automatic Alert System for the Care Cascade of Hepatitis-C-Virus Infection in Patients Undergoing Elective Surgery

Jae Seung Lee[1,2,3], Ho Soo Chun[4], Hye Won Lee[1,2,3], Mi Na Kim[1,2,3], Beom Kyung Kim[1,2,3], Jun Yong Park[1,2,3], Do Young Kim[1,2,3], Sang Hoon Ahn[1,2,3], Seung Up Kim[1,2,3]

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**Aims:** The care cascade for hepatitis C virus (HCV) faces a significant obstacle due to poor awareness, especially in patients undergoing elective surgery. To address this issue, we introduced an electronic medical record (EMR)-based automatic alert system in 2021 to enhance the awareness among surgical healthcare providers regarding HCV screening and referral rates.

**Methods:** Implemented in a tertiary medical center in South Korea, the system alerts surgeons to order preoperative anti-HCV antibody tests, and if needed, consult hepatologists at discharge for patients undergoing elective surgery.

**Results:** After implementation, the system significantly increased HCV screening rate for 76,310 patients, compared with 129,065 patients undergoing surgery between 2016 and 2020 (82·8–96·8%, $P<0·001$). Out of 73,834 patients who were tested for anti-HCV antibody, the system alerted 12,048 (16·3%) patients. However, out of 463 patients who tested positive for anti-HCV antibody after system implementation, only 42 (15·3%) out of 275 (59·4%) who required consultation were referred to hepatologists. Linkage failure was associated with other surgery departments than hepatobiliary and transplant surgery departments (odds ratio [OR]=5·940, 95% confidence interval [CI], 3·080–12·410, $P<0·001$) and shorter hospitalization duration (OR=0·980, 95% CI, 0·950–0·990, $P=0·012$).

**Conclusions:** Although EMR-based automatic alert system was effective in increasing HCV screening for patients undergoing elective surgery; however, it could not link them to care cas-

cade in surgery departments. Combining more proactive approaches, such as reflex testing or a call-back strategy, would be beneficial.

**Keywords:** Hepatitis C, Electronic based alert system, Notification system, Care cascade

Saturday, June 29, 2024, 09:30-10:20

## 14. MASLD, Clinical 2

### OP-74

### Bariatric Surgery Improves MRI-Determined Hepatic Proton Density Fat Fraction and Metabolic Dysfunction-Associated Steatohepatitis in Patients with Obesity: A Systematic Review and Meta-Analysis

Juchul Hwang[1], Hyeyoung Hwang[1], Seong Hee Kang[2], Jeong-Ju Yoo[3], Mi Young Choi[4], Dong Eun Lee[5], Dae Won Jun[6], Hyunjae Shin[1], Bo Hyun Kim[1], Yuri Cho[1]

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**Aims:** Bariatric surgery has been reported to be an effective way to improve metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction steatohepatitis (MASH) in obese individuals. The current systemic review aimed to assess the changes in MRI-determined hepatic proton density fat fraction (MRI-PDFF) and nonalcoholic fatty liver disease activity score (NAS) after bariatric surgery in MASLD/MASH patients with obesity.

**Methods:** We searched various databases including PubMed, OVID Medline, EMBASE, and Cochrane Library. Primary outcomes were the changes in intrahepatic fat on MRI-PDFF and histologic features of MASH.

**Results:** Thirty studies with a total of 3,134 patients were selected for meta-analysis. Bariatric surgery significantly reduced BMI (ratio of means, 0.79) and showed 72% of reduction of intrahepatic fat on MRI-PDFF at 6 months after bariatric surgery (ratio of means, 0.28). NAS was reduced 60% at 3–6 months compared to baseline, 40% at 12–24 months, and 50% at 36–60 months. Nineteen studies revealed that the proportion of patients with steatosis decreased by 44% at 3–6 months, 37% at 12-24 months, and 29% at 36-60 months; lobular inflammation by 36% at 12–24 months and 51% at 36-60 months; ballooning degeneration by 38% at 12–24 months; significant fibrosis (≥ F2) by 18% at 12-24 months and by 17% at 36–60 months after surgery.

**Conclusions:** Bariatric surgery significantly improved MRI-PDFF and histologic features of MASH in patients with obesity. Bariatric surgery might be the effective alternative treatment option for patients MASFD/MASH who do not respond to life style modification or medical treatment.

**Keywords:** MASLD, Obesity, Bariatric surgery, MRI-PDFF

### OP-75

### Changes in Liver Stiffness and Controlled Attenuation Parameters of Transient Elastography According to Weight Change in Non-Alcoholic Fatty Liver Patients

Seong Kyun Na, Hyo Young Lee

Department of Internal Medicine, Inje University Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

**Aims:** The Controlled attenuation parameter (CAP) and the liver stiffness (LS) of transient elastography (TE) are widely used to measure the degree of fatty liver and liver fibrosis. We investigated whether there were significant changes in CAP and LS according to the amount of weight loss in patients with nonalcoholic fatty liver disease (NAFLD).

**Methods:** The patients with NAFLD at Jeju National University Hospital in Korea who had TE tests more than once while losing body weight were analyzed. CAP and LS were compared between the time of the first test and the time of the weight was most lost during the follow-up.

**Results:** A total of 410 patients were analyzed and 74.6% of patients lost body weight during the follow-up period. Patients who lost weight were divided into 5 groups according to the amount of weight loss (WL), and all groups showed significant CAP change (-25.62 in the 0 to 3% WL group, -21.52 in the 3 to 5% WL group, -41.92 in the 5 to 7% WL group, -32.79 in the 7 to 10% WL group, -74.16 in the more than 10% WL group, all p-values < 0.05). The mean LS change by group was +0.75 in the 0 to 3% WL group, -0.30 in the 3 to 5% WL group, +0.40 in the 5 to 7% WL group, -0.40 in the 7 to 10% WL group, –1.31 in the more than 10% WL group, and was significant only in the more than 10% WL group ($P$=0.002). There was a significant correlation between WL and CAP in the 3 to 5% WL group (Pearson's r=0.300, $P$=0.006) and in the 5 to 7% WL group (Pearson's r=0.330, $P$=0.025), and a significant correlation between WL and LS in the more than 10% WL group (Pearson's r=0.413, $P$=0.010).

**Conclusions:** In patients with NAFLD, there was a significant correlation between weight loss and CAP, and LS decreases significantly when weight loss is greater than 10% of baseline body weight.

**Keywords:** Fatty liver, Body weight, Liver stiffness, Controlled attenuation parameter

Table. Changes of variables in weight loosing group.

| Variables (Pre, post, p-value) | All (n=306) | WL < 3 % (n=97) | 3%<WL< 5 % (n=82) | 5%<WL< 7% (n=46) | 7%<WL< 10% (n=43) | WL>10% (n=38) |
|---|---|---|---|---|---|---|
| BMI, mean ± SD | 29.17 ± 4.09<br>27.60 ± 3.92<br>(<0.001) | 28.60 ± 4.02<br>28.13 ± 3.95<br>(<0.001) | 29.26 ± 4.24<br>28.12 ± 4.08<br>(<0.001) | 29.24 ± 3.76<br>27.49 ± 3.51<br>(<0.001) | 29.76 ± 4.09<br>27.37 ± 3.74<br>(<0.001) | 29.66 ± 4.34<br>25.50 ± 3.60<br>(<0.001) |
| Changes in weight (kg), mean ± SD | -4.28 ± 3.60 | -1.28 ± 0.75 | -3.04 ± 0.68 | -4.67 ± 1.00 | -6.63 ± 1.44 | -11.47 ± 3.79 |
| Transient elastography | | | | | | |
| CAP, mean ± SD | 306.95 ± 41.55<br>272.95 ± 52.63<br>(<0.001) | 308.78 ± 38.85<br>283.16 ± 54.20<br>(<0.001) | 298.12 ± 42.36<br>276.60 ± 44.60<br>(<0.001) | 313.85 ± 38.61<br>271.93 ± 56.96<br>(<0.001) | 304.79 ± 46.34<br>272.00 ± 46.34<br>(<0.001) | 315.45 ± 42.66<br>241.29 ± 56.05<br>(<0.001) |
| LS, mean ± SD | 7.84 ± 4.73<br>7.83 ± 5.38<br>(0.985) | 7.80 ± 5.23<br>8.55 ± 6.22<br>(0.056) | 7.78 ± 3.80<br>7.48 ± 3.85<br>(0.513) | 8.92 ± 7.26<br>9.32 ± 8.39<br>(0.575) | 7.38 ± 2.71<br>6.98 ± 2.82<br>(0.390) | 7.27 ± 2.78<br>5.96 ± 1.72<br>(0.002) |
| APRI score, mean ± SD | 0.60 ± 0.42<br>0.40 ± 0.32<br>(<0.001) | 0.57 ± 0.38<br>0.44 ± 0.35<br>(<0.001) | 0.63 ± 0.41<br>0.40 ± 0.31<br>(<0.001) | 0.63 ± 0.52<br>0.38 ± 0.32<br>(<0.001) | 0.64 ± 0.49<br>0.39 ± 0.36<br>(0.008) | 0.55 ± 0.31<br>0.32 ± 0.19<br>(0.001) |
| FIB-4 score, mean ± SD | 1.60 ± 1.20<br>1.44 ± 1.18<br>(0.001) | 1.68 ± 1.18<br>1.58 ± 1.21<br>(0.267) | 1.60 ± 1.00<br>1.47 ± 1.14<br>(0.125) | 1.83 ± 1.82<br>1.51 ± 1.58<br>(<0.001) | 1.50 ± 0.92<br>1.33 ± 1.01<br>(0.196) | 1.19 ± 0.84<br>1.04 ± 0.69<br>(0.332) |

Abbreviations: APRI, AST to platelet ratio index; BMI, body mass index; CAP, controlled attenuation parameter; FIB-4, fibrosis-4; LS, liver stiffness; SD, standard deviation; WL, weight loss.

## OP-76

### Mobile Lifestyle Intervention with Partial Meal Replacements Improves Liver Functions in Metabolic Dysfunction Associated Steatotic Liver Disease; A Randomized Controlled Trial

Eunbyul Cho[1], Sunwoo Kim[2], Soonkyu Kim[2], Ju Young Kim[3], Hwa Jung Kim[4], Yumi Go[3], Yu-jeong Lee[3], Haesol Lee[3], Siye Gil[3], Sung Kwan Yoon[3]

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**Aims:** As obesity rates rise, metabolic dysfunction associated steatotic liver disease (MASLD) emerges as a significant public health concern worldwide. Therapeutic lifestyle changes are universally recommended for individuals with MASLD. The advent of digital health technologies have opened new pathways for the delivery of lifestyle modification program. Among these interventions, meal replacements have become a practical approach to weight management. While numerous studies have explored dietary substitutes or mobile apps separately, a combined approach involving both interventions has not been previously investigated. The aim of the study was to evaluate the short term mobile intervention coupled with partial meal replacements in patients with MASLD.

**Methods:** In this trial, 88 adults with MASLD and a BMI ≥ 25 kg/m$^2$ from a health examination center were randomized into an intervention group (n=24) using a mobile app with partial meal replacements or a control group (n=25) receiving standard educational materials. Liver enzymes, lipid profiles, and anthropometric measures were assessed at baseline and after 4 weeks. Intention-to-treat analyses were used for statistical evaluations.

**Results:** In the study, 24 participants in the intervention group and 25 in the control group completed the trial. Significant reductions were observed in the intervention group for alanine aminotransferase (ALT) (-28.32vs. -10.67, *P*=0.006) and gamma glutamyl transferase (GGT) ( -27.76 vs. 2.79, *P*=0.014). No significant changes were noted in aspartate aminotransferase (AST), body weight or waist circumference in the intervention group.

**Conclusions:** The 4 weeks of mobile lifestyle intervention incorporating partial meal replacements have shown efficacy in improving liver enzymes profiles in patients with MASLD. This strategy demonstrates potential for mitigating elevated liver enzymes without necessitating alterations in body weight or waist circumference. Further comprehensive, longer periods of researches are needed to substantiate and elaborate on these preliminary outcomes.

**Keywords:** Metabolic dysfunction associated steatotic liver disease, Diet, High-protein low-carbohydrate, Mobile application, Lifestyle risk reduction

## OP-77

### Sequential Diagnostic Approach by Using FIB-4 and ELF for Predicting Advanced Fibrosis in Metabolic-Associated Steatotic Liver Disease

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**Aims:** Hepatic fibrosis is a critical predictor of liver-related mortality in patients with liver diseases. Various screening non-invasive tests (NITs) are available, and the American Association for the Study of Liver Diseases (AASLD) proposed a two-step approach, focusing on diagnostic accuracy, cost, and accessibility. This study aims to evaluate the diagnostic accuracy of fibrosis in metabolic-associated steatotic liver disease (MASLD) patients by utilizing the previously proposed two-step approach, starting with the serum-based fibrosis-4 index (FIB-4) and subsequently employing the Enhanced Liver Fibrosis (ELF) test.

**Methods:** This clinical data and liver biopsies were used for MASLD patients between 2018 and 2023. Various NITs were

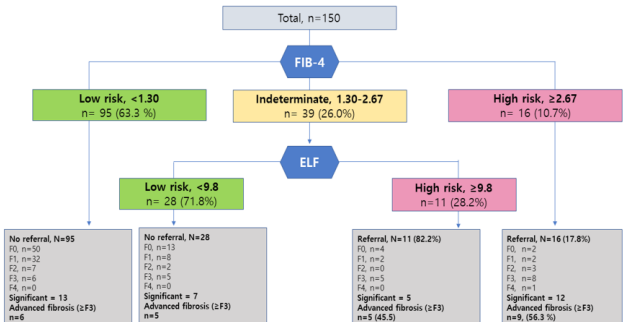
utilized. The degree of fibrosis was determined based on the results of the liver biopsy. The diagnostic performance of these NITs was assessed using the Area Under the Receiver Operating Characteristic curve (AUROC). Moreover, the diagnostic performance of each test, both when used independently and within the two-step strategy using FIB-4 following ELF, was further analyzed using sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV).

**Results:** A total of 150 MASLD patients were included, with a mean age of 46.6 years (median 48 years), 53.3% being male, and 27.3% having type 2 diabetes. The performance of the NITs in identifying advanced fibrosis was as follows: The AUROC of the aminotransferase-to-platelet ratio index, FIB-4, Non-Alcoholic Fatty Liver Disease (NAFLD) fibrosis score, and ELF for advanced fibrosis (≥ F3) were 0.799 (95% CI, 0.726-0.860), 0.732 (95% CI, 0.656-0.803), 0.662 (95% CI, 0.528-0.796), and 0.812 (95% CI, 0.740-0.871), respectively. The combination of FIB-4 ≥ 1.30 and ELF score ≥ 7.7 showed a sensitivity of 76.0%, specificity of 72.0%, PPV of 53.77%, NPV of 87.5%, and accuracy of 73.2% in predicting the diagnosis of advanced fibrosis. Additionally, the combination of FIB-4 ≥ 1.30 and ELF score ≥ 9.8 demonstrated a sensitivity of 56.0%, specificity of 89.6%, PPV of 69.8%, NPV of 82.6%, and accuracy of 79.5% in predicting the diagnosis of advanced fibrosis. This approach allowed the exclusion of 28 individuals (71.8%) from unnecessary liver biopsies.

**Conclusions:** Our study demonstrated that applying NITs previously used in NAFLD to MASLD patients for predicting fibrosis levels did not show inferiority. Therefore, it revealed that implementing a two-step strategy for MASLD patients at primary healthcare facilities, following the AASLD clinical guidelines, can early predict advanced fibrosis. Consequently, this suggests that adopting the diagnostic approach previously utilized for NAFLD patients in MASLD cases can lead to a reduction in unnecessary referrals or biopsies.

**Keywords:** Non-invasive biomarkers, Diagnostic accuracy, Metabolic-associated steatotic liver disease, Hepatic fibrosis

Figure 1. Real-world 2 STEP Algorithm for identify Fibrosis with **MASLD ( advanced diagnosis performance )**




## OP-78

### Effect of Thyroid Hormones on the Progression of NAFLD in a Prospective Cohort

**Sae Kyung Joo**, Heejoon Jang, Donghyeon Lee, Won Kim

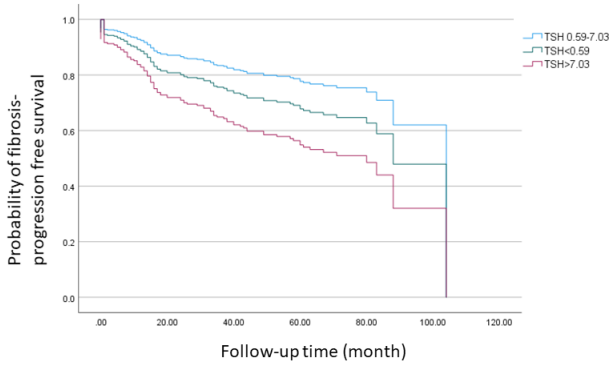
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul, Republic of Korea

**Aims:** Thyroid hormones have been demonstrated to be strongly associated with increased intrahepatic steatosis and the degree of liver fibrosis. However, recent studies have shown inconsistent results in the relationship between thyroid status and metabolic dysfunction-associated steatotic liver disease (MASLD). In this study, we aimed to evaluate the effect of thyroid function on liver fibrosis progression in a biopsy-proven prospective cohort.

**Methods:** A total of 632 subjects with biopsy-proven MASLD (mean age, 52.35 years; 51.4% male) in Boramae Medical Center were enrolled in this study. The patients were divided into three groups based on their thyroid-stimulating hormone (TSH) levels, which were measured according to the Korea National Health and Nutrition Examination Survey (KNHANES) cutoff level (reference range 0.59 to 7.03 mIU/L). To determine changes in hepatic fibrosis, liver stiffness was measured using the FibroScan®.

**Results:** The results indicated that 22 patients exhibited elevated TSH levels and that 113 (17.9%) of the 632 patients exhibited progression of hepatic fibrosis. The findings demonstrated that during follow-up evaluation, the subclinical hypothyroidism group (TSH > 7.03 mIU/L) was associated with the progression of hepatic fibrosis. Multivariate analyses, adjusted for age, sex, and body mass index (BMI), demonstrated a significant independent association between the degree of thyroid dysfunction and liver fibrosis progression (for subclinical hypothyroidism: odds ratio, 2.25; 95% CI, 1.04-4.88; *P*=0.039) (Fig.1).

**Conclusions:** TSH levels may be an important predictor of the development of liver fibrosis in patients with MASLD in this prospective cohort.



**Keywords:** MASLD, Liver fibrosis, Thyroid hormone, Thyroid function

Saturday, June 29, 2024, 09:30-10:20

## 15. LC & Others, Basic

### OP-79

### Verification of Liver Regeneration Using Vascularized Hepatic Microtissue Spheroids Fabricated by Bioprinting

**Jiyoon Byeon**[1], Minji Park[3], Jae-Hun Kim[4], Soraya Salas-Silva[1], Tae Hun Kim[1], Dokyoung Lee[5], Jin-Hyung Shim[3], Won-Soo Yun[3], Songwan Jin[3], Ji Hyun Shin[1], Dongho Choi[1]

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**Aims:** To comprehend the pathophysiology of liver diseases, it is important to implement regeneration processes *in vivo*. In previously reported studies, mouse chemically induced hepatic progenitors (mCdHs) demonstrated liver regeneration in the disease mouse model. It has not been revealed whether there is any difference between the single-cell mixture of mCdHs and the three-dimensional (3D) structured microtissues with endothelial cells. This study aims to apply a 3D bioprinting approach to the liver disease model, to confirm transplant feasibility, and validate its effects.

**Methods:** To generate mCdHs from adult Td-Tomato EGFP mice, primary mouse hepatocytes (mPHs) were isolated and cultured in reprogramming media for 7 days. The mCdHs were characterized in comparison to mPHs, and their long-term maintenance and hepatic differentiation potential were successfully confirmed *in vitro*. We fabricated three types of microtissue spheroids from mCdHs and mouse endothelial cells (mECs) using bioprinting technology and confirmed liver regeneration after transplanting them *in vivo*.

**Results:** Single-cell mixtures of mCdHs and vascularized microtissue spheroids (core-shell, segmented, non-structured) were transplanted into the livers of FAH-/- and FRG-/- mice. Biochemical analysis results on day 10 showed that AST, ALT, and T.BIL levels decreased in all groups compared to the PBS group (negative control). Notably, the single-cell group showed relatively higher AST and ALT levels. Immunohistochemistry and H&E staining revealed positive expression rate differences in the transplanted liver area.

**Conclusions:** This study utilizing 3D bioprinting and mCdHs demonstrated promising results in terms of hepatocyte function and supported the potential of utilizing liver disease modeling and transplantation therapies.

**Keywords:** Microtissue spheroids, Mouse chemically induced Hepatic progenitors (mCdHs), Liver regeneration

### OP-80

### Clusterin Deficiency Exacerbates Cholestatic Liver Disease through ER Stress and NLRP3 Inflammasome Activation

**Hye-Young Seo**, So-Hee Lee', Ji Yeon Park, Seong Hwan Cho, Jae Seok Hwang, Mi-Kyung Kim, Byoung Kuk Jang

Keimyung University School of Medicine

**Aims:** Cholestatic liver disease, characterized by impaired bile flow leading to the accumulation of harmful metabolites and toxins, results in liver damage. Inflammatory cytokines play a crucial role in the progression of this condition. This study investigates the potential anti-inflammatory effects of clusterin, a glycoprotein known for its roles in cell death, lipid transport, and cellular protection, on liver injury induced by a DDC diet.

**Methods:** The study examined the impact of clusterin on liver injury using C57BL/6 mice and Clusterin knockout mice fed a DDC diet for 10 to 20 days. Both primary kupffer cells (KC) and hepatocytes (HC) from these mice were analyzed. Assessments included Sirius red staining, immunohistochemistry, real-time RT-PCR, ELISA, and western blot analysis to determine the effects of clusterin.

**Results:** In Clusterin knockout mice, elevated levels of ALT, AST, collagen, and aSMA were observed post DDC diet-induced liver injury. These mice also showed increased ER stress markers (CHOP, ATF6, p-eIF2alpha) and inflammasome markers (NLRP3, ASC, caspase1, IL1beta protein expression, and IL1beta and IL18 secretion). Thapsigargin, an ER stress inducer, escalated the NLRP3 inflammasome response in primary KC and HC, which was reduced by overexpressing clusterin.

**Conclusions:** This study demonstrates that the absence of clusterin exacerbates ER stress and NLRP3 inflammasome activation in mice fed a DDC diet. Conversely, overexpression of clusterin suppresses ER stress and NLRP3 activation. Therefore, clusterin deficiency is linked to an increased inflammatory response in the liver, which is associated with the upregulation of ER stress.

**Keywords:** Clusterin, Cholestatic liver disease, ER stress, NLRP3 inflammasome

## OP-81

### Characterizing the Exhausted CD8 T Cell Subset in Liver Fibrosis

Jeong-Hyuk Yoon, Nam Hee- Kim, Yong-Hyun Han

Kangwon National University

**Aims:** Liver fibrosis, marked by the aberrant build-up of extracellular matrix proteins, significantly undermines hepatic functionality. Immune mechanisms, particularly those driven by CD8 T cells, demonstrate mixed effects in various liver ailments, such as fibrosis, hepatitis. Through employing single-cell RNA sequencing, this study has identified an increase in a specific CD8 T cell subset in CCl4-induced liver fibrosis. These cells are distinguished by markers indicative of exhaustion and senescence. Given the identification of this cell population, our research aims to advance the understanding of their roles and functionalities within liver fibrosis and to explore potential therapeutic strategies targeting this subset.

**Methods:** Liver fibrosis was induced in murine models via CCl4 administration, diluted with corn oil, over 5-7 weeks. Following induction, immune cells were isolated using collagenase D and subjected to single-cell RNA sequencing and flow cytometry, identifying and characterizing the newly discovered cell population of interest. This methodology facilitated assessment of alterations in cell proportions and phenotypic characteristics.

**Results:** The analysis demonstrated an increase in cells expressing exhaustion markers (PD-1, LAG3, TIM3, CTLA4) and exhibiting a phenotype characteristic of tissue-resident memory cells, indicative of their adaptation to the fibrotic hepatic environment. Additionally, these cells were found to express the aging marker GzmK. Furthermore, a notable augmentation in the proportion of cDC2 cells, along with a specific subset of PD-1+ CXCR6+ CD44+ CD8 T cells, was observed in CCl4-treated mice compared to controls, a pattern similarly detected in mice subjected to an FPC diet.

**Conclusions:** This study identifies a PD-1+ CD8 T cell subset within CCl4-induced liver fibrosis, uncovering their potential significance in disease progression. Given the undefined functions and phenotypes of this subset in the context of liver fibrosis, future efforts will be dedicated to conducting comprehensive research to elucidate their roles and explore therapeutic possibilities within Liver fibrosis.

**Keywords:** Liver fibrosis, T cell

## OP-82

### Characterization and Establishment of Autologous Hepatic Progenitors for the Development of Maple Syrup Urine Disease Treatment

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**Aims:** Maple syrup urine disease (MSUD) is a rare autosomal recessive metabolic disorder. It can result in neonatal death due to the accumulation of branched-chain amino acids (BCAA) in the blood. Currently, the treatment for MSUD involves a lifelong low-protein diet and peritoneal dialysis, which are challenging to maintain, and neurological symptoms persist. It is suggested that the utilization of mouse chemically derived hepatic progenitors (mCdHs) could significantly contribute to the development of a fundamental treatment. To achieve this, it is imperative to initially characterize MSUD and establish autologous mCdHs from neonatal mice.

**Methods:** BCKDHA (Branched chain keto acid dehydrogenase $\alpha$) +/-mice were obtained from the Canadian Mouse Mutant Repository (CMMR) and bred to generate BCKDHA-/-mice with a 266-bp deletion on Chromosome 7. For characterization, BCAA concentrations were measured from plasma, and BCKDHA mRNA expression levels were assessed. BCKDHA-/-mouse-derived mCdHs were generated by HGF, A83-01 and CHIR99021 from mouse primary hepatocytes(mPHs) isolated using MACS with an E-cadherin antibody.

**Results:** We observed that BCKDHA-/-mice had a survival rate of less than 12 days after birth. Additionally, we detected significantly increased BCAA concentrations and decreased BCKDHA mRNA expression levels in BCKDHA-/- mice. Due to the low survival rate, we isolated mPHs from postnatal day 7 and successfully established BCKDHA-/-mouse-derived mCdHs.

**Conclusions:** It is suggested that these established mCdHs could be utilized for gene editing and ex-vivo therapy. Furthermore, it is proposed that transplantation of edited mCdHs could provide a potential therapeutic approach for the treatment of MSUD.

**Keywords:** MSUD, Characterization, Hepatic progenitors

## OP-83

### Differentiation of Human Chemically Derived Hepatic Progenitor Cells to Cholangiocytes on 3D Printed Silicone Stents for Preventing Biliary Complications

Salas Silva Elsy Soraya[1], Haerin Jeon[1], Taeyoung Eom[2], Suk-Hee Park[3], Jinsoo Rhu[2], Ji-Hyun Shin[1], Dongho Choi[1]

[1]Department of Surgery, Hanyang University Medical Center, Republic of Korea, [2]Department of Transplantation Surgery, Samsung Medical Center, Republic of Korea, [3]School of Mechanical Engineering, Pusan National University, Republic of Korea

**Aims:** Biliary complications represent a significant challenge following living-donor liver transplantation (LDLP), with an incidence rate of up to 25%. Among these complications, Biliary stricture leads to digestive issues, jaundice, and abdominal discomfort. Current treatments for biliary stricture, such as endoscopic therapy and stent placement, are constrained by limitations in reach, visibility, and temporally efficacy. This study proposes a solution employing 3D Y-shaped silicone stents coated with human chemically derived hepatic progenitors (hCdHs) to overcome these limitations.

**Methods:** The generation of hCdHs involved the treatment of HGF, CHIR99021, and A83-01 compounds from human primary hepatocytes (hPHs) isolated from the human liver. These hCdHs were seeded onto silicone stents and underwent a 14-day differentiation into cholangiocytes. Immunofluorescence staining confirmed the presence of hCdH-cholangiocytes (hCdH-Chols) on the stents, and qPCR analysis identified cholangiocyte differentiation markers.

**Results:** Immunofluorescence images demonstrated an increase in cell population of hCdH-Chols as hCdHs differentiated. Furthermore, PCR results showed a significant upregulation in cholangiocyte marker gene expression of hCdH-Chols on the stent compared to hCdHs, resembling or surpassing the expression levels in hCdH-Chols cultured in 2D environment.

**Conclusions:** This study highlights the successful differentiation of hCdHs into cholangiocytes on silicone stents. These results suggest a promising patient-specific therapeutic strategy in treatment of biliary tract diseases.

**Keywords:** Bile duct, Silicone stents, Cell reprogramming

Saturday, June 29, 2024, 09:30-10:30

## 16. LC Clinical & Liver Failure 2

### OP-84

### Non-Cirrhotic Portal Hypertension(NCPH): Demographic, Clinicopathological, Short And Long Term Outcome of Shunt Surgery – PSRS- A Tertiary Care Hospital Experience in Eastern India (Odisha)

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**Aims:** NCPH includes extrahepatic portal vein obstruction (EHPVO) and non cirrhotic portal fibrosis (NCPF).Shunt surgery is commonly indicated in endoscopically refractory varices, symptomatic hypersplenism, severe thrombocytopenia, Portal biliopathy. PSRS is most commonly performed Aims : To study Demographic, clinicopathological & short term and long term Surgical outcomes in patients who underwent PSRS .

**Methods:** All patients diagnosed as NCPH between January 2016 and December 2022 at IMS&SUM Hospital,Bhubaneshwar were retrospectively reviewed. patients who underwent PSRS procedure were evaluated postoperatively using clinical, laboratory parameters, Ultrasound Doppler and dynamic CT Portography.

**Results:** Of 66 patients (49(74.2%) EHPVO, 17(25.7%) NCPF), mean age 27.15±7.72years, 38 males and 28 females. Mc symptom was UGI bleed (Hematemesis(33). On endoscopy, 55(83.3%) patients had esophageal varices, Among 54 patients who underwent surgery, 38(69.1%)proximal splenorenal shunt(PSRS), 6(10.9%)had splenectomy with devascularization(SD), and 10(18.2%) had only splenectomy(OS). Mc Indications for surgery was variceal bleeding(VB) requiring multiple EVL(81.8%,n=45). Major complications affected 10.9%(n=6). Over 41.9±15.27months' mean follow-up. Of shunted patients, patent shunts and complete variceal regression occurred in 30. Shunt patency rate using ultrasound Doppler and dynamic CT portography 90% and 80% respectively after 1 year and decreased to 85% and 70% after 2 years.

**Conclusions:** Conclusion: In Post PSRS patients short term outcome is good while shunt patency rate decreases over time - 91.6%,89.28%,80% at 1year,3 &5 year respectively. Dynamic CT portography is useful modality for assessment of shunt patency in early and late postoperative periods. PSRS caused marked resolution (80%) of portal biliopathy symptoms. SD is acceptable alternative where shunt is not feasible.

**Keywords:** PSRS, SHUNT, NCPH

### OP-85

### Prognostic Value of Geriatric Nutritional Index in Patients with Decompensated Cirrhosis: A Single-Center Cohort Study

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**Aims:** Nutritional assessment is critical in patients with decompensated liver cirrhosis to maintain quality of life and improve survival. Nevertheless, the predictive value of nutritional index for the outcome of decompensated cirrhosis remains uncertain. This study aims to determine the potential prognostic value of nutritional index in predicting the liver transplantation (LT)-free survival of decompensated cirrhosis.

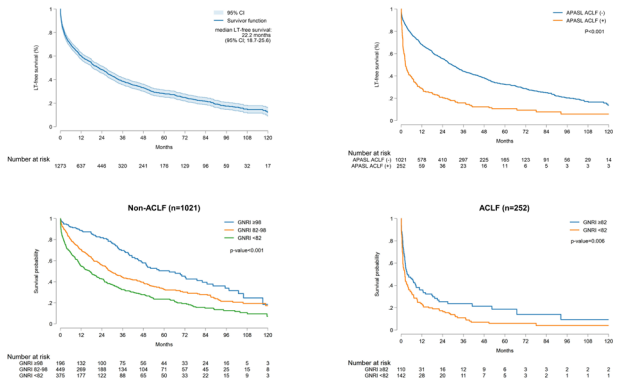
**Methods:** This is a single-center, retrospective study that included consecutive patients presenting with first-onset decompensated complications to Uijeongbu St. Mary's Hospital

from January 2013 to December 2022. Nutritional assessment in this study utilized the geriatric nutritional risk index (GNRI), which was calculated based on serum albumin levels, body weight, and height. The primary end point was LT-free survival.

**Results:** The study included 1273 patients, with a median age of 57 years, of whom 69.5% were male. Alcoholic-related liver disease was the most common cause of liver disease in this cohort (65.2%), followed by chronic hepatitis B (15.9%), non-alcoholic steatohepatitis (11.6%), chronic hepatitis C (3.7%), and autoimmune hepatitis or primary biliary cholangitis (3.5%). At the time of the first admission, the most common complications observed were ascites (71.2%), followed by variceal bleeding (52.2%), hepatic encephalopathy (26.6%), spontaneous bacterial peritonitis (5.4%), and hepatorenal syndrome (11.8%). GNRI values were used to classify the participants into three risk groups: normal (> 98; n=208), mild to moderate risk (82–98; n=547), and severe risk (< 82; n=517) (refer to Table 1). The median LT-free survival was 22.2 months (95% CI; 18.7-25.6 months). We conducted analysis based on ACLF; ACLF group (n=1021) and non-ACLF (n=252). The median LT-free survival was 29.5 months (95% CI, 26.4-33.1) in the non-ACLF group and 2.6 months (95% CI, 2.1-3.8) in the ACLF group ($P$<0.001), respectively (refer to Figure 1). In the non-ACLF group, Age ≥ 55 (HR 1.54; 95% CI 1.31-1.82, $P$<0.001), MELD ≥ 20 (HR 1.71; 95% CI 1.41-2.09, $P$<0.001), Child-Pugh class B (HR 1.50; 95% CI 1.13-1.99, $P$=0.005), Child-Pugh class C (HR 1.91; 95% CI 1.40-2.60, $P$<0.001), GNRI 82-98 (HR 1.40; 95% CI 1.08-1.83, $P$=0.013), and GNRI < 82 (HR 1.79; 95% CI 1.35-2.38, $P$<0.001) were independent predictors of LT-free survival. In the ACLF group, GNRI < 82 (HR, 1.12; 95% CI, 1.02-1.23, $P$=0.021) was only independently associated with LT-free survival.

**Table 1.** Distribution of patients based on GNRI values

| GNRI | Total (n=1273) | Non-ACLF (n=1021) | ACLF (n=252) | P-value |
|---|---|---|---|---|
| ≥ 98 | 208 (16.4%) | 196 (19.2%) | 12 (4.8%) | < 0.001 |
| 82-98 | 547 (43.0%) | 449 (44.0%) | 98 (38.9%) | |
| < 82 | 517 (40.6%) | 375 (36.8%) | 142 (56.3%) | |




**Conclusions:** In conclusion, nutritional index is independent predictor of LT-free survival in patients with decompensated cirrhosis irrespective of ACLF. Integrating nutritional index with established prognostic factors may improve prognostic accuracy and guide treatment decisions.

**Keywords:** Liver cirrhosis, Nutritional assessment, Survival

## OP-86

### Sarcopenia as an Independent Factor for Mortality in Liver Cirrhosis Patients with Spontaneous Bacterial Peritonitis

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Department of Internal Medicine, Jeonbuk National University Medical School and Research Institute of Clinical Medicine of Jeonbuk National University Hospital-Jeonbuk National University Medical School, Jeonju, South Korea

**Aims:** This study aimed to investigate the initial treatment response and mortality of spontaneous bacterial peritonitis (SBP) in cirrhotic patients according to the presence of the sarcopenia.

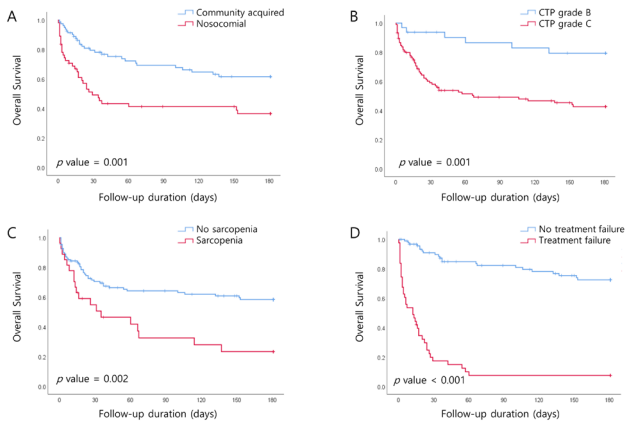
**Methods:** Data were retrospectively reviewed for patients with liver cirrhosis who were admitted for treatment of SBP at Jeonbuk National University Hospital from January 2004 to December 2020. Sarcopenia was measured using the skeletal muscle index at the third lumbar vertebra and defined as the lowest quintile.

**Results:** A total of 137 patients were enrolled in the study, with sarcopenia cut-off values set at 35.82 for men and 30.49 for women. In the demographic and baseline characteristics, there were no statistically significant differences related to the presence of sarcopenia, except for hemoglobin levels. Clinical outcomes were compared based on the presence of sarcopenia, revealing no difference in treatment response according to sarcopenia status. While there were no significant differences in short-term mortality rates at 7 and 30 days, the sarcopenia group exhibited statistically significant higher mortality rates at 3 months, 6 months, 12 months, and in-hospital. Additionally, we conducted a Cox regression analysis on 6-month survival, identifying four significant predictors of mortality in the multivariate analysis: acquisition type (nosocomial vs. community-acquired), CTP grade C versus B, treatment failure, and sarcopenia, with sarcopenia showing an odds ratio of 7.647 (95% CI 1.231-47.501, $P$=0.029). In the Kaplan-Meier survival curve, we observed that survival was significantly differentiated by the four major predictors of mortality, as evidenced by p-values from the log-rank test.

**Conclusions:** Sarcopenia did not show a significant difference in baseline characteristics or treatment response in cirrhotic patients with SBP. However, it was confirmed as an independent risk factor for prognosis after SBP treatment, along with

other established factors such as nosocomial infection, CTP grade C, and treatment failure.

**Keywords:** Sarcopenia; Liver cirrhosis, Spontaneous bacterial peritonitis, Treatment outcome




## OP-87

### Wearable Technology for the Management of Liver Cirrhosis and Hypertension: A New Tool

Manvendra Singh[1], Deepika Singh[2]

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**Aims:** In India, liver cirrhosis and hypertension is a prevalent and important causes of mortality. Wearable smartwatches today include functions for heart rate monitoring, liver diseases and cardiovascular disease detection, and health-related information. We did a feasibility study to investigate the use of wearable smart watches to data from patients and collect data from sensors.

**Methods:** Approaches Adults from the central region of India who experienced viral hepatitis screening in their primary care physicians' offices were evaluated as part of this prospective cohort screening study between March 2022 and October 2022. Four machine learning-based models, -naive bayes (NB), and random forest (RF) K nearest neighbors (KNN), support vector machine (SVM) were used, and their predictive abilities were evaluated, using the clinical characteristics of the patients that were taken from a structured poll.

**Results:** 110 patients participated, regularly use the watches, and completed the study. The binary models of logistic regression showed that lower compliance with lifestyles, lower compliance with medications, and higher total compliance are important predictors of compliance. The heart rate and data of the accelerometer were determined from the devices directly. Secondary results such as questionnaire survey, heart rate, and physical activity were provided with an average day of 60.2, 61.3, and 58.2 respectively. Patients are requested to fill in the feedback on the wearable smart watch devices related to the secondary function of these watches and how the system could be amended and manage their diseases.

**Conclusions:** We speculated that participants with hypertension and liver cirrhosis continuously wear and use the wearable system and provide positive feedback for this technology.

**Keywords:** Wearble, Management, Liver cirrhosis

## OP-88

### Risk of Serious Infection in Patients with Chronic Liver Disease: A Nationwide Population-Based Cohort Study

Won Sohn[1], Hyunwoo Oh[1], Ju-Yeon Cho[2], Jung Hee Kim[3], Jae Yoon Jeong[4], Yong Kyun Cho[1], Byung Ik Kim[1]

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**Aims:** This study aimed to investigate the risk of serious infection in patients with chronic liver disease.

**Methods:** This cohort study from the Korean National Health Insurance Service included a population-based data collected from 1,699,159 patients with chronic liver disease between 2009 and 2021. The definition of serious infection was hospital admissions with ICD-10 codes for acute meningitis, acute osteomyelitis, bacteremia, pneumonia, pyelonephritis, serious gastrointestinal infection, skin and soft tissue infections, spontaneous bacterial peritonitis, and COVID-19 infection. We compared the development of serious infection, the admission of intensive care unit (ICU), and mortality between chronic liver disease/compensated cirrhosis and decompensated cirrhosis.

**Results:** The mean age of the patients was 57.4 years, with 55.6% of them being men. The most common cause of chronic liver disease was chronic hepatitis B (59.5%). The study population consisted of 1,614,085 patients (95%) with chronic liver disease/compensated cirrhosis and 85,074 patients (5%) with decompensated cirrhosis. During the follow-up period, 12.5% of patients with chronic liver disease/compensated cirrhosis, and 23.9% of patients with decompensated cirrhosis experienced serious infections ($P$<0.01). The most common infections were pneumonia, followed by serious gastrointestinal infection, pyelonephritis, bacteremia, skin and soft tissue infections, spontaneous bacterial peritonitis, acute osteomyelitis, acute meningitis, and COVID-19 infection. The risk of serious infections is higher in decompensated cirrhosis than in chronic liver disease/compensated cirrhosis (adjusted hazard ratio [HR] 2.43 with confidence interval [CI]: 2.38-2.47). Patients with decompensated cirrhosis had higher admission rate on ICU for serious infections com-

pared to chronic liver disease/compensated cirrhosis: 16.9% vs. 1.8%, *P*<0.01). The mortality rates were 4.2, 40.0, and 107.7 per 1,000 person years in patients with no, 1, and ≥ 2 serious infections. The adjusted HRs for all-cause mortality in patients with 1 and ≥ 2 serious infections, compared to no serious infection were 5.48 (95% CI: 5.41-5.56), and 11.20 (95% CI: 11.00-11.40).

**Conclusions:** The risk of serious infection is higher in patients with decompensated cirrhosis. The mortality in patients with chronic liver disease is growing as the risk of serious infection increases.

**Keywords:** Liver cirrhosis, Decompensation, Infection

## OP-89

### Terlipressin Given by Continuous Intravenous Infusion versus Intravenous Boluses in the Treatment of Hepatorenal Syndrome: A Systematic Review and Meta-Analysis

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**Aims:** Available guidelines recommend terlipressin with albumin as part of the management of hepatorenal syndrome. To date, there is no consensus on whether terlipressin should be given via bolus or continuous intravenous infusion. The study aims to compare the effectiveness and safety of continuous intravenous infusion versus intravenous boluses of terlipressin in the treatment of adult patients with HRS.

**Methods:** Searches for eligible studies were made in PubMed, EMBASE, the Cochrane Library, and ClinicalTrials.gov. Included studies were randomized controlled trials (RCTs) enrolling adult patients with HRS. Primary outcome is response to therapy defined as decrease in serum creatinine or regression of acute kidney injury (AKI), while secondary outcomes are safety in terms of drug-related events, mortality, and transplant-free survival. The reviewers independently screened the studies and assessed the methodological quality using the Cochrane Risk of Bias tool. Random-effects meta-analysis was done using Review Manager 5.4.

**Results:** A total of three studies, one high quality and two moderate quality RCTs, were included, involving a total of 240 patients. Pooled analysis showed that continuous infusion was as effective or better than bolus infusion in achieving the primary outcome (RR 1.12, 95% CI 0.95-1.32, $I^2$=0%). In one study, 28- and 90-day mortality were not significantly different, while 90-day transplant-free survival was not significantly different between continuous and bolus groups from another trial (53% vs 69% *P*=0.26). Higher incidence of adverse events was also reported in the bolus group, RR 0.36, 95% CI 0.14-0.93 (*P*=0.02).

**Conclusions:** There is moderate certainty evidence to suggest that continuous infusion of terlipressin leads to more frequent regression of AKI than bolus infusion, and that continuous infusion is associated with lower adverse events. Larger RCTs with higher quality are needed to ascertain the effects on mortality, need for renal replacement therapy, and transplant-free survival.

**Keywords:** Hepatorenal syndrome, Terlipressin, Bolus infusion, Continuous infusion

Saturday, June 29, 2024, 09:30-10:30

# 17. DILI & Infection

## OP-90

### Thromboembolic Event Risk Factors in Patients with Liver Abscesses: Development of a Predictive Nomogram

Jaejun Lee[1,2], Soon Woo Nam[1,3], Jung Hyun Kwon[1,3], Dong Jae Shim[4], Seung Hwan Baek[4], Soon Kyu Lee[1,3]*

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**Aims:** Thromboembolism, a serious complication in patients with liver abscesses, can lead to organ deterioration if left untreated. However, factors associated with thromboembolism in these patients remain poorly understood. We aimed to identify the factors associated with thromboembolism in patients with liver abscesses.

**Methods:** Data from 325 patients diagnosed with liver abscesses between March 2019 and June 2023 were retrospectively collected. Clinical and laboratory variables associated with thromboembolic events and metastatic infections were analyzed using logistic regression. A nomogram for predicting thromboembolism was constructed using significant predictors.

**Results:** Among the 325 patients, the median age was 68.0 years, and included 129 women. Fifty patients experienced thromboembolic events and 44 had metastatic infections. Significant predictors for thromboembolic events included white blood cell (WBC) ≥ 20 000/μL (odds ratio [OR] 3.401, *P*=0.002), platelet count < 100 000/μL (OR 3.291, *P*=0.004),

and abscess septation (OR 2.704, *P*=0.007). Age ≥ 65 years (OR 0.457, *P*=0.040), WBC ≥ 20 000/ $\mu$L (OR 3.340, *P*=0.005), and abscess septation (OR 2.909, *P*=0.008) were identified as factors associated with metastatic infections. A nomogram was constructed to predict thromboembolism using the following four variables: WBC ≥ 20 000/ $\mu$L, platelet count < 100 000/ $\mu$L, albumin < 2.8 g/dL, and abscess septation, and demonstrated an AUROC of 0.755.

**Conclusions:** High WBC count, low platelet count, and abscess septation were identified as risk factors for thromboembolic events in patients with liver abscesses. The nomogram established for thromboembolism prediction will allow clinicians to identify at-risk patients.

**Keywords:** Liver abscess, Thromboembolism, Metastatic infections, Septation

## OP-91

### Modulation of Endoplasmic Reticulum Stress by Synergetic Effect of Kaempferol and Resveratrol to Enhances Improvement in Liver Disease

**Neha Sharma**, Anand Krishna

Department of Life Science, Devi ahilya University and Shri Vaishnav Vidyapeeth Vishwavidyalaya, India

**Aims:** Non-alcoholic fatty liver disease (NAFLD) is a widespread chronic liver condition with substantial clinical significance. Endoplasmic reticulum (ER) stress plays a pivotal role in driving inflammatory responses, lipid metabolism, and insulin signal transduction among NAFLD condition. Therefore, targeting ER stress represents a promising therapeutic approach for NAFLD management. This study investigates the synergistic effect of kaempferol and resveratrol in modulating ER stress to enhance NAFLD improvement

**Methods:** We investigated the synergistic effects of kaempferol and resveratrol on ER stress modulation and their impact on NAFLD improvement. Utilizing *in-vitro* and *in-vivo* in rat models of NAFLD, co-administration of kaempferol (15 mg/kg/day) and resveratrol (15 mg/kg/day) exerted a potent synergistic effect in reducing ER stress markers, Along with the lipid profiling we have done phosphorylated eukaryotic initiation factor 2 $\alpha$ (p-eIF2 $\alpha$), activating transcription factor 6 (ATF6), Serum glutamate pyruvic transaminase (SGPT),gamma-glutamyl transpeptidase ( $\gamma$ -GT), Insulin resistance, homeostatic model assessment of insulin resistance (HOMA-IR), and Histology of liver tissue

**Results:** The combined treatment effectively reduced hepatic steatosis, inflammation, and fibrosis in high-fat diet-induced NAFLD rats. Kaempferol and resveratrol synergistically activated AMPK and PPAR $\alpha$ while decreasing p-eIF2 $\alpha$ levels. Hepatic TG content decreased by 35%, VLDL levels by 20%, and HDL levels increased, indicating improved lipid metabolism. SGPT and $\gamma$ -GT levels decreased, suggesting enhanced liver function and insulin sensitivity, supported by HOMA-IR improvements. Histological analysis showed significant enhancements in liver tissue architecture

**Conclusions:** Overall, our findings demonstrate that the synergistic action of kaempferol and resveratrol effectively alleviates ER stress and improves NAFLD by targeting multiple signalling pathways. These results provide novel insights into the therapeutic potential of natural compounds in the management of NAFLD and improving lipid profile, liver function, and insulin sensitivity, thus highlighting its therapeutic potential in managing metabolic liver disorders.

**Keywords:** Endoplasmic reticulum stress, Kaempferol and resveratrol, Insulin resistance, Activating transcription factor 6

## OP-92

### Pterostilbene Loaded Lipid Polymer Hybrid Nanoparticles Protect against Hepatic Ischemia-Reperfusion Injury in Rats via Alteration of Bcl-2/Bax and NF-κB/SMAD-4 Pathways

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Pharmaceutical Sciences, SHUATS, India

**Aims:** Hepatic ischemia/reperfusion injury (IRI) represents a significant form of liver damage that can result in severe organ failure, often associated with procedures such as liver surgery, liver transplantation, and shock. This study outlines the formulation and characterization of lipid-polymer hybrid nanoparticles (LPHNPs) loaded with pterostilbene (PT). The nanoparticles were scrutinized for their effectiveness against hepatic injury induced by ischemia/reperfusion (IR), and the underlying mechanisms were evaluated.

**Methods:** Swiss Wistar rats were used in the study and PT-LPHNPs was orally given to the rats. The hepatic, non-hepatic, oxidative stress parameters, cytokines, inflammatory and apoptosis parameters were estimated. mRNA expression of apoptosis parameters were estimated. Immunohistochemical analysis for hepatic SMAD-4 and NF- $\kappa$ B was carried out in addition to histopathological investigation.

**Results:** The PT-LPHNPs exhibited the particle size (163.2 nm), entrapment efficiency (96.53%) and zeta potential (-0.660 mV). The TEM and photomicrograph images showed the dense spherical shape of optimized aforementioned formulation. PT-LPHNPs remarkably suppressed the level of hepatic parameters like AFP, AST, ALT, ALP; non-hepatic parameters such as TBL, GGT. PT-LPHNPs significantly (*P*<0.001) altered the level oxidative stress parameters viz., MDA< SOD, CAT, GSH, GPx; inflammatory cytokines like TNF- $\alpha$, IL-1 $\beta$, Il-6, IL-10, IL-18, IL-33; inflammatory parameters like COX-2, iNOS, VEGF, PGE2, NF- $\kappa$ B, respectively. PT-LPHNPs treatment remarkably suppressed

the NF-κB and SMAD-4 protein expression. LPHNPs treatment remarkably altered the expression of Bax, Bcl-2 and caspase-3.

**Conclusions:** The current finding suggest that PT-LPHNPs possesses a potential effect against hepatic injury via alteration of Bcl-2/Bax and NF-κB/SMAD-4 pathways.

**Keywords:** Hepatic ischemia-reperfusion injury, Pterostilbene loaded lipid polymer hybrid nanoparticles, NF-K B/SMAD-4 pathways

## OP-93

### Antihyperlipidemic and Anti-Obesity Effects of Germinated Chickpea (Cicer arietinum) Sprouts Flour Supplementation on Liver Function and Glucose Metabolism in Wistar Male Rats

**Yogesh Dayma**, Shewta Choudhary

Life Sciences, Jawaharlal Nehru University, New Delhi, India

**Aims:** This study investigates the antihyperlipidemic and anti-obesity effects of chickpea (Cicer arietinum) sprouts flour supplementation on adipogenesis, insulin resistance, glucose tolerance, and liver function in Wistar rats fed a high-fat high-fructose diet (HFD).

**Methods:** Rats were divided into control (n=10) and HFD (n=20) groups for eight weeks. Intervention involved dividing the HFD group into two subgroups: HFD (n=10) and germinated chickpea sprouts flour supplementation (10gm/body weight) group (n=10), for 12 weeks. At 12 weeks, all rats were assessed for adipogenesis, insulin resistance, glucose tolerance, and liver function. Phospho-AKT1 protein levels, hepatic malondialdehyde (MDA), oxidative stress, and biochemical parameters were measured.

**Results:** Germinated chickpea sprouts flour supplementation maintained plasma glucose and liver hormone levels, increased insulin receptor (INSR) and protein kinase B (AKT) mRNA expression, phospho-AKT1 protein concentration, phosphofructokinase (PFK) mRNA, pyruvate kinase (PK) mRNA, and activated protein kinase (AMPK) mRNA expression, and reduced glucose triglyceride index (TyG), glucose, insulin, HOMA-IR, hypercorticosteronemia, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase compared to the HFD group. These effects contributed to the reduction of gluconeogenesis, hyperinsulinemia, and adiposity.

**Conclusions:** Germinated chickpea sprouts flour supplementation emerges as a promising alternative for modulating adipogenesis and glucose metabolism without interfering with liver hormones in animals with insulin resistance induced by a high-fat high-fructose diet.

**Keywords:** Animal model, Cicer arietinum prouts, Liver functions

## OP-94

### Enhancing Liver Health in Type 2 Diabetes: CD26 Inhibitors & Glycine Max Antioxidants Synergy

**Anand Krishna Singh**, Purnima Tripathi

Department of Science, Shri Vaishnav Vidypeeth Vishwavidyalaya, India

**Aims:** Non-alcoholic fatty liver disease (NAFLD) is the predominant chronic liver ailment globally, afflicting over half of type 2 diabetes mellitus (T2DM) patients due to exacerbated insulin resistance, oxidative stress, and inflammatory disruptions. A promising avenue for T2DM treatment involves leveraging the incretin hormone GLP-1. Dipeptidyl peptidase-IV (DPP-IV/CD26) inhibitors, sourced from *Glycine max*'s phenolic-rich fraction, may exhibit pleiotropic effects via the presence of incretin hormone receptors in diverse tissues, including the liver. Our study explores the potential impact of DPP-IV inhibitors with antioxidant capabilities on NAFLD in a T2DM rat model

**Methods:** Wistar rats underwent T2DM induction via a high-sucrose diet and dexamethasone. Biochemical, toxicological, and histological parameters were assessed. Evaluations encompassed serum DPP-IV inhibition, glycosylated hemoglobin, HOMA-IR, hepatic lipid peroxidation, SGOT, SGPT, and tissue antioxidants. Serum lipid profiles were examined to correlate with the antiperoxidative effects of *Glycine max's* phenolic-rich fraction.

**Results:** Diabetes induction via corticosteroid and high sucrose diet was confirmed by HOMA-IR (2.5%), HOMA-β (36.3%), and HOMA sensitivity (44.3%). In-vitro DPP-IV inhibition assay demonstrated 63.1±2.8%, while serum activity was 41.9±1.3%. The DPP-IV inhibitors lowered aminotransferases (SGOT & SGPT) and alkaline phosphatase, elevated insulin, and reduced HbA1c. Triglyceride and cholesterol levels normalized. *Glycine max* extract exhibited superior antioxidant capacity, safeguarding against lipid peroxidation, and preserving liver histoarchitecture, emphasizing positive outcomes post-DPP-IV inhibitor treatment.

**Conclusions:** DPP-IV inhibitors along with antioxidant properties improve insulin sensitivity, reduce oxidative stress and toxicity which lead to improve liver dysfunction in T2DM.These findings also suggest that GLP-1 in liver has beneficial effects on NAFLD.

**Keywords:** Dipeptidyl peptidase-IV, NAFLD, Diabetic mellitus, Incretin hormones

## OP-95

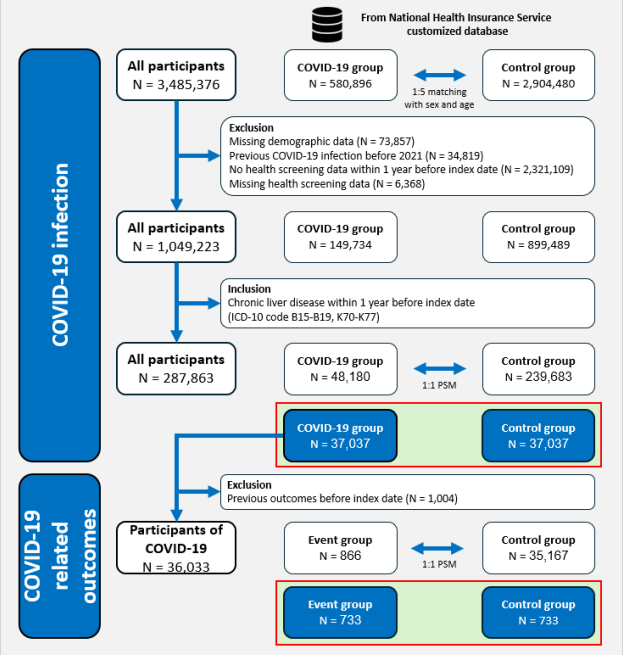
### Association between Ursodeoxycholic Acid Use and COVID-19 in Individuals with Chronic Liver Disease in South Korea

**Sang Yi Moon**[1,2], Minkook Son[2,3], Yeo Wool Kang[1], Yang Hyun Baek[1]

[1]Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea; [2]Department of Data Sciences Convergence, Dong-A University Interdisciplinary Program, Busan, South Korea; [3]Department of Physiology, Dong-A University College of Medicine, Busan, South Korea

**Aims:** Conflicting results have been reported regarding the effects of ursodeoxycholic acid (UDCA) administration on COVID-19 infection in individuals with chronic liver disease (CLD), which warrant further investigation. In this study, we aim to evaluate the association between UDCA administration and COVID-19 infection and its related outcomes in individuals with CLD.

**Methods:** A customized COVID-19 research database (n=3,485,376) was created by integrating data from the National Health Insurance Service (NHIS) and the Korea Disease Control and Prevention Agency's COVID-19 databases. UDCA prescription information for the 365 days before the COVID-19 diagnosis was used to calculate each participant's cumulative defined daily dose (cDDD) and cumulative exposure duration (cED). The primary endpoint was the first confirmed positive result for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In addition, we identified severe COVID-19-related outcomes. Multivariate logistic regression was utilized to calculate adjusted odds ratios (OR) with 99% confidence intervals (CI).




**Results:** For this study, individuals with CLD were identified from a customized COVID-19 research database, PSM was applied, and 74,074 individuals were included in the analysis. The participants' average age was 57.5 years, and 52.1% (19,277) of those in each group were male. The study showed that individuals with prior exposure to UDCA had a significantly lower adjusted OR of 0.80 (95% CI: 0.76–0.85, P-value < 0.001) for COVID-19 infection than those without exposure. Furthermore, the adjusted OR for COVID-19-related outcomes was also significantly lower in the UDCA exposure group at 0.67 (95% CI: 0.46–0.98, P-value: 0.04). Subgroup analyses based on cDDD and cED showed consistent trends of decreased risk with greater exposure to UDCA.

**Conclusions:** Our large observational study highlights the potential use of readily available UDCA as an adjunctive therapy for COVID-19 in individuals with CLD.

**Keywords:** UDCA, COVID-19, Chronic liver disease

Saturday, June 29, 2024, 09:30-10:20

## 18. ALD & Genetics

### OP-96

### Protective Effect of Hepatic Stellate Cell-Derived Retinoids in Alcohol-Induced Steatotic Liver Disease

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**Aims:** Despite acetaldehyde being highly mutagenic and carcinogenic, early stage of alcohol-associated liver disease (ALD) is predominantly presented with hepatic steatosis. We previously reported that hepatocytes and their neighboring hepatic stellate cells (HSCs) form a glutamate-mediated bidirectional loop pathway to induce steatosis, indicating the role of HSCs in the pathogenesis of ALD. This study aims to identify a novel metabolic synapse between hepatocytes and HSCs through which retinoids exert protective effect on hepatocytes in ALD.

**Methods:** Wild-type and alcohol dehydrogenase class 3 knockout (ADH5 KO) male mice were fed with liquid diet containing 4.5% ethanol (EtOH) or an isocaloric maltose-dextrin (Pair) for 8 weeks. Serum biochemical assessment, including bile acids (BAs) measurement, was performed. Liver tissues were subjected to GeoMX spatial transcriptomics, bulk RNA-sequencing and western blot analyses. Freshly isolated HSCs and hepatocytes were analyzed for gene expressions or subjected to in vitro experiments.

**Results:** Following chronic alcohol consumption, the serum level of BAs was increased. In qRT-PCR, genes related to BA transporters (Abcc3, Abcc4) and retinoic acid (RA)-degrading enzyme (Cyp26a1) were elevated in EtOH-fed hepatocytes compared to pair-fed controls. Moreover, loss of retinol-storing lipid droplets was observed in freshly isolated HSCs, in which the expression of retinol metabolism-related genes (Adh5, Aldh1a1, Rarb), as well

as Nr1h4, which encodes the BA receptor FXR, was upregulated in HSCs of EtOH-fed mice. In vitro, FXR stimulation in HSCs increased Adh5 expression and RA production, while RA treatment suppressed Myc and γ-H2AX, as well as xCT-encoding Slc7a11 in EtOH-exposed hepatocytes. In ADH3 KO mice, we observed an aggravation in steatosis and liver injury, implicating the protective effect exerted by HSCs and their retinoids.

**Conclusions:** Our study reveals that, upon chronic alcohol consumption, hepatocytes and HSCs form a metabolic synapse through metabolites including BAs and RAs by which hepatocytes may be protected against alcohol-induced steatosis and liver injury.

**Keywords:** Retinoids, Hepatic stellate cells, Bile acids, Metabolic synapse

## OP-97

### Gut Microbiota Dysbiosis in Alcoholic Liver Disease Progression: Therapeutic Insights via Gut-Liver Axis

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**Aims:** This systematic review aims to explore the impact of gut microbiota dysbiosis on the pathogenesis and progression of alcoholic liver disease (ALD), while also investigating potential therapeutic interventions targeting the gut-liver axis.

**Methods:** A comprehensive search was conducted across major scientific databases, including PubMed, Web of Science, and Scopus, up to January 2024. Studies examining the association between gut microbiota composition and ALD progression, as well as therapeutic interventions modulating the gut-liver axis, were included. Quality assessment was performed using established criteria for systematic reviews.

**Results:** A total of 67 relevant articles were identified, comprising both preclinical and clinical studies. The analysis revealed a consistent dysbiosis in gut microbiota composition among ALD patients, characterized by decreased diversity and altered abundance of specific taxa. Furthermore, dysbiotic gut microbiota was found to contribute to ALD progression through various mechanisms, including increased intestinal permeability, microbial translocation, and production of harmful metabolites. Therapeutic interventions targeting the gut-liver axis, such as probiotics, prebiotics, and fecal microbiota transplantation, demonstrated promising effects in ameliorating ALD severity and improving liver function.

**Conclusions:** Gut microbiota dysbiosis plays a crucial role in the pathogenesis and progression of ALD, highlighting the significance of the gut-liver axis in disease development. Therapeutic strategies aimed at restoring gut microbiota homeostasis hold potential for mitigating ALD progression and improving clinical outcomes. These findings underscore the importance of further research in elucidating the complex interplay between gut microbiota and ALD, ultimately facilitating the development of novel therapeutic approaches.

**Keywords:** Alcoholic liver disease, Gut microbiota dysbiosis, Gut-liver axis, Therapeutic interventions

## OP-98

### Psyllium Fiber Improves Hangovers and Inflammatory Liver Injury by Inhibiting Intestinal Drinking

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**Aims:** Excessive alcohol intake often leads to hangovers and inflammatory damage to the liver, a major health concern. Current treatment options for hangovers are still insufficient, highlighting the urgent need for new therapeutic approaches. Psyllium fiber (PF) is well-known for its gastrointestinal benefits, but its effect on hangovers is less explored.

**Methods:** We utilized a mouse model with a single binge drinking (4 g/kg) to induce hangover and inflammatory liver injury. Intestine and liver injury were serologically and histologically estimated. Hangover symptoms were assessed using cylinder and footprint tests to objectively quantify hangover symptoms in mice.

**Results:** Binge drinking significantly activated alcohol-metabolizing enzymes in the small intestine and liver, leading to inflammatory damage. Concurrently, there was an increase in alcohol metabolites such as acetaldehyde and acetone, which showed a positive correlation with hangover symptoms in mice. Interestingly, the oral administration of PF (100 mg/kg) alongside alcohol consumption significantly reduced the activity of these enzymes and lowered the levels of alcohol metabolites. Mice treated with PF exhibited a considerable improvement in hangover symptoms and a reduction in hepatic inflammation, compared to control groups. Furthermore, *in vitro* experiments using HepG2 cell lines and semipermeable membranes demonstrated that PF effectively inhibits alcohol absorption into the body.

**Conclusions:** In conclusion, PF demonstrates a potential protective effect against alcohol-induced hangover and liver injury by inhibiting the absorption of alcohol and lowering hangover-related alcohol metabolites. This study suggests that PF could be an effective therapeutic option for managing the

adverse effects of excessive alcohol consumption.

**Keywords:** Psyllium fiber, Hangover, Alcohol-induced liver injury, Alcohol Absorption

## OP-99

### Genome-Wide Association Study Identifies PTPRD Associated with Metabolic Dysfunction-Associated Steatotic Liver Disease in South Korea

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**Aims:** Numerous single nucleotide polymorphisms (SNPs) related to metabolic dysfunction-associated steatotic liver disease (MASLD) have been identified individually by Genome-Wide Association Studies (GWASs) in Western countries. However, there remains a persistent unmet need to conduct GWAS research exploring the genetic background of MASLD in non-Western populations. Our study aimed to identify genetic variants in patients with MASLD in South Korea.

**Methods:** We performed a GWAS in a discovery group of 414 biopsy proven MASLD patients, alongside a control group of 1,064 healthy control. A replication analysis was conducted in a cohort of 1,246 participants.

**Results:** Nine SNPs in *PTPRD* on chromosome 9p23 and one SNP in *RUNX3* on chromosome 1p36.11 showed a significant association with MASLD at genome-wide significance ($P$=5.0×$10^{-8}$). The nine variants in *PTPRD* were all successfully replicated in the replication cohort ($P$<0.0001). In our cohort, we also observed significant associations with previously reported GWAS signals, such as *PNPLA3* at 22q13 and *SAMM50* at 22q13.31.

**Conclusions:** Our study discovered novel associations between *PTPRD* at 9p23 and MASLD in Korean patients. These findings enhance our understanding of the genetic pathophysiology of MASLD in non-European populations.

**Keywords:** GWAS, MASLD, PTPRD

## OP-100

### Identification of Alcoholic Hepatitis-Related and Mesenchymal Stem Cell Treatment Target Genes

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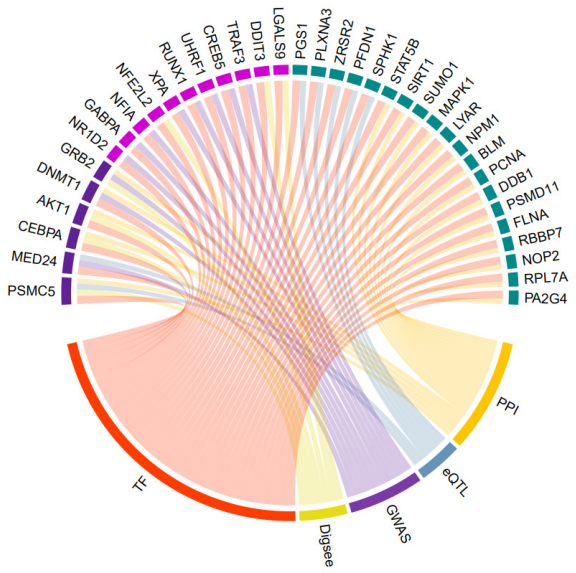
**Aims:** Alcoholic hepatitis (AH) is a life-threatening condition and widespread chronic liver condition that places patients at risk of short-term mortality if it is not properly managed. With insufficient knowledge and understanding of the mechanisms of AH, it often presents challenges to clinicians. This study aimed to identify transcriptomic biomarkers and cell therapy targets for AH.

**Methods:** We conduct a systematic meta-analysis of published human gene expression studies on liver biopsies and blood derived gene data. We collected three liver AH transcriptome datasets and a blood AH dataset. Two AH prognosis datasets were compiled, which are liver gene expression datasets. Using inverse weighted variance-based method mounted in METAL software, the candidate genes related to AH in liver and blood tissues and annotated them as the liver-blood AH meta genes. Three MSC datasets were curated for gene identification in stem cell response. Meta-analysis was implemented on the individual cohort-specific summary statistics obtained from differential expression methods to identify the AH-related biomarkers. To narrow down the candidate hub genes among stem cell treated data, TF database, protein-protein interaction network, disease-gene association database, and disease- and expression-related SNP database were used to analysis.




**Results:** Four steps of meta-analysis, MSC-Tx target genes were identified. With multiple lines of external evidences, external verification was performed and finally 47 upstream AH-related genes were presented. The analysis contains some genes that

have not been previously characterized in the context of alcoholic liver disease.

**Conclusions:** We present key genes involved in the progression of AH and provide a meta-analysis of results in a objective, statistically-based format. And at the same time, we suggest this biomarkers that can predict the prognosis of AH and treatment response. By using these genes, we can confirm the genetic changes caused by stem cell treatment and this can be used to lay the foundation for targeted cel l therapy or function-enhanced genetic therapy.

**Keywords:** Alcoholic liver disease, Stem cell, Alcoholic hepatitis

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## 19. Liver Transplantation 2

### OP-101

### A 9-Year Single-Center Experience of 310 Cases of Pure Laparoscopic Donor Right Hepatectomy

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**Aims:** While laparoscopic donor hepatectomy is becoming more prevalent, the outcomes of pure laparoscopic donor right hepatectomy (PLDRH) are still under-reported. This study aimed to present outcomes and experience of PLRDH in a large-volume single center.

**Methods:** This retrospective study included 310 living donors undergoing PLRDH between November 2014 and August 2023 at Asan Medical Center in Seoul. Postoperative complications of donors and recipients were assessed based on Clavien-Dindo classification and multivariate logistic regression analyses were performed to identify donor risk factors for recipient complications.

**Results:** This study shows postoperative outcomes of 310 PLDRH donors and corresponding recipients. One donor (0.3%) required open conversion and there was no mortality. There were two donors (0.65%) with major complications (Clavien-Dindo grade III) including intra-abdominal bleeding and wound problem. There were no biliary or vascular complications of donors. Regarding recipient outcomes, there were 66 cases (21.3%) of major biliary complications and 38 cases (12.3%) of major vascular complications. Multivariate analaysis showed donor risk factors for biliary stricture in recipients were graft weight ($P$=0.017, OR 1.003, 95 % CI 1.001–1.006) and donor risk factor for recipient hepatic vein complications were graft weight ($P$=0.026, OR 1.004, 95 % CI 1.001–1.008) and the presence of inferior right hepatic veins ($P$=0.048, OR 2.402, 95 % CI 1.007–5.729).

**Conclusions:** PLDRH is a feasible and safe surgical procedure when performed at a highly experienced transplant center. To avoid biliary and vascular complications of donor, meticulous laparoscopic techniques and preoperative and accurate intraoperatieve anatomical assessment are essential.

**Keywords:** Laparoscopic, Living-donor hepatectomy, Liver transplantation

### OP-102

### Evaluating the Most Suitable EGFR Equations for Predicting the Risk of End-Stage Renal Disease in Liver Transplant Recipients

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**Aims:** End-stage renal disease (ESRD) following liver transplantation (LT) is a pivotal factor in determining long-term patient outcomes. However, there is a lack of research on which eGFR equations are most effective in predicting ESRD. This study aims to evaluate the prognostic accuracy of various eGFR equations in predicting the risk of ESRD in LT recipients.

**Methods:** We evaluated 1,370 adult LT patients from 2005 to 2022, assessing the risk of ESRD using Fine and Gray's competing risk analysis with death as a competing event. The performances of four eGFR equations (CKD-EPI 2009, CKD-EPI 2021, MDRD4, GRAIL) based on preoperative creatinine levels were compared.

**Results:** The 5-year, 10-year, and 15-year incidences of ESRD in our cohort were 2.0%, 4.4%, and 9.1%. In the multivariate Cox model, diabetes mellitus (HR 3.59, 95% CI 1.79-7.20, $P$<0.001) and pre-operative hemoglobin (HR 0.75, 95% CI 0.60-0.93, $P$=0.010) were significant ESRD risk factors. In the competing risk analysis, adjusting for these factors, only CKD-EPI 2009 and 2021 equations showed increased ESRD risk with advancing CKD stage. Subgroup analysis in patients without pre-transplant dialysis revealed increased ESRD risk with advancing CKD stage in the CKD-EPI 2009 equation [Stage 2 (HR 1.53, 95% CI 1.15-2.02, $P$=0.003), Stage 3 (HR 1.85, 95% CI 1.28-2.66, $P$=0.001), Stage 4-5 (HR 2.03, 95% CI 1.19-3.44, $P$=0.009), using Stage 1 as reference].

**Conclusions:** The CKD-EPI equations appear to offer a better prediction for post-transplant ESRD, suggesting their potential utility in the preoperative risk stratification of LT recipients.

**Keywords:** End-stage renal disease, Liver transplant, Glomerular filteration rate

## OP-103

### Economics Analysis of Liver Transplantation in Asia

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**Aims:** With the technical advances and improvements in perioperative management and immunosuppressants, liver transplantation is the standard treatment for patients with end-stage liver diseases. In Asia, a shortage of deceased donor liver grafts is the universal problem to be faced with in all transplant centres. This study aims to analyse liver transplantation in Asian countries.

**Methods:** Using data obtained from the Global Observatory on Donation and Transplantation and the World Bank, 8 countries of Asia were selected to see how the economic growth, health expenditure, average protein supply, and Prevalence of anemia among women of reproductive age (15-49 years) affect the liver transplantation. This study employed data from 2010-2019 and then analyzed using Panel Data analysis.

**Results:** From the results of the panel data regression, it is known that variables of economic growth, health expenditure have a significantly positive influence on liver transplantation. Meanwhile, the variable of the average food supply has a negative influence and the prevalence of anemia among women of reproductive age (15-49 years) insignificant influence. The result indicates health expenditure can increase the liver transplantation by 3%. The rise of economic growth also can increase liver transplantation. If economic growth rises by 1%, it is followed by an increase in liver transplantation by as much as 1%. In addition, the average food supply can be determined as a factor that affects liver transplantation.

**Conclusions:** There have been important educational and legislative developments to reduce donor refusal rates and technological innovations with normothermic perfusion are dramatically improving utilisation of marginal grafts.

**Keywords:** Liver, Transplantation, Economics analysis

## OP-104

### Impact of Non-Stenting Eversion Technique in Biliary Stricture Incidence Post-LDLT: A Critical Analysis

**Ju-Eun Shim**, Seok-Hwan Kim, In-Sang Song, Gwang-Sik Chun, Sun-Jong Han

HepatoBiliary Pancreas Surgery, Chungnam National University Hospital, Republic of Korea

**Aims:** This study delves into the non-stenting eversion technique's effectiveness in living donor liver transplantation (LDLT) and its role in minimizing the incidence of biliary strictures. Biliary strictures present a significant postoperative challenge in LDLT, affecting patient outcomes and healthcare systems.

**Methods:** We conducted a retrospective analysis of 84 LDLT cases, focusing on 75 patients who underwent LDLT using the non-stenting eversion technique. The study meticulously recorded the incidence of biliary strictures and the necessity for interventions like percutaneous transhepatic biliary drainage (PTBD) or endoscopic retrograde biliary drainage (ERBD).

**Results:** Among the 75 patients, 12 (14.3%) developed biliary strictures that required intervention. Additionally, three (4%) patients encountered bile leakage, necessitating percutaneous catheter (PCD) insertion. These incidences were critically compared with existing data on traditional stenting techniques.

**Conclusions:** The findings indicate that the non-stenting eversion technique in LDLT holds a comparative efficacy to traditional stenting methods, with a parallel incidence rate of biliary strictures. The technique emerges as a viable and potentially safer alternative to managing biliary complications, significantly advancing surgical methods in LDLT. This study underscores the importance of ongoing research and innovation in surgical practices to enhance transplant outcomes and reduce complications.

**Keywords:** Living donor liver transplantation, No stent, Bile duct anastomosis

## OP-105

### The Modified APOLT in LDLT with Small-for-Size Graft in Cirrhotic Patient by NAFLD

**JaRyung Han**, Young Seok Han

Liver transplantation and Hepatobiliary-Pancreas Surgery, Department of Surgery, Daegu Catholic University Medical Center, Daegu Catholic University School of Medicine, Republic of Korea

**Aims:** Living donor liver transplantation has limitation due to donor pool. The combination of APOLT and RAPID concept (Resection And Partial Liver Transplantation with Delayed total hepatectomy) could be a feasible procedure in terms of LDLT using small-for-size grafts. We will present about the modified APOLT in cirrhotic patient.

**Methods:** 70-year-old female with liver cirrhosis by NAFLD referred our department for liver transplantation consultation. She had no viral hepatitis, alcohol abuse and toxic hepatitis history. Her family volunteered liver donation and MELD score was 16. Her daughter was diagnosed with moderate fatty change of liver and was refused as living donor. Her son was 43-year-old, and there were no specific findings in living donor evaluation. In volumetry, right lobe was 1117g and left lobe was 467g and the remnant left liver volume was 29%. Considering the donor's condition, we decided LDLT with left lobe graft by two-stage liver transplantation, RAPID concept according to the actual graft weight.

**Results:** We performed laparoscopic living donor hepatecto-

my to produce extended left lobe graft. Actual graft weight was 400g, APOLT with RAPID concept was performed. At first, extended left hepatectomy with caudate lobectomy was performed in recipient. The prepared left lobe graft was implanted with auxiliary partial liver orthotopic liver transplantation technique. And the right portal vein was ligated. The patient's liver function was normalized within two weeks, but decreased kidney function and generalized edema including pulmonary edema was continued. Severe atrophic change of remnant recipient's right liver was identified in postoperative CT scan, the transplanted left lobe was significantly enlarged. The recipient's total hepatectomy was postponed. The patient recovered well, and the liver graft function was normalized.

**Conclusions:** Occasionally, LDLT with small-for-sized graft may be an unavoidable option for recipients who cannot find a suitable living liver donor. The introduction of APOLT, ALPPS, or RAPID concept can be an amazing technique for successful LDLT in these specific and difficult situations.

**Keywords:** Modified APOLT (auxiliary partial orthotopic liver transplantation), RAPID (resection and partial liver transplantation with delayed total hepatectomy), Small-for-size-graft, Donor pool expansion

## OP-106

### The Comparison between Duct-to-Duct(DTD) And Choledochoduodenostomy(CDD) in Deceased Donor Liver Transplant; Should the Main Technique Be Changed?

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Surgery, Khonkaen University, THAILAND

**Aims:** Three primary techniques for bile duct reconstruction in orthotopic liver transplantation include duct to duct (DTD), choledochojejunostomy (CDJ) and choledochoduodenostomy (CDD).The most frequently performed procedure is DTD,as it follows the same anatomical route and serves the same physiological function.The least common option is CDD, which is a simple procedure, faster technique and easier endoscopic access.There is limited information available regarding the outcome of CDD post-liver transplant, particularly in comparison to DTD.Thus,we provided our initial experience comparing CDD and DTD outcomes.

**Methods:** All 65 patients who underwent liver transplant between January 2021 and May 2023 were included in this study in a consecutive manner.The biliary reconstruction techniques were chosen based on the timing of the operation.DTD was selected from January 2021 to October 2022, followed by the selection of CDD from November 2022 to May 2023. All data were collected and analyzed.

**Results:** There were no discernible differences in clinicopathological parameters between the two groups. The median cold ischemic time was similar between the two groups ($P$=0.08). The operative time in the DTD group was significantly longer (368 min) compared to the CDD group (274 min)($P$=0.027). Biliary complication was 24.51%(DTD 28.6% vs CDD 4.55% $P$=0.023).After thoroughly evaluating all relevant factors through multivariate analysis, it was found that the observed difference did not reach statistical significance.

**Conclusions:** From our data, biliary complications associated with CDD is comparable to DTD.It is evident that CDD may offer a more secure approach to biliary reconstruction in liver transplantation.However, a larger population is necessary to draw further conclusions.

**Keywords:** Choledochoduodenostomy, Duct-to-duct, Liver transplantation

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## 20. HCC, Basic 2

## OP-107

### Elucidating the Role of Liquid-Liquid Phase Separation in Hepatocellular Carcinoma: From Single-Cell Analysis to Prognostic Biomarkers

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**Aims:** We aimed to explore the predictive value and immuno-therapeutic responses of liquid-liquid phase separation-related signature in HCC.

**Methods:** In our study, we delved into the characteristics of liquid-liquid phase separation at multiple omics levels. By utilizing single-cell and transcriptome analysis, we applied the lasso-cox to identify liquid-liquid phase separation-related signature (LLPSRS). In order to enhance the practicality of LLPSRS, we established and externally validated a LLPSRS nomogram, providing a quantitative prognostic tool for HCC patients. Furthermore, we investigated the mechanism of LLPSRS according to transcriptome, genomic, and single-cell levels, revealing important connections between LLPSRS, HCC prognosis, and immune landscape. Finally, we examined the different responses of the risk subgroups to immune checkpoint inhibitors and their sensitivity to major LLPSRS targeted drugs.

**Results:** A risk-predictive scoring model of 9 LLPSRS was constructed by the data from TCGA after LASSO-COX regression analysis and was validated by the data from ICGC. The overall survival of the high-risk group was significantly lower than that of the low-risk group both in the TCGC and ICGC dataset

(*P*<0.05). Time-dependent ROC evaluated the performance of this model in high AUC values. The nomogram, combining the risk score and clinical features, showed a solid prognostic ability. GO and KEGG analyses revealed the potential pathway of the gene signature. Correlations between the LLPSRS signature and clinicopathological characteristics, tumor microenvironment, immunotherapy response, and chemotherapy sensitivity had shown the significant clinical guidance value.

**Conclusions:** This model has high accuracy in predicting the outcomes of HCC patients, but also reveals the potential mechanisms of LLPSRS in HCC, which paving the new avenues for personalized treatment and immuno-therapy development.

**Keywords:** Hepatocellular carcinoma, Liquid-liquid phase separation, Single-cell, Tumor microenvironment, Immunotherapy, Prognostic signature

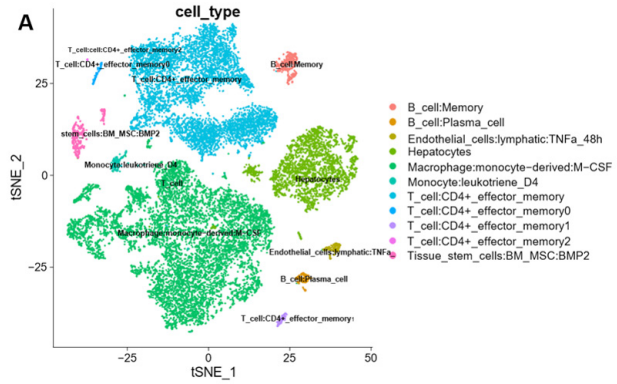



**Figure 1.** A: t-SNE plot showing the cell types identified by marker genes.

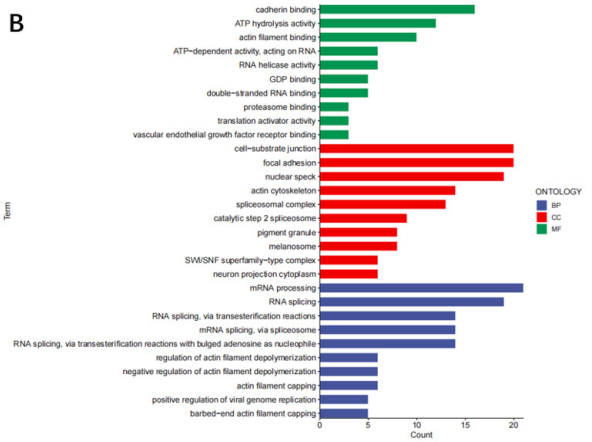



**Figure 2.** A: GO enrichment of the LLPSRGs.

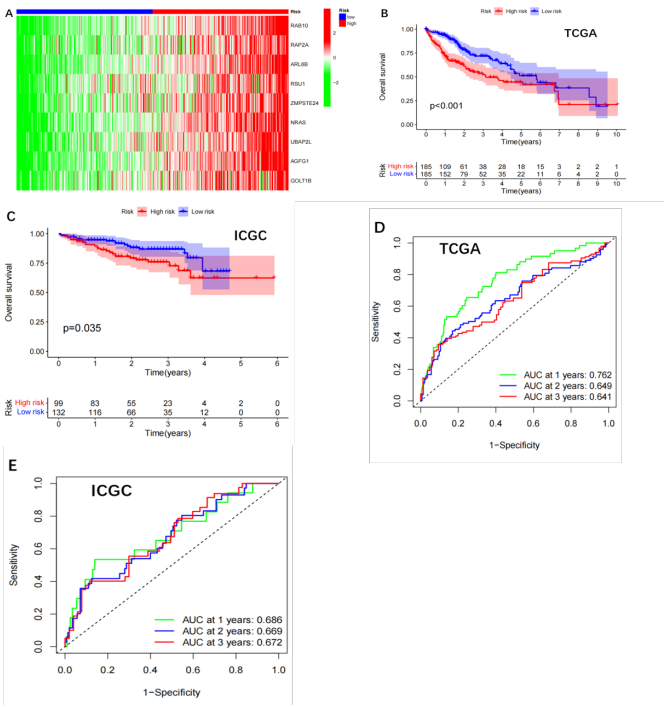



**Figure 3.** Validation of the accuracy of the LLPSRS models to predict patient prognosis. (A) A heat map showing the differential expression of nine LLPSRDEGs in groups at high and low risk. (B, C) Survival curves for the TCGA cohorts and ICGC cohorts respectively. Time-dependent ROC curves for TCGA cohorts(D) and (E) for ICGC.

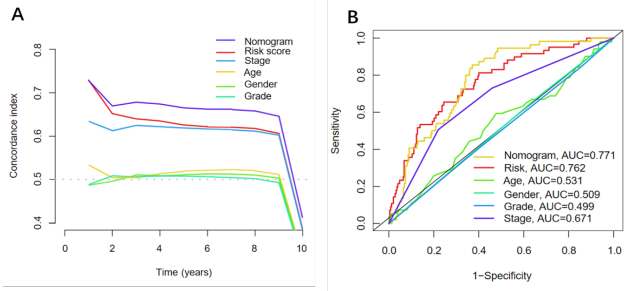
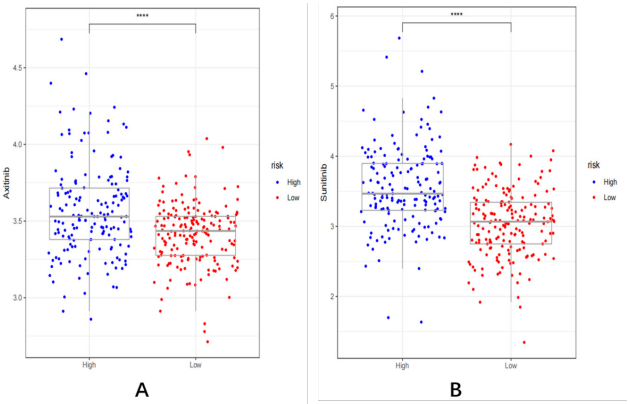



**Figure 4.** (A) C-index curves for Nomogram, risk scores and clinical parameters. (B) Multi-indicator ROC analysis of the TCGA cohort.



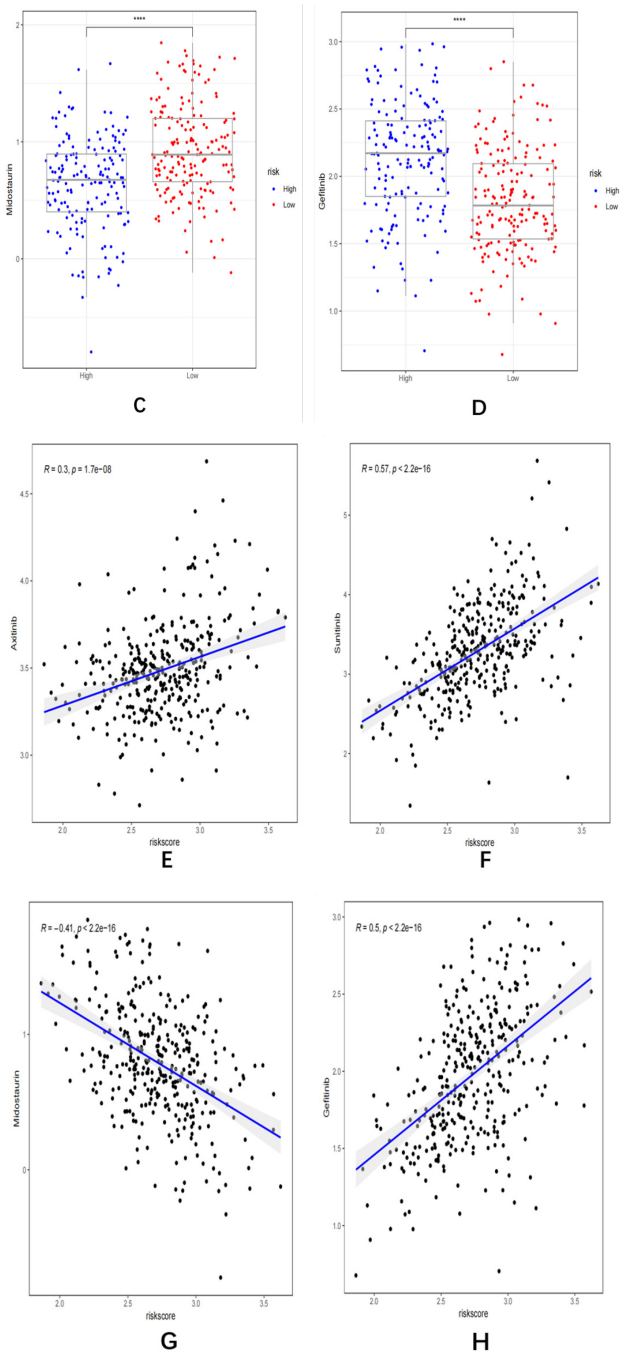



**Figure 5.** Association between the ICDRS and drug sensitivity and validation of the genes. (A-D) A comparison of the sensitivity to tyrosine kinase inhibitors (TKIs) and EGFR-TKI inhibitors, including Axitinib, Sunitinib, Midostaurin, and Gefitinib, between high- and low-risk groups. (E-H) The correlation between the risk score and the half-maximal inhibitory concentration (IC50) of small molecule drugs, including Axitinib, Sunitinib, Midostaurin, and Gefitinib, in HCC.

## OP-108

### Exploring Biflavonoid Derivatives as Promising PD-L1 Inhibitors for Immune Checkpoint Therapy in Hepatocellular Carcinoma by Virtual Screening, and Molecular Interaction Analysis

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**Aims:** The immune checkpoint involving the overexpression of programmed cell death protein-1 (PD-1) and programmed death-ligand-1 (PD-L1) on the surface of hepatocellular carcinoma cells has become a promising target for immunotherapy. Cancer cells commonly use PD-1/PD-L1 binding to avoid the immune system. PD-1/PD-L1 checkpoint inhibition has been proven to improve survival in patients with metastatic cancer. Recently, PD-L1/PD-1 antibody-based inhibitors have been approved. Small-molecule inhibitor development is prioritized as BMS202 drugs, a biphenyl derivative, were the first PD-L1 inhibitors. Based on their chemical structure similarities, biflavonoid derivatives, naturally produced anticancer medicines, has the potency to inhibit PD-L1.

**Methods:** This study employed a virtual screening method to examine 100 biflavonoid derivative compounds from the ZINC database to the binding site of PD-L1. The Autodock Vina software was used, followed by molecular interaction analysis using Biovia Discovery Studio. The adsorption, distribution, and toxicity (ADMET) characteristics were assessed using the online prediction tool pkCSM.

**Results:** Out of the 100 biflavonoid derivatives compounds, 24 exhibited superior binding interaction, as evidenced by the lowest binding energy observed in ZINC000207027026, compared to the BMS202 compound. The interaction between the aromatic ring and the hydrogen bond acceptor moiety is crucial regarding pharmacophores, with the pi bonding of the aromatic ring and hydrogen bonding playing significant roles (Figure 1). Furthermore, it was shown that incorporating non-aromatic substituents into the backbone reduced the binding affinity. The amino acid residues TYR122, LYS124, TYR56, and LYS75 were found to interact with the inhibitor molecules within the active site. ZINC000207027026 exhibits drug-like characteristics according to Lipinski criteria and ADMET prediction.

**Conclusions:** In conclusion, biflavonoid has the potential to be a candidate for inhibiting PD-L1. This research provides valuable insights into the field of drug discovery, specifically focusing on the novel molecules of immune checkpoint inhibitor therapeutic medicines.

**Keywords:** Immune checkpoint blockade, Biflavonoid, Hepatocellular carcinoma

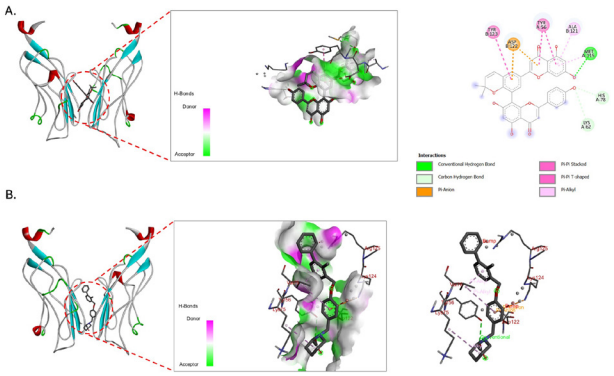


Figure 1. The binding and molecular interaction of the small molecules to the PD-L1 (A) ZINC000207027026, (B) BMS202

## OP-109

### Circulating exoPD-L1 Predicts the Outcome of Patients with HCC Who Received Atezolizumab-Bevacizumab

Yu Rim Lee[1], Gyeonghwa Kim[2], Young Oh Kweon[3], Won Young Tak[3], Soo Young Park[3], Jung Gil Park[4], Jeong Hwa Lee[3], Yun Kee Jo[2], Hee Jin Cho[2], Min Kyu Kang[5], Seung Hyun Cho[6], Jihoon Hong[6], An Na Seo[7], Keun Hur[2]

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**Aims:** Hepatocellular carcinoma (HCC) is a highly aggressive disease that is usually diagnosed at an advanced stage. Advanced HCC has limited treatment options and often has a poor prognosis. Atezolizumab-bevacizumab significantly improved survival rates as a first-line treatment and became the new standard of care. The interaction between the programmed cell death receptor 1 (PD-1) and its ligand (PD-L1) contributes to immune evasion and exosomal PD-L1 is a marker of poor outcome after surgery or chemotherapy in patients with various types of cancers. However, the role of PD-L1-containing exosomes in patients with advanced HCC receiving atezolizumab-bevacizumab is remains to be elucidated. We therefore determined the prognostic significance of circulating exosomal PD-L1 in advanced HCC patients receiving atezolizumab-bevacizumab.

**Methods:** This study enrolled 28 HCC patients receiving atezolizumab-bevacizumab between Dec 2020 and Jan 2023. Exosomes were extracted from serum samples using the ExoQuick Exosome Precipitation Solution. Exosomal PD-L1 was detected by Exocounter.

**Results:** The total number of exosomes and PD-L1 positive exosomes increased significantly as the mUICC stage of HCC progressed ($P<0.05$). Comparing between the early and advanced stage, the number of Exosomal PD-L1 significantly increased in the advanced stage. The overall survival and progression-free survival were significantly lower in patients with lower circulating levels of exosomal PD-L1 (log-rank test: $P=0.015$ and 0.007, respectively).

**Conclusions:** In conclusion, this study has provided strong evidence that circulating exosomal PD-L1 are novel prognostic markers and therapeutic targets for advanced HCC who received atezolizumab-bevacizumab.

**Keywords:** Hepatocellular carcinoma, Immune checkpoint inhibitors, Exosome

## OP-110

### Glypican-3 Peptide-Linked Chimeric Antigen Receptor-Macrophages (pCAR-M): A Novel Therapeutic Strategy for Hepatocellular Carcinoma (HCC)

Rainbow Wing Hei Leung[1], Carmen Oi Ning Leung[1], Clarence Tsun Ting Wong[1,2], Terence Kin Wah Lee[1,2]

[1]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, [2]State Key Laboratory of Chemical Biology and Drug Discovery, The Hong Kong Polytechnic University, Hong Kong

**Aims:** Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. Recently, chimeric antigen receptor macrophages (CAR-Ms) have emerged as a new cell therapy for solid cancers, involving the transfer of an edited CAR gene into macrophages via viral infection. However, this method is costly, involves tedious procedures, has long-term safety concerns, and lacks flexibility. The purpose of this study is to explore a novel chemical ligation approach that can help address the above limitations in the potential treatment of HCC.

**Methods:** A novel bioconjugation method called the phthalaldehydeamine capture (PAC) reaction was used to produce peptidic CAR-Ms (pCAR-Ms) targeting Glypican-3 (GPC3) in HCC cells. The specificity and efficacy of pCAR-Ms were assessed using an *in vitro* phagocytosis assay in a co-culture system, while the *in vivo* efficacy was evaluated using HCC xenograft models from HCC cell line and patient-derived tumor xenografts (PDTXs).

**Results:** Using an *in vitro* co-culture system, we demonstrated the specificity and efficacy of pCAR-Ms against GPC3, as evidenced by a significant increase in the number of phago-

cytosed cells with high GPC3 expression compared to their low-expression counterparts, by flow cytometry and fluorescence microscopy. The specificity of pCAR-Ms was further demonstrated in GPC3-knockdown HCC cells, with a significant decrease in the phagocytic rate. Using an HCC xenograft model derived from MHCC-97L cells and PDTXs, we confirmed the specific homing of pCAR-Ms to tumor sites via the intravenous injection of lipopolysaccharide (LPS)-differentiated pCAR-Ms. Strikingly, pCAR-Ms efficiently suppressed HCC tumor growth when compared with parental macrophages and the no treatment control, without notable side effects. Multiplexed IHC staining revealed that pCAR-Ms effectively infiltrated HCC tumors, demonstrating the superior infiltration capacity of the pCAR-Ms.

**Conclusions:** We provided evidence of potency, infiltrating capacity, and specificity of non-viral-based pCAR-Ms in targeting HCC with simple and short production time, and increased flexibility.

**Keywords:** Hepatocellular carcinoma, Chimeric antigen receptor, Macrophages, Glypican-3

## OP-111

### Unraveling Immune-Activated Tumor Microenvironment Correlated with Clinical Response to Atezolizumab plus Bevacizumab in Advanced Hepatocellular Carcinoma

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[1]Division of Gastroenterology and Hepatology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Department of Health Science and Technology, Samsung Advanced Institute for Health Science and Technology, Sunkyunkwan University, Seoul, Korea; [3]Samsung Genome Institute, Samsung Medical Center, Seoul, 06351, Korea

**Aims:** In advanced hepatocellular carcinoma (HCC), tumor microenvironment (TME) can significantly influence cancer progression and treatment response. Although atezolizumab plus bevacizumab has shown treatment efficacy, mechanisms and prognostic biomarkers for such combined treatment remain unclear.

**Methods:** We analyzed single-cell transcriptomic and TCR sequencing data from 18 HCC patients including 12 patients undergoing atezolizumab plus bevacizumab.

**Results:** An activated immune landscape marked by cytotoxic T cells, tissue-resident markers, and elevated CCL3 in tumor-associated macrophages (TAMs) was found to be correlated with favorable treatment response. Validation in an independent cohort confirmed these findings' prognostic significance. Additionally, our study identified tumor endothelial cells (TECs) with antigen-presenting abilities as contributors to immunotherapy efficacy.

**Conclusions:** These insights into immune-related molecular subtypes and TME characterization offer valuable information for patient stratification that could facilitate the development of personalized HCC treatment strategies.

**Keywords:** Hepatocellular carcinoma, Atezolizumab plus bevacizumab, Single-cell RNA, Tumor microenvironment

## OP-112

### A Novel Mitochondrial Micropeptide HRMM Interacts with ATP5B to Promote Energy Metabolism and Hepatocellular Carcinoma Progression

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**Aims:** Emerging evidence has shown that the small open reading frames (smORFs) inside long non-coding RNAs (lncRNAs) could encode functional micropeptides. However, their roles in cellular energy metabolism and hepatocellular carcinoma (HCC) progression remain largely unknown. Therefore, the search for functional micropeptides that target energy metabolism may provide a potential biological target for HCC therapy.

**Methods:** We combined ribosome profiles, RNA-seq and mass spectrometry methods to explore the translational potentials of lncRNAs in HCC tissues, and confirmed the function of selected lncRNA-encoded peptides in HCC cell lines.

**Results:** Here, we identified a 94-amino acid micropeptide encoded by lncRNA-X in HCC. Subsequently, we also characterized its conservation across humans and mice, localization to mitochondria and the synergistic functions in HCC. This micropeptide was highly expressed in HCC tissues and cells, which could be activated by HNF4A, high expression of this micropeptide predicted poor prognosis of HCC patients, and enhanced the ATP synthase activity via interacting with the ATP5B and thereby promoted HCC cell proliferation as well as the production of reactive oxygen species (ROS). Hence, this micropeptide was termed HNF4A-regulated micropeptide for energy metabolism (HRMM). Furthermore, knocking out HRMM in HCC cells, we found that HRMM, but not its lncRNA, could suppress cell proliferation and mitochondrial ATP production.

**Conclusions:** Taken together, this study reveals that the putative lncRNA encodes a new functional peptide in HCC cells

and provides a novel potential biomarker and target for the diagnosis and treatment of HCC.

**Keywords:** Micropeptide, lncRNA, Hepatocellular carcinoma, Energy metabolism

Saturday, June 29, 2024, 09:30-10:30

## 21. HCC, Clinical 3

### OP-113

### Impact of Virtual Reality Education on Disease-specific Knowledge and Anxiety for Hepatocellular Carcinoma Patient Scheduled for Liver Resection: A Randomized Controlled Study

**Jaehun Yang**[2], Jinsoo Rhu[1], Juhee Cho[3], Danbee Kang[3], Soyoung Lim[1], Heesuk Lee[4], Gyu-Seoung Choi[1], Jongman Kim[1], Jae-Won Joh[1]

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**Aims:** Hepatocellular carcinoma (HCC) is a significant health concern, and the complexity of liver anatomy poses challenges in conveying radiologic findings and surgical plans to patients. This study aimed to evaluate the impact of a virtual reality (VR) education program on anxiety and knowledge in HCC patients undergoing liver resection.

**Methods:** From January 1, 2022, to February 28, 2023, 88 patients at Samsung Medical Center were enrolled in a randomized controlled trial. Participants were divided into VR group (n=44) and control group (n=44). VR group received patient-specific 3D liver model education through VR platform, while control group underwent conventional explanation processes. Both groups completed pre- and post-intervention questionnaires assessing anxiety (using STAI-X-1, STAI-X-2, and VAS) and knowledge about liver resection.

**Results:** There was no significant difference in pre-explanation anxiety and knowledge scores between two groups. Post-explanation, VR group exhibited a more significant reduction in STAI-X-1 scores (-4.14±7.5) compared to control group (-0.84 ±5.7) ($P$=0.023*). Additionally, VR group demonstrated superior post-explanation knowledge scores (17.20±2.6) than control group (13.42±3.3) ($P$<0.001*). The change in knowledge scores was also notably higher in VR group (5.86±3.7) compared to control group (2.63±3.3) ($P$<0.001*). VR group reported a satisfaction score of 45.65±4.16 out of 50.

**Conclusions:** The VR education program significantly improved knowledge and reduced anxiety among HCC patients compared to conventional methods. This study suggests that VR can be a valuable tool in patient education, enhancing comprehension and alleviating pre-surgical anxiety.

**Keywords:** Hepatocellular carcinoma, Virtual reality, Liver resection

### OP-114

### Clinical Course and Prognosis of Long-Term Survivors of Hepatocellular Carcinoma

**Soon Sun Kim**[1], Jonghyun Lee[2], Sang Bong Ahn[3], Young Eun Chon[4], Eileen Yoon[5], Soung Won Jeong[6*], Dae Won Jun[5*]

[1]Department of Gastroenterology, Ajou University School of Medicine, Suwon; [2]Department of Medical and Digital Engineering, Hanyang University College of Engineering, Seoul; [3]Department of Internal Medicine, Eulji University College of Medicine, Seoul; [4]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam; [5]Department of Internal Medicine, School of Medicine, Hanyang University, Seoul; [6]Department of Internal Medicine, Soonchunhyang University College of Medicine, Soonchunhyang University Seoul Hospital, Seoul, Republic of Korea.

**Aims:** This study investigated the long-term prognosis and clinical course of patients who survived for more than 5 years after HCC diagnosis.

**Methods:** This retrospective cohort study used data from the Korean National Health Insurance Service database. A total of 35,348 subjects newly diagnosed with HCC between January 2008 and December 2010 were followed up until December 2018.

**Results:** A total of 11,514 (32.6%) survived for 5 years after diagnosis of HCC among 35,348 patients diagnosed with HCC. Five-year survivors had a higher proportion of females, younger age, more frequent etiology of HBV, less frequent liver cirrhosis, diabetes mellitus, and hypertension, and received curative treatment more frequently than non-survivors. The additional 1-, 3-, and 5-year survival rates were 90.7%, 77.6%, and 68.4%, respectively. Patients who underwent curative treatment as the first treatment for HCC showed a higher additional 5-year survival rate than those treated with non-curative therapy (74.5% vs. 64.2%). Among the HCC survivors, 44.4% underwent HCC retreatment 5 years after HCC diagnosis. The additional 5-year survival rate was 54.9% in the HCC retreatment group. The overall 5- and 10-year cumulative probabilities of secondary primary malignancies in HCC survivors were 15.36% and 27.54%, respectively. The most frequent second primary malignancy was prostate cancer, followed by colorectal and pancreatic cancers.

**Conclusions:** Our study highlights that a significant proportion of patients with HCC achieve long-term survival beyond 5 years, with favorable outcomes associated with curative treatments.

**Keywords:** Hepatocellular carcinoma, Cancer survivor, Prognosis, Survival

## OP-115

### Heavy Smoking Increases Early Mortality Risk in Patients with Hepatocellular Carcinoma after Curative Treatment

Jaejun Lee[1,2], Jong Young Choi[1,2], Soon Kyu Lee[1,3*]

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**Aims:** While cigarette smoking has been associated with an increased risk of hepatocellular carcinoma (HCC) incidence, its connection to HCC mortality remains underexplored. We sought to evaluate the impact of smoking on early mortality in HCC following curative treatment.

**Methods:** Data from the Korean Primary Liver Cancer Registry were examined for HCC patients who underwent liver resection or radiofrequency ablation between 2015 and 2018. Smoking cumulative dose was assessed in pack-years. The primary outcome was 3-year overall survival (OS).

**Results:** Among 1924 patients, 161 were classified as heavy smokers (≥ 40 pack-years). Heavy smokers exhibited lower 1-, 2-, and 3-year survival rates of 91.2%, 85.5%, and 77.1%, respectively, compared to non-smokers (1-, 2-, and 3-year survival rates of 96.0%, 90.4%, and 83.3%, respectively), with a significant difference observed in 3-year OS ($P$=0.016). The assessment of smoking pack-years in relation to 3-year overall survival revealed a dose-dependent pattern, with the hazard ratio (HR) exceeding 1.0 at 20 pack-years and continuing to rise until 40 pack-years, reaching its peak at 1.21 (95% confidence interval: 1.01, 1.45). Multivariate Cox-regression analysis revealed that heavy smoking (HR 1.443, $P$=0.046), age ≥ 60 (HR 1.290, $P$=0.050), underlying cirrhosis (HR 1.406, $P$=0.008), tumor size > 3 cm (HR 1.871, $P$<0.001), vascular invasion (HR 2.406, $P$<0.001), and Child-Pugh class A (HR 0.353, $P$<0.001) were associated with 3-year OS. Subgroup analyses of patients with tumor size < 3 cm, absence of vascular invasion, and meeting Milan criteria showed inferior outcomes for heavy smokers in all three subgroups.

**Conclusions:** Heavy smoking, defined as a history of more than 40 pack-years, was linked to poorer 3-year survival outcomes for HCC patients undergoing curative treatments, underscoring the importance of smoking cessation in this population.

**Keywords:** Smoking, Hepatocellular carcinoma, Liver resection, Radiofrequency ablation

## OP-116

### Efficacy and Safety of First-line Systemic Therapy in Child-Turcotte-Pugh B, Unresectable Hepatocellular Carcinoma Patients: Atezolizumab Plus Bevacizumab vs. Sorafenib

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**Aims:** The superiority of the combination of atezolizumab with bevacizumab (atezo/bev) in unresectable hepatocellular carcinoma (uHCC) patients with marginal liver function remains uncertain. The goal of the study is to compare the efficacy and safety of atezo/bev to sorafenib in real-world patients with uHCC with marginal liver function.

**Methods:** This single institution retrospective cohort study analyzed patients with uHCC whose liver function improved from Child-Pugh B to Child-Pugh A through supportive care, and subsequently received atezo/bev (n=32) or sorafenib (n=32) as first-line therapy between August 2020 and February 2023. Outcomes were progression free survival (PFS), overall survival (OS), and adverse events (AEs).

**Results:** This single institution retrospective cohort study analyzed patients with uHCC whose liver function improved from Child-Pugh B to Child-Pugh A through supportive care, and subsequently received atezo/bev (n=32) or sorafenib (n=32) as first-line therapy between August 2020 and February 2023. Outcomes were progression free survival (PFS), overall survival (OS), and adverse events (AEs).

**Conclusions:** Atezo/bev may be recommended as the first-line treatment of choice for patients with marginal liver function, especially for those with Child-Pugh B7, based on both efficacy and safety.

**Keywords:** Child-turcotte-pugh (CTP) class B, Atezolizumab/bevacizumab, Sorafenib

## OP-117

### Failure to Achieve Textbook Outcomes: Stratifying Risk among Patients Undergoing Hepatectomy for Hepatocellular Carcinoma

Han Liu[1], Feng Wei[1], Yong-Kang Diao[1], Si-Yuan Wang[1], Ying-Jian Liang[1], Yi-Fan Wu[1], Qi-Xuan Zheng[1], Xian-Ming Wang[1], Guo-Yue Lv[1], Tian Yang[1]

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**Aims:** The concept of textbook outcomes (TOs) has gained increased attention as a critical metric to assess the quality and success of outcomes following complex surgery. A simple yet effective scoring system was developed and validated to predict risk of not achieving textbook outcomes (non-TOs) following hepatectomy for hepatocellular carcinoma (HCC).

**Methods:** Using a multicenter prospectively collected database, risk factors associated with non-TO among patients who underwent hepatectomy for HCC were identified. A predictive scoring system based on factors identified from multivariate regression analysis was used to risk stratify patients relative to non-TO. The score was developed using 70% of the overall cohort and validated in the remaining 30%.

**Results:** Among 3 681 patients, 1 458 (39.6%) failied to experience a TO. Based on the derivation cohort, obesity, American Society of Anaesthesiologists score(ASA score), Child-Pugh grade, tumor size, and extent of hepatectomy were identified as independent predictors of non-TO. The scoring system ranged from 0 to 10 points. Patients were categorized into low (0-3 points), intermediate (4-6 points), and high risk (7-10 points) of non-TO. In the validation cohort, the predicted risk of developing non-TOs was 39.0%, which closely matched the observed risk of 39.9%. There were no differences among the predicted and observed risks within the different risk categories.

**Conclusions:** A novel scoring system was able to predict risk of non-TO accurately following hepatectomy for HCC. The score may enable early identification of individuals at risk of adverse outcomes and inform surgical decision-making, and quality improvement initiatives.

**Keywords:** Hepatectomy, Hepatocellular carcinoma, Textbook outcome

## OP-118

### Identification of Plasma Protein Biomarkers Associated with Tyrosine Kinase Inhibitor Resistance in Hepatocellular Carcinoma Patients

Su Jin Kim[1,2], Moon Gyeong Yoon[1], Geum Ok Baek[1], Ji Eun Han[1], Soon Sun Kim[1], Jae Youn Cheong[1], Jung Woo Eun[1], Hyo Jung Cho[1]

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**Aims:** Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide. Tyrosine Kinase Inhibitors (TKIs) and Immune Checkpoint Inhibitors (ICIs) are commonly utilized as first-line systemic therapies to impede cancer progression. However, the emergence of drug resistance poses a challenge in the effective treatment of HCC patients receiving TKI therapy. Thus, we aimed to identify plasma protein biomarkers associated with TKI resistance in HCC patients.

**Methods:** In our study, plasma samples from Ajou University Hospital were obtained and classified into TKI Non-Responder (NR) and TKI Responder (R) groups. Sequentially, we analyzed the samples using proximity extension immunoassay technology (Olink Proteomics, Uppsala, Sweden) with the Olink® Target 96 Immuno-Oncology panel for 61 patients. Significant differentially expressed proteins (DEPs) with adjusted p-values < 0.05 were identified.

**Results:** Our analysis revealed 5 candidate protein markers distinguishing NR (progressive disease [PD], stable disease [SD]) from R (partial response [PR]) patients in the first group. Specifically, TKI_RM#3 showed a 2.4-fold decrease in the R group ($P$=0.02), and ROC analysis yielded an AUC of 0.76 (95% CI: 0.57-0.95, $P$=0.03). In the subsequent analysis, the Non-Responder group was defined as PD (N=24), and the Responder group as SD/PR (n=36). Six significant markers were identified, with TKI_RM#8 showing a 2.15-fold decrease in the R group ($P$=0.001). Additionally, ROC analysis revealed an AUC of 0.76 (95% CI: 0.63-0.88, $P$<0.001).

**Conclusions:** These findings underscore the potential of TKI_RM#3 and TKI_RM#8 as plasma protein biomarkers for predicting TKI resistance in HCC patients, thus aiding in risk stratification and guiding therapeutic decision-making.

**Keywords:** Hepatocellular carcinoma, Tyrosine kinase inhibitor, Olink® target 96 panel, Plasma

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# 22. Biliary & Pancreatic Disease

## OP-119

### Role of Procalcitonin in Guiding Antimicrobial Usage in Acute Pancreatitis – A Randomized Clinical Trial

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**Aims:** Prophylactic antibiotics has no role in acute pancreatitis(AP) and it has been observed that 23.5% of cases received it without evidence of infection. Procalcitonin (PCT) based algorithm can differentiate bacterial sepsis from systemic inflammatory response. Hence Procalcitonin-based algorithm guided antibiotic usage will lead to reduced antibiotic usage in patients with acute pancreatitis without any adverse outcomes.

**Methods:** A single-center, prospective, single blinded RCT carried out in the Department of Surgery. A total of 152 patients with AP were randomly assigned to nPCT group (n=73) and PCT group (n=71). Patients in PCT group were treated with antibiotics based on PCT values (To start or continue antibiotics when the PCT value was > 1ng/ml and discontinue or avoid antibiotics if PCT is < 1ng/ml). Otherwise, both groups received standard of care. Duration of antibiotics, Length of hospital stay, Mortality and readmission rates were measured and analyzed.

**Results:** The proportion of patients receiving antibiotics in nPCT group was 45.2% (33 patients) and in PCT group it was 36.6% (26 patients). Although there was 9% reduction in patients receiving antibiotics in the PCT group, it was not statistical significant (*P*=0.295). There was no significant difference between groups induration of antibiotic usage, length of hospital stay, readmission, and mortality rates. Subgroup analysis, based on severity of pancreatitis was not statistically significant.

**Conclusions:** Procalcitonin based antibiotic therapy reduced antibiotic usage by 9% in our study population. Further studies are needed to test the role of procalcitonin in guiding antibiotic usage in Indian population.

**Keywords:** Procalcitonin, Acute pancreatitis, Antimicrobial usage

## OP-120

### Endoscopic Ultrasonography (EUS) Hepaticogastrostomy (HGS) versus Choledochoduodenostomy (CDS) in ERCP-Failed Malignant Biliary Obstruction: A Systematic Review and Meta-Analysis

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**Aims:** Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard in managing malignant biliary obstruction. The success of ERCP has limitations, whereas surgical biliary bypass and percutaneous transhepatic approaches, as alternative modalities, come with significant costs, longer durations, and higher levels of mortality and morbidity. Endoscopic ultrasonography (EUS)-guided biliary drainage with two approaches, hepaticogastrostomy (EUS-HGS) and choledochoduodenostomy (EUS-CDS), is a favored and evolving alternative modality. This study aims to compare the efficacy and safety of EUS-HGS and EUS-CDS.

**Methods:** We conducted a systematic review and meta-analysis by searching PubMed, ScienceDirect, Cochrane Library, and Scholar databases up to August 2023, based on the 2020 Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. We identified randomized and non-randomized studies comparing the efficacy and safety of EUS-HGS and EUS-CDS. Outcome measures included technical and clinical success, side effects, and mean procedure time.

**Results:** Nine non-randomized studies and two randomized controlled trials involving 537 patients (225 EUS-HGS, 312 EUS-CDS) were analyzed. No difference was found in technical success (OR, 0.83; 95% CI, 0.41-1.68; I2=0%) and clinical success between the two procedures (OR, 0.96; 95% CI, 0.51-1.81; I2 = 9.94%). Side effects were significantly higher in EUS-HGS (OR, 2.01, 95% CI, 1.14-3.59; I2=0%). No significant difference in mean procedure time was observed between the two procedures (0.13; 95% CI, -0.15-0.41; I2=34.89%).

**Conclusions:** There are differences in efficacy and safety between EUS-HGS and EUS-CDS. EUS-CDS has a faster procedure time, lower risk of side effects, and ease of puncture during the procedure.

**Keywords:** Hepaticogastrostomy, Choledochoduodenostomy, ERCP failure

## OP-121

### Impact of Sarcopenia on Surgical Outcomes in Patients Undergoing Pancreaticoduodenectomy (PD): A Tertiary Care Center Experience in ODISHA- INDIA

Swamy Rajesh Hududgur, Satyaprakash Ray Chudhury, Jyotirmay Jena, Sumit S Mohanty

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**Aims:** Sarcopenia is common in pancreatic cancer and influence postoperative outcomes. Studies show perioperative complications, mortality, worse survival increase with sarcopenia. Aim: To study association of preoperative Sarcopenia with immediate & delayed postoperative complications & surgical outcome in patients undergoing Pancreaticoduodenectomy(PD).

**Methods:** A single center, Prospective Study from Jan 2022 to July 2023. All patients of suspected periampullary & HOP malignancies included and investigations done to establish diagnosis, operability. Pts assessed for BMI, MAC, Hand grip test and CT analysis-skeletal muscle area(SMA) at L3 vertebrae & L3

SMI (skeletal muscle index). Cut off for sarcopenia: < 36.5 $cm^2$/m2(males) and < 30.2 $cm^2/m^2$(Females) taken.

**Results:** Total 57 patients underwent PD, 45.6% are females, and 54.3% males. 26 (45.6%) [12(45.16%) female, 14 (53.8%) male] have sarcopenia. The mean age was 58.59. The mean SMI Index in sarcopenia group (30.86±3.39)(P value < 0.001), SMI values [(33.78±3.28) vs(43.2± 1.49)]male, [(27.45±1.84) vs (36.92±0.96)]female. Preop Biliary drainage required in 15(57.6% vs 8(25.8%) (*P*=0.0147).Sarcopenic patients are associated with low albumin levels - 3.269(±0.349)(*P*=0.0086) ,mid-arm circumference [24.86±4.9cm(p value < 0.001)], Handgrip strength values [32.21±9.3(p value0.011)].In sarcopenia group (n=26), 10(38.46%)pancreatic leak(CR-POPF), 6(23%)bile leak, 10(38.46%)DGE, total 20(76.9%) cases had late complications. ICU stay, hospital stay, Infective complications[11(45.45%)(p value 0.029)] were higher in sarcopenia group. On multivariate analysis low serum albumin < 3.5(*P*<0.038), sarcopenia (*P*=0.036) were significant.

**Conclusions:** Sarcopenia is associated with adverse postoperative outcomes and represent independent risk factor for infectious complications after PD. Identifying sarcopenia patients before surgery enable to implement prehabilitation and targeted interventions to optimize and enhance surgical outcomes.

**Keywords:** Sarcopenia, Pancreaticoduodenectomy, POPF

## OP-122

### Perineural Invasion Signature from Spatiotemporal Transcriptomics Data Shows Distinct Tumor Biology with Therapeutic Resistance in Advanced Biliary Tract Cancer

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**Aims:** Perineural invasion is a well-known predictive pathologic factor associated with poor prognosis in pancreaticobiliary cancers. Recently, a new emerging technology, spatial transcriptomics, has emerged in cancer research to reveal complex tumor biology harboring in situ pathologic information of tumor microenvironment. This study aims to the identification of specific transcriptomic signatures for perineural invasion using the spatial transcriptomic technique with temporally collected patient samples.

**Methods:** Formalin-fixed paraffin-embedded blocks from initial biopsy and post-mortem autopsy samples (gallbladder, liver, peritoneum, lung) were enrolled in this study. Twenty-four areas of interest from six immunofluorescence slides with four morphology markers from the patient's FFPE blocks were selected and the RNA sample for tumor, stroma, and tumor-infiltrating lymphocytes from each AOI was sequenced using GeoMx Human Whole Transcriptome Atlas platform.

**Results:** Tumor stroma and TILs showed distinct gene expression patterns according to their unique tumor microenvironments. Interestingly, the tumor samples showing perineural invasion have unique and discriminative transcriptomic profiles with differentially expressed gene sets. Inter and intra-tumoral heterogeneity with distinct tumor phenotypes were identified from comprehensive pathway analysis using single-sample gene-set enrichment analysis. The in-silico analysis for drug response prediction showed differential responses for currently available cancer therapeutics according to temporal tumor progression and spatial tumor context with their unique environments specific to perineural invasion.

**Conclusions:** Spatiotemporal transcriptomic analysis reveals clinically relevant tumor heterogeneity for perineural invasion in advanced biliary tract cancer. Inter and intra-tumoral heterogeneity showing different therapeutic opportunities warrant translational research for clinically relevant molecular deciphering with clinical samples in the era of precision surgical oncology.

**Keywords:** Advanced biliary tract cancer, Spatial transcriptomics, Perineural invasion

## OP-123

### The Role and Mechanism of TRAIP in Cholestatic Liver Injury

Jiaping Liu[1,2,3], Shuangdi Duan[1,2,3], Yong Wang[1,2,3], Mingbei Zhong[1,2,3], Gangping Feng[1,2,3], Shilian Chen[1,2,3], Guozheng Huang[1,2,3], Qiuli Xie[1,2,3], Shuangjiang Li[1,2,3], Songqing He[1,2,3], Guandou Yuan[1,2,3,*]

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**Aims:** Cholestatic liver injury (CLI) is a key initial step in the development and progression of cholestatic liver disease, but its mechanism remains unclear. TRAIP (TRAF-interacting protein, also known as TRIP or RNF206) E3 ubiquitin ligase has recently been shown to play key roles in various cellular processes, including NF-κB activation, DNA damage response, mitosis, and tumorigenesis etc. Here, we aim to explore the role and mechanism of TRAIP in CLI, which has never been reported.

**Methods:** Mice with liver-specific overexpression (HTG) and knockout (LKO) of TRAIP and their control littermates were subject to bile duct ligation (BDL) and 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) induced CLI models. Serum and

liver tissues were harvested at different time as indicated to detect the changes in liver injury, inflammation, proliferation, and fibrosis between $TRAIP^{HTG}$/$TRAIP^{LKO}$ mice and their control littermates. High-throughput RNA sequencing (RNA-seq) of the liver tissues from $TRAIP^{HTG}$ mice and their WT littermates at day 3 after BDL was used to investigate the mechanism of TRAIP in CLI. RNA-seq data were further validated by western blotting and quantitative real time polymerase chain reaction using liver tissues from different CLI mouse models and immortalized hepatic cells treated with different bile acids.

**Results:** The expression levels of TRAIP were significantly up-regulated in liver tissues from biliary atresia patients, different CLI mouse models and AML-12 cells treated with different bile acids when compared to their controls. In BDL and DDC induced mouse CLI models, $TRAIP^{HTG}$ alleviated the liver damage, inflammation, immune cells infiltration, and cholestatic liver fibrosis when compared to the control littermates, while $TRAIP^{LKO}$ played the the opposite effect, which promoted liver damage, inflammation, immune cells infiltration, and liver fibrosis in these CLI mouse models, indicating that TRAIP plays a protective role in CLI. RNA-seq data showed that TRAIP mediated cell apoptosis, autophagy and regulated PI3K/Akt/mTOR signaling pathway in BDL model. We further validated these findings in liver tissues from BDL and DDC induced mouse CLI models and AML-12 cells treated with various bile acids. Taken together, TRAIP may promote cell survival and homeostasis by promoting the initiation of autophagic signaling after cholestasis, which induced the expression of TRAIP, resulting in alleviating hepatic inflammatory infiltration and fibrosis.

**Conclusions:** TRAIP alleviates CLI through promoting hepatic cell autophagy under cholestatic stress by regulating PI3K/Akt/mTOR signaling. Targeting TRAIP or autophagic signaling may be a promising treatment for CLI.

**Keywords:** Cholestatic liver injury, Traip, Inflammation, Autophagy

## OP-124

### Compliance to ASGE ESGE Guidelines for the Diagnosis of Choledocholithiasis in Patients Submitted to Laparoscopic Cholecystectomy for Acute Biliary Disease

**Matteo Maria Cimino**, Matteo Porta, Giulia Lamperti, Kurihara Hayato

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**Aims:** The American Society of Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) have published guidelines for choledocholithiasis treatment. This study aimed to assess compliance to these guidelines in a prospective series of patients submitted to emergency cholecystectomy.

**Methods:** Data for choledocholithiasis standard reference tests were retrospectively reviewed from November 2021 to September 2023.

**Results:** 122 patients were included. Twenty-two (19.0%), 89 (73.0%), and 11 (8.0%) patients were classified into low-, intermediate-, and high-risk groups according to the ASGE guidelines, and 54 (44.3%), 62(50.8%), and 6(4.9%) according to the ESGE guidelines. Intermediate risk group, 21 (23.6%) patients underwent CholangioMRI or echoendoscopy (CE) in the ASGE group and 27 (43.5%) patients in the ESGE group. Patients that underwent CE in the ASGE group had a longer LOS 8.06 vs 4.47 (CI 95% 1.17 to 5.04*P*=0.002) shorter operative time 80.9 vs 113.6 min (CI 95% -52.16 to -13.28 *P*=0.001) and the same post operative complications (OR 0.53 CI 95% 0.16-1.99 *P*=0.37). Patients that underwent CE in the ESGE group had a longer LOS 10.5 vs 5.4 (CI 95% 1.38-8.18 *P*=0.0065) same operative time 82 vs 74 min (CI 95% -14.55 to 34.65 *P*=0.41) and the same post operative complications (OR 0.42 CI 95% 0.09-1.97 *P*=0.42).

**Conclusions:** Patients with intermediate risk of choledocholithiasis has a rate of compliance in our institution of 23.6% 43.5% for the ASGE and ESGE guidelines respectively. Rate of postoperative complications in patients submitted to CE are comparable with patients not submitted to CE. CE prologs the LOS.

**Keywords:** Choledocholithiasis, Gallbladder, Cholelithiasis

10TH The Liver Week Anniversary
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# E-Poster Exhibition

**PE-01~PE-10** HBV, Basic
**PE-01~PE-17** HBV, Clinical
**PE-01~PE-05** HCV, Basic
**PE-01~PE-09** HCV, Clinical
**PE-01~PE-02** Alcoholic Liver Disease
**PE-01~PE-03** Autoimmune Liver Disease
**PE-01~PE-08** Cell Biology and Molecular Biology
**PE-01~PE-02** Genetic
**PE-01~PE-07** Drug and Toxic Injury
**PE-01~PE-01** Liver Cirrhosis, Portal Hypertension with Cx. Basic
**PE-01~PE-10** Liver Cirrhosis, Portal Hypertension with Cx. Clinical
**PE-01~PE-03** Liver Failure, Acute
**PE-01~PE-16** Liver, Infectious Disease
**PE-01~PE-15** MASLD, Basic
**PE-01~PE-26** MASLD, Clinical
**PE-01~PE-21** Liver Cancer, Basic
**PE-01~PE-48** Liver Cancer, Clinical
**PE-01~PE-16** Liver Transplantation
**PE-01~PE-22** Biliary and Pancreatic Disease
**PE-01~PE-14** Surgery, Technical Issues
**PE-01~PE-24** Others

# HBV, Basic

## PE-01

### In Silico and *in vitro* Anti-Hepatitis B Virus Activity of Bioassay-Guided Compound Quercetin and Myricetin-3-O-Rhamnoside from Pistacia Lentiscus

Deepika Singh

Department of Pharmaceutical Sciences, Shuats, India

**Aims:** Acute and chronic hepatitis B are disorders of the liver brought on by the hepatitis B virus (HBV). The current study describes the column-guided isolation and structural characterization of two anti-HBV compounds from Pistacia lentiscus utilizing an HBV-reporter cell culture paradigm, as well as the molecular docking elucidation of the mode of action.

**Methods:** Pistacia lentiscus leaves recently demonstrated *in vitro* anti-hepatitis B virus (HBV) action, and quercetin and other flavonoids were identified by HPTLC. Here, we describe the bioassay-directed fractionation of Pistacia lentiscus leaves using column chromatography and the isolation of two flavonoinds from the n-butanol fraction, as well as the determination of their structures (1H, 13C, and 2D-NMR) and evaluation of their antiviral activities (HBsAg and HBeAg assay) in HBV-reporter HepG2.2.2.15 cells.

**Results:** The HBV polymerase (Pol/RT) and capsid (Core) proteins, as well as the host-receptor sodium taurocholate co-transporting polypeptide (NTCP), were subjected to further molecular docking. Myricetin-3-O-rhamnoside and quercetin were recognized as the two isolated bioactive substances that are to be isolated from Pistacia lentiscus. In comparison to myricetin-3-O-rhamnoside, quercetin considerably decreased the synthesis of HBsAg and HBeAg by 43% and 36%, respectively, and by roughly 58% and 64%, respectively. The two anti-HBV flavonoids' greater affinity for Pol/RT than NTCP and Core was revealed by molecular docking.

**Conclusions:** both chemical compounds isolated from Pistacia lentiscus were found to be effective by binding to viral Pol/RT and Core as well as host NTCP proteins and suggested potential virus inactivation mechanisms

**Keywords:** Hepatitis, *In vitro*, In silico

## PE-02

### Hepatitis B and Hepatitis C Viruses as Aetiological Factors for Liver Cancer in Sri Lanka; A Narrative Overview

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**Aims:** Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) are viral infections that pose a significant threat around the globe, targeting liver-related complications. The review aimed to review the role of HBV and HCV for liver cancer in Sri Lanka.

**Methods:** Peer-reviewed articles were searched in the PubMed database and a grey literature search was performed, including the Sri Lanka National Immunization Program, National Cancer Registry, National prevention programs for sexually transmitted infection and Thalassemia. Record identification was done in March 2024 using seven key terms: Liver Cancer, hepatitis B, hepatitis C, prevalence, vaccination, preventive measures, and Sri Lanka. The search was limited only to English and the period between 2000-2024.

**Results:** A total of 16 records including 11 peer-reviewed articles and five gray literatures were selected. In the year 2021, Crude incidence rate of liver cancer of males and females were 4.3/100 000 and 2.2/100 000 respectively. The highest 5-year age specific-incidence rates of liver cancer were reported among males and females of 70-74 age group (Males 38.5/100 000and females 14.8/100 000). The age standardized incidence rate of liver cancer was 4.1/100 000 in males and 1.9/100 000 in females. The highest liver cancer cases were reported in western province (CR=9.8/100 000 in males, CR=4.4/100 000 in females). Crude death rates of liver cancer among males and females were 6.1/100 000 and 2.7/100 000 respectively. The main causes of liver cancers in Sri Lanka are alcoholic and non-alcoholic fatty liver diseases. HBV and HCV are not recognized as primary cause for liver cancers because the prevalence of HBV and HCV in Sri Lanka is more lower due to high vaccination coverage, free screening high risk population, antiviral drug treatment.

**Conclusions:** The implementation of free preventive measures and treatment by the Sri Lankan government has significantly contributed to the reduction of HBV and HCV prevalence in the country. As a result, HBV and HCV are not the primary cause of liver cancer in Sri Lanka.

**Keywords:** Hepatitis B virus, Hepatitis C virus, Liver cancer

## PE-03

### Risk Factors for Mother-to-Child Transmission Using the National Hepatitis B Perinatal Transmission Prevention Program Database in Korea, 2002-2021

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**Aims:** The aim of this study was to define risk factors associated with mother-to-child transmission (MTCT) and to create

supporting evidence for the national Hepatitis B Perinatal Transmission Prevention Program (HBPTPP) in Korea.

**Methods:** We analyzed HBPTPP mother-infant pair data enrolled from 2002 to 2021. The major outcome was HBsAg status of infant resulted by post-vaccination serological testing. Additionally, we used prescription records of antivirals against hepatitis B virus (telbivudine, tenofovir disoproxil fumarate) from 2010 to 2021 by data linkage with the National Health Insurance claims data. To select significant risk factors by maternal HBeAg status based on the data from 34 to 42 weeks of pregnancy, multivariate logistic regression analysis was used.

**Results:** Data from 232,242 mother-infant pairs were analyzed. Among 154,331 (66.5%) infants with post-vaccination serological testing results, 3,620 (2.3%) were HBsAg-positive. Over the past 20 years, the incidence of MTCT has shown a decreasing trend, approximately 3.1% points from 4.1% in 2002 to 1.0% in 2021. However, the rate was high 5.5% (1822/32986) for infants of HBeAg-positive mothers. Maternal antiviral prescription in pregnant period, old age, HBeAg (-), delivery type (C-section) and breastfeeding were significant factors to decrease risk of MTCT. Among the HBeAg-positive, there was a significant difference in the antiviral prescription 0.7% (11/1692) compared to the non-prescription 4.9% (789/16264) [aOR, 7.71; 95% CI, 4.24-14.02]. The result was similar for HBeAg-negative group, with a rate of 0.7% (302/44888). However, in HBeAg-negative group, there was no significant difference observed between antiviral prescription and non-prescription.

**Conclusions:** To eradicate hepatitis B virus on a national level, MTCT must be further reduced. In order to achieve this, it is necessary to introduce strong additional preventive measures, including quantitative HBV DNA testing for mothers with chronic hepatitis B and administering antiviral prophylaxis at the third trimester of pregnancy with HBV-DNA ≥ 200,000 IU/mL into the HBPTPP.

**Keywords:** Mother-to-child transmission, Hepatitis B virus, Immunization program, Post-exposure prophylaxis

## PE-04

### COVID-19 Vaccination Outcomes in Living Donor Liver Transplant Recipients: Influence of Combined Immunosuppressant and HBV Antiviral Therapy

Ryunjin Lee[1], Eunkyeong Lee[1], Young-In Yoon[3], Jiwan Choi[1], Jooyoung Lee[1], Jiye Kim[1], Seoon Kang[1], Hye-In An[1], Sung-Han Kim[2], Sung-Min Kim[3], Eun-Kyoung Jwa[3], Gil-Chun Park[3], Jung-Man Namgoong[4], Gi-Won Song[3], Eunyoung Tak[1], Sung-Gyu Lee[3]

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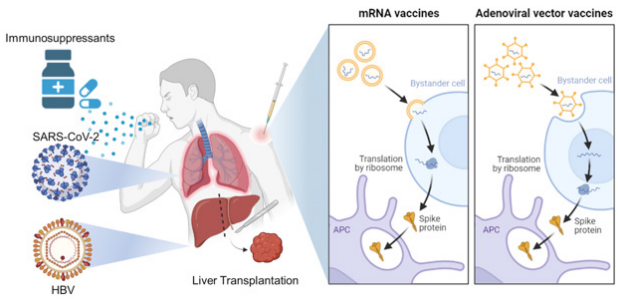
**Aims:** The global pandemic caused by the highly contagious SARS-CoV-2 virus led to emergency approval of COVID-19 vaccines like ChAdOx1 nCoV-19, mRNA-1273, and BNT162b2 to mitigate the escalating morbidity and mortality. However, limited research exists on quantifying the impact of these vaccines, particularly on immunocompromised individuals, highlighting the need for further investigation in this area.

**Methods:** From June 2021, we followed up on the effectiveness of the vaccine for patients taking immunosuppressive drugs after living-donor liver transplantation (LDLT). A total of 105 immunocompromised individuals participated, of which 50 patients with hepatitis B were taking antiviral drugs. Patients were assessed to analyze how the combination of immunosuppressive and antiviral drugs affected the efficacy of the BNT162b2, mRNA-1273, and ChAdOx1 nCoV-19 COVID-19 vaccines.

**Results:** Before and after the vaccinations, patients were monitored to establish differences between immunosuppressed patients and those additionally taking antiviral drugs. In immunocompromised patients taking antiviral drugs for hepatitis B, we confirmed that the effect of the COVID-19 vaccine was reduced when compared to immunocompromised patients. Interestingly, 23 patients (11 without and 12 additionally with hepatitis B drug administration) encountered breakthrough infections, and although there was a minor discrepancy in vaccine efficacy among the patients taking antiviral drugs for hepatitis B, it did not reach statistical significance.

**Conclusions:** Additional COVID-19 vaccination is recommended for patients taking immunosuppressive drugs and hepatitis B antiviral drugs after LDLT.

**Keywords:** Hepatitis B virus, Living-donor liver transplantation, Anti-viral drug, Coronavirus



## PE-05

### Targeting the X Gene of HBV Genotype B: Identification of Promising siRNA Antivirals

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**Aims:** Hepatitis B virus (HBV) infection continues to pose a significant global health threat, particularly with the challenges presented by Hepatitis B genotype B. The X gene of HBV holds considerable importance in viral replication and disease progression, rendering it a compelling target for antiviral interventions. This research sought to investigate the potential of small interfering RNA (siRNA) molecules as antiviral agents against the X gene of HBV genotype B.

**Methods:** Using advanced bioinformatics tools and sequence analysis, we crafted siRNA sequences tailored to target conserved regions within the X gene of HBV genotype B. These siRNA candidates underwent thorough screening and evaluation to assess their specificity, efficacy, and potential off-target effects. Employing the siDirect platform, we generated siRNA molecules, employing a sequential filtering bioinformatics approach to pinpoint prospective antiviral siRNAs targeting the X gene of HBV genotype B. The siRNA Scales tool facilitated the selection process, followed by additional scrutiny using MaxExpect and DuplexFold to determine the folding free energy of the siRNAs and the binding free energy between the guide strand and the target, respectively. Prediction of siRNA efficacy was conducted using siPred.

**Figure 1.** The graphical view of the three siRNAs.

**Results:** A total of three siRNAs were successfully designed based on the comprehensive genome analysis of HBV genotype B. Subsequent assessments using various bioinformatics methodologies identified these siRNAs as capable of effectively silencing the X gene region of HBV genotype B, exhibiting efficacy levels ranging from 84.08 to 90.8.

**Conclusions:** This research presents three siRNA molecules with potential for serving as candidates in antiviral siRNA therapy against HBV genotype B. Nonetheless, it remains imperative to validate the predicted siRNAs through laboratory experiments.

**Keywords:** X Gene, HBV, Small interfering RNA (SIRNA)

## PE-06

### Current Issues of HBV Epidemiology in the Rural Province Ha Giang, Vietnam

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**Aims:** The most of the prevalence of chronic HBV infection is in the Asia–Pacific region, including Vietnam. We conducted this cross-sectional survey to evaluate the prevalence of HBV infection among indigenous people of rural province Ha Giang, Vietnam.

**Methods:** A total of 1427 rural inhabitants aged 18-83 years were including in our study. The ratio of males to females was 1:2.25. They all belonged to different ethnic minority groups residing in five districts, Yen Minh, Bac Me, Đong Van, Vi Xuyen, Bac Quang in the Ha Giang province, Vietnam. Among the 1427 participants, 634 were from H'mong ethnic, 472 from Tay ethnic, 161 from Dao ethnic, 160 from other smallest ethnic. Serum samples from participants were tested for HBV specific serological markers using ELISA-kits (RPC «Diagnostic Systems», Russia). All HBsAg-positive samples were tested for DNA HBV and HBV genotypes by RT-PCR.

**Results:** Totally, the prevalence of HBsAg was 11.1% (159/1427; 95%CI: 9.6-12.9), anti-HBc – 54.5 % (778/1427; 95%CI: 51.9-57.1), anti-HBs – 36.5% (521/1427; 95%CI: 34.1-39.0). Positive for Anti-HBc and negative for anti-HBs was detected in 14.4% (205/1427; 95%CI: 12.6-16.3). Among the H'mong ethnic group the prevalence rates for HBsAg, anti-HBc and anti-HBs were 13.3% (84/634; 95%CI: 10.8-16.1), 47.5% (301/634; 95%CI: 43.6-51.4), and 35.3% (224/634; 95%CI: 31.7-39.1); among the Tày ethnic group – 8.9% (42/472; 95%CI: 6.7-11.8), 58.5% (276/472; 95%CI: 54.0-62.8), 37.1% (175/472; 95% CI: 32.8-41.5), among the Dao ethnic group – 12.4% (20/161; 95%CI: 8.2-18.4), 68.9% (111/161; 95%CI: 61.4-75.6), 39.8% (64/161; 95%CI: 32.5-47.5), other smallest ethnic groups – 8.1% (13/160; 95%CI: 4.8-13.4), 56.3% (90/160; 95%CI: 48.5-63.7), 37.5% (60/160; 95%CI: 30.4-45.2), respectively. DNA HBV were detected in 10.1% (144/1427; 95%CI: 8.6-11.8). A total of 144 Positive for DNA HBV were genotyped, HBV genotype C was in 35,42% ((51/144), genotype B – in 25,69 % (37/144).

**Conclusions:** In our study, the high prevalence of HBV infection among indigenous people belonging to different ethnic mi-

norities of rural province Ha Giang was shown.

**Keywords:** Hepatitis B, Ethnic minority, Rural, Vietnam

## PE-07

### Rapid Diagnostic Test (RDT) Hepatitis B Surface Antigen (HBsAg) for Pregnant Women in Indonesia

**Putri Ayu**[1], Syafriyon[2], Derizal[3], Oktrial Budiarto[4], Arman Saputra[5]

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**Aims:** Hepatitis B transmission in endemic areas such as Indonesia generally occurs vertically, especially during the perinatal period and 95% of babies infected during the perinatal period will develop chronic hepatitis B. One of the prevention efforts is Early Detection of Hepatitis B (DDHB) in pregnant women using the Rapid Diagnostic Test (RDT) Hepatitis B Surface Antigen (HBsAg).This research aims to identify Early Detection of Hepatitis B (DDHB) or RDT in pregnant women in Indonesia in 2021. The data used is the 2021 Indonesian health profile from the Ministry of Health of the Republic of Indonesia.

**Methods:** The data used is the 2021 Indonesian health profile from the Ministry of Health of the Republic of Indonesia.

**Results:** The results show that in 2021, HBsAg RDT for pregnant women/risk groups has been implemented in 478 districts/cities or 93% spread across 34 provinces. There are 29 provinces that have reached the target. The provinces with the highest achievement (100%) were 27 provinces, while there were five provinces that had not achieved the target, including Papua (41.4%), West Papua (61.5%), North Sumatra (75.8%), West Kalimantan (85.7%), and Southeast Sulawesi (88.2%). In 2021, 60.3% of pregnant women will carry out DDHB out of the target number of pregnant women in 2021 of 4,887,405 pregnant women. The number of pregnant women who were tested for hepatitis B using the HBsAg RDT in 2021 was 60.3% of the targeted pregnant women. This achievement shows an increase compared to the previous year, namely 51.4% of pregnant women who were reached by examination. The results of the HBsAg RDT examination in 2021 found that 1.6% of pregnant women showed reactive results, where there was a decrease from 2020, namely 1.7% of pregnant women who were declared reactive.

**Conclusions:** So, the reduction in reactive patients due to DDHB or HBsAg RDT in pregnant women shows that it is a good thing to prevent transmission of the hepatitis B virus.

**Keywords:** Rapid Diagnostic Test (RDT), Hepatitis B surface antigen (HBSAG), Pregnant women, Indonesia

## PE-08

### Effectiveness of Counseling Using Video Media to Increase Knowledge about Hepatitis B

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**Aims:** The Hepatitis B virus has infected two billion people in the world, 240 million of whom develop chronic Hepatitis B, as many as 1.5 million people die every year due to hepatitis. Indonesia is the country with the second highest hepatitis B endemicity among the South East Asian Region (SEAR) countries after Myanmar (Gozali, 2020). Various efforts have been made to increase public knowledge regarding hepatitis, one of which is outreach using video media. This research aims to determine the effect of counseling using videos on increasing knowledge about hepatitis B in Indonesia.

**Methods:** This research is a literature review using journals from 2020 to 2023. From the synthesis results, three journals were obtained that were in line with the research objectives.

**Results:** Based on the results of the analysis, the results obtained were: 1) Jafar, et al (2020) using 25 students, using the Wilkoxon Signed Rank Test, 2) Yanti, et al (2021) with a total of 54 samples of pregnant women, each with 27 respondents. into 27 control groups and experimental groups. Using the Wilkoxon Signed Rank Test, 3) Supadmi, et al (2022) followed by 25 teenagers, using descriptive analysis. From these three studies, it was found that respondents' level of knowledge about hepatitis B increased after participating in socialization using videos.

**Conclusions:** This proves that video outreach is an effective medium for hepatitis B education activities to the public.

**Keywords:** Hepatitis B

## PE-09

### Prevalence Of Hepatitis B Virus Infection among Health Care Workers in a Secondary Health Center, Single-Center Study

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[1]Molor Clinic; [2]Mongolian National University Science and Technology; [3]Dornod Medical Center, Mongolia

**Aims:** There is a wide variation of hepatitis B virus (HBV) infection in the Asia–Pacific region. The prevalence of chronic HBV infection is highest (8.1%) in Mongolia. Healthcare workers (HCWs) are at high risk of contracting HBV infection through their occupation. We aimed with this cross-sectional study to determine HBV prevalence, HCW vaccination status, and the risk factors for HCWs contracting HBV infection in Dornod

province, Mongolia.

**Methods:** We enrolled 500 HCWs from a Dornod Medical Center. Their demographics, medical histories, and risk factors for contracting blood-borne infections were collected using a standardized questionnaire. Serum samples were tested for HBV markers by ELISA techniques, PCR, and an anti-HBs rapid test. HCWs were divided into two subgroups: those at risk of contracting HBV (rHCW 69.3%) via exposure to potentially infectious materials, and those considered not at risk of contracting HBV (nrHCW, 30.8%).

**Results:** The overall prevalence of chronic HBV infection (HBsAg+, anti-HBc+, anti-HBs-) was 8.4% (42/500). Chronic HBV infection was found in 8.9% of rHCW versus 6.4% of nrHCW (*P*-value = 0.484). HCWs susceptible to HBV (HBsAg-, anti-HBc-, anti-HBs-) comprised 31.3%. there was a significantly higher risk for contracting HBV (anti-HBc+) among those HCW at occupational risk (rHCW) of older age (odds ratios (OR) in rHCW 3.786, *P*<0.0001 vs. nrHCW 1.415, *P*=0.606) and among those HCW being employed more than 11 years (OR 2.51, *P*<0.0001***).

**Conclusions:** Our finding of a greater than 8 % prevalence rate of chronic hepatitis B among healthcare workers, should help fuel efforts for regional testing, vaccination, and treatment efforts to align with the WHO goals of elimination of hepatitis B and C by 2030.

**Keywords:** Chronic HBV infection, Health care workers, Vaccination

## PE-10

### Risk Factors for Hepatitis B Incidence in Pregnant Women in Indonesia

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Management Education, Yogyakarta State University, Indonesia

**Aims:** Hepatitis B is a dangerous infectious disease which is one of the biggest causes of death in women. Indonesia is an endemic country for this disease, around 23 million Indonesian people have been infected with Hepatitis B. Specifically for Hepatitis B, Indonesia is one of the countries in the Southeast Asian region with highest prevalence rate. In this population, most of the transmission comes from the mother to child transmission route.

**Methods:** The purpose of the literature review is to determine the factors that cause Hepatitis B in pregnant women. *T*he research design used in this study is to use the Literature review method. This technique is carried out with the aim of expressing various theories that are relevant to the problem being faced or being researched as reference material in the discussion of research results. In this study, the authors chose a quantitative research article with a cross sectional design or case control design with using scientific research from 2018 to 2022.

**Results:** The results showed that there is a relationship between parity (*P*=0.000), level of education (*P*=0.025), age at first marriage (*P*=0.007), frequency of spouse's marriage (*P*=0.008), sexual partner (*P*=0.031), spouses's hepatitis B status (*P*=0.001), history of spouse's mobility (*P*=0.007), family history of hepatitis B (*P*=001), health worker support (*P*=0.027), and history of needle use (*P*=0.013) with the incidence of hepatitis B in pregnant women.

**Conclusions:** Parity, level if education, age at first marriage, frequency of spouse's marriage, sexual partners, spouses's hepatitis B status, history of spouse's mobility, family history of hepatitis B, and health worker support are risk factors for the incidence of hepatitis B in pregnant women. Among all the risk factors found, sexual partners are the most risky factors for the incidence of hepatitis B in pregnant women in Indonesia.

**Keywords:** Hepatitis B, Pregnant women

**LITERACY SOURCE**

| AUTHOR | YEAR | TITLE | RESULTS |
|---|---|---|---|
| Dwiana Kartika Putri, 1Rina Hanum,1Hotma Juliana Simanjuntak | 2019 | FACTORS AFFECTING PREGNANT WOMEN IN DO HEPATITIS EXAMINATION | tatistical test results obtained p-value = 0.017 and OR = 9.032 on knowledge variables. The value of p-value = 0.049 and OR = 8.288 on the husband's support variable. The value of p-value = 0.027 and OR = 11.039 on the variable of health worker support. Where p-value <α (0.05). Conclusions in the study there are factors (knowing, husband's support and health worker support) that affect pregnant women in conducting hepatitis examination in the Martoba Pematang Siantar Health Center Work Area in 2019. |
| Pratono1, Asri C. Adisasmita2 | 2019 | RISK FACTORS FOR HEPATITIS B EVENTS IN PREGNANT WOMEN IN THE DKI JAKARTA REGION 2015 – 2016 | Based on the results of multivariable analysis, it was found that pregnant women working in the non-formal field would tend to be protected 27% greater than Hepatitis B infection with OR = 0.73 (95% CI = 0.56 - 0.94). It was also found that pregnant women who had blood transfusions had a risk of 28.6 times greater risk of getting Hepatitis B with an OR = 28.62 (95% CI = 7.67 - 106.7). Pregnant women who have> 1 sex partner and who live at home with Hepatitis B patients at 21.4 and 20.4 times greater risk of getting Hepatitis B with OR = 21.47 (95% CI = 1.35 - 345.43) and OR = 20 (95% CI = 9.35 - 45)., |
| Putu Lusita Nati Indriani1, Helni Anggrain | 2021 | FACTORS AFFECTING THE OCCURRENCE OF HEPATITIS IN PREGNANT WOMEN | The results of the analysis of the relationship between age statistical tests showed p value = 1.0, parity with p = 0.142, and socio-economic with p = 0.12, it can be concluded that there is no relationship, and the results of research on the relationship between education and p = 0.02, occupation with p=0.001, sources of information with p=0.009, and the role of health workers with p=0.00; Based on the results of this study, there is a relationship between education, occupation, sources of information and the role of health workers with maternal knowledge about hepatitis B |
| Syifa Mustika, Dian Hasanah | 2018 | Prevalence of Hepatitis B Infection in Pregnant Women in Malang | Hepatitis B prevalence was obtained as much as 1% and 8% positive anti-HBs was found in patients with negative HBsAg. |
| Yanyan Mulyani*, Vaurel Nurul Salsabil | 2020 | Pengetahuan Dan Sikap Ibu Hamil Tentang Pencegahan Penularan Penyakit Hepatitis B Pada Janin Di Puskesmas Ciaparay Kabupaten Bandung Tahun 2019 | Hasil dari penelitian ini adalah sebanyak 34 responden (53.1%) memiliki pengetahuan kurang. 19 responden (29.7%) memiliki pengetahuan cukup, dan 11 responden (17.2%) memiliki pengetahuan baik. Sedangkan 28 responden (43.8%) memiliki sikap negative, dan 36 responden (56.2%) memiliki sikap positif. |
| Margaretha Pither1*, Andi Yusuf2, Rahmawati Aziz3* | 2021 | Risk Factors for Hepatitis B Incidence in Pregnant Women in East Luwu District | The statistical test showed that the level of education (p-value = 0.027; OR = 2.705; 95% CI: 1.197-6.113), parity (p-value = 0.023; OR = 2.846; 95% CI: 1.228-6.697), and sexual partner (p-value = 0.031; OR = 9.333; 95% CI: 1.121- |

# HBV, Clinical

## PE-01

### Efficacy and Safety of Switching Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in Virologically Suppressed Chronic Hepatitis B Patients with Antiviral Resistance: Preliminary Data

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Department of Internal Medicine, Yonsei University College of Medicine

**Aims:** Tenofovir disoproxil fumarate (TDF) monotherapy effectively suppresses viral replication in patients with multidrug-resistant chronic hepatitis B (CHB). However, TDF users are at risk of kidney dysfunction and osteopenia. We conducted this ran-

domized open-label study to compare the efficacy and safety of switching from TDF to tenofovir alafenamide (TAF) in these patients.

**Methods:** This prospective, open-label study was conducted at a single tertiary medical center. Current TDF users for CHB who experienced multidrug resistance (e.g., resistance to more than two non-potent nucleos(t)ide analogs or to entecavir) were enrolled between 2021 and 2023. Patients were randomized into two groups: continuing TDF (TDF group) and switching to TAF (TAF group). Virologic response was defined as HBV DNA < 20 IU/mL.

**Results:** We preliminary analyzed 14 patients (11 males) in the TDF group and 30 (23 males) in the TAF group who underwent one-year follow-up after study enrollment. Baseline characteristics between the TDF and TAF groups were not statistically different: age (median 60.5 vs. 63.0 years, *P*=0.686), body mass index (median 22.8 vs. 23.6 kg/m$^2$, *P*=0.326), estimated glomerular filtration rate (eGFR) (median 95.0 vs. 88.5 mL/min/1.73$^2$, *P*=0.110), HBeAg positivity (64.3% vs. 70.0%, *P*=0.738), and bone mineral density of the spine (median -0.8 vs. -0.5, *P*=0.357) and femur (-1.1 vs. -1.0, *P*=0.668), respectively. After 1 year, all patients maintained virologic response regardless of the group. The median value of eGFR was increased in the TAF group, although the change was not statistically significant between the groups (95.0 to 92.2 mL/min/1.73$^2$ in the TDF group and 88.5 to 92.0 mL/min/1.73$^2$ in the TAF group, *P*=0.075). The median spine BMD value improved in the TAF group (spine: -0.8 to -1.2 in the TDF group and -0.5 to -0.3 in the TAF group, *P*=0.022).

**Conclusions:** Preliminary data suggests that switching from TDF to TAF is effective in patients with multidrug-resistant CHB. Kidney function and osteopenia were also improved after the switch.

**Keywords:** Tenofovir disoproxyl fumarate, Tenofovir alafenamide, Chronic hepatitis B, Osteoporosis

## PE-02

### FIB-5 versus FIB-4 Index for Assessment of Hepatic Fibrosis in Chronic Hepatitis B Affected Patients

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**Aims:** Chronic hepatitis B virus (HBV) infection is one of the major health problems worldwide. Use of non-invasive tests for assessment of hepatic fibrosis such as the FIB-4 index could be used to avoid liver biopsy. Another promising noninvasive test, FIB-5, could also be used to detect significant hepatic fibrosis. The aim of the study was to compare the use of FIB-5 and FIB-4 as noninvasive markers to assess chronic HBV-related hepatic fibrosis.

**Methods:** This study was done on 176 chronic HBV patients who underwent liver biopsy. Grading and staging of liver fibrosis was done according to the METAVIR scoring system. FIB-5 and FIB-4 scores were calculated for all patients.

**Results:** As regards FIB-4 for differentiation between non-significant fibrosis (group I) and significant fibrosis (group II), at a cutoff level of 1.28 with positive predictive value (PPV) 41.4% and specificity 48% while at a cutoff level of 7.08 with PPV 98.8% and specificity 98% for FIB-5.

**Conclusions:** As regards both scores, the FIB-5 score was more specific than FIB-4 for diagnosing significant from nonsignificant hepatic fibrosis in patients with chronic HBV infection.

**Keywords:** FIB-5, FIB-4, Fibrosis, Biopsy, Chronic HBV

## PE-03

### Metabolic Dysfunction-Associated Steatotic Liver Disease Is not Independently Associated with Complete Response to Oral Antiviral Treatment in Chronic Hepatitis B

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**Aims:** The impact of metabolic dysfunction-associated steatotic liver disease (MASLD) on treatment response following nucleos(t)ide analogue (NA) treatment for chronic hepatitis B (CHB) patients has not been clearly elucidated. The aim of this study is to investigate the impact of MASLD on complete viral response (CVR) and biochemical response in CHB patients who received NA treatment.

**Methods:** We retrospectively recruited CHB patients receiving NA therapy from January 2014 to December 2020. CHB patients with decompensated cirrhosis or hepatocelluar carcinoma were excluded. All patients were divided into CHB group and CHB with MASLD group according to MASLD diagnostic criteria. Therapeutic response related data were recorded and compared at multiple time points. Kaplan-Meier and Cox regression analyses were utilized to estimate the impact of MASLD on complete virological response (CVR).

**Results:** A total of 460 patients were enrolled (356 CHB without MASLD, 104 CHB with MASLD). The majority of patients were male (55.3%) and HBeAg-positive (55.2%). In comparison to non- MASLD patients, those with MASLD were more likely to be HBeAg-positive (65.4% vs. 52.2%, *P*=0.018), have hypercholesterolemia (22.9% vs. 12.5%, *P*=0.009), and present

with a higher mean HBV DNA titer (6.56±1.45 vs. 6.26±1.47, *P*=0.064). They also had a higher mean BMI (25.3±3.4 vs. 22.9 ±4.5 kg/m$^2$, *P*<0.001) at baseline. Both groups achieved similar rates of ALT normalization (MASLD vs non- MASLD; 100% vs 99.7%, *P*=0.588), and HBsAg seroclearacne (2.9% vs 3.7%, *P*=0.707) during the follow-up of up to 65 months. The cumulative rates of CVR at week 96 was observed to be lower in MASLD patients compared to non-MASLD patients (81.1% vs 91.3%, *P*=0.001). However, multivariate analysis revealed that MASLD was not independently associated with CVR outcomes, and higher baseline HBV DNA and HBeAg positivity at baseline was negatively associated with achieving CVR.

**Conclusions:** The presence of MASLD did not negatively affect CHB treatment outcomes of complete virologic response or biochemical response.

**Keywords:** Chronic hepatitis B, Metabolic dysfunction-associated steatotic liver disease, Antiviral treatment

## PE-04

### Comparison of the Effects of Entecavir and Tenofovir Disoproxil Fumarate on Recurrence of Hepatocellular Carcinoma after Surgical Resection in Chronic Hepatitis B

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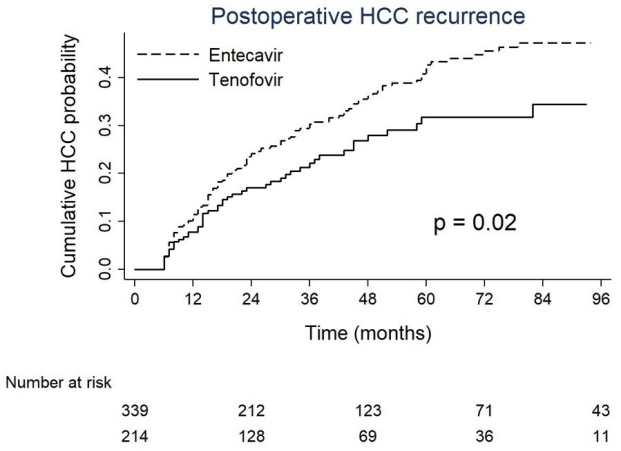
**Aims:** Use of nuleos(t)ide analogues (NAs) such as entecavir (ETV) or tenofovir disoproxil fumarate (TDF) may reduce the risk of hepatocellular carcinoma (HCC) recurrence after curative resection in patients with chronic hepatitis B. However, there is a disagreement regarding whether ETV or TDF provide a same beneficial effect after surgical treatment of HCC. Therefore, we investigated the effect of TDF or ETV on recurrence and progression-free survival of HCC after curative surgery in chronic hepatitis B patients

**Methods:** This retrospective cohort study analyzed 510 patients who received either ETV (n=308) or TDF (n=202). The exclusion criteria consisted of individuals who were treated with nucleotide analogues other than ETV or TDF, those with concurrent cancers other than HCC, and those with a follow-up duration of less than 6 months. The curative surgery included hepatectomy, lobectomy, sectionectomy, segmentectomy, and tumorectomy. The laboratory data was extracted from the closest date before the surgery. We used Kaplan-Meier estimation to evaluate HCC recurrence and progression-free survival in patients treated with ETV or TDF, and used a multivariable-adjusted cox proportional hazard model to compare the results between the two groups. The cumulative HCC recurrence rate was calculated by subtracting the survival value from 100 percent.

**Results:** The median age of patients was 61 years (ETV group 62 years, TDF group 59 years) and 78.48% were male (ETV group 76.4%, TDF group 81.8%). The median follow-up duration was 32 months (ETV group 33 months, TDF group 32 months). The cumulative HCC recurrence rate was 9, 21, 27 and 38% after 12, 24, 36 and 60 months, respectively. By multivariable-adjusted analysis, more recurrence was observed with younger patients (hazard ratio[HR] = 0.970, 95% CI = 0.955-0.986, *P* value = 0.000), male (HR = 1.704, 95% CI = 1.117-2.600, *P* value = 0.013), lower albumin level (HR = 0.543, 95% CI = 0.389-0.757, *P* value = 0.000) and use of TDF compared to ETV (HR = 0.612, 95% CI = 0.434-0.864, *P* value = 0.005).

**Conclusions:** This study showed that TDF treatment was associated with a significantly lower risk of HCC recurrence following curative surgery compared to ETV treatment among patients with chronic hepatitis B infection. Further research is required to determine the long-term effect of ETV and TDF on HCC recurrence and progression-free survival.

**Keywords:** HBV, Entecavir, Tenofovir disoproxil fumarate, HCC




## PE-05

### Association of Nucleos(T)Ide Analog Therapy with Parkinson Disease in Patients with Chronic Hepatitis B Virus Infection: Preliminary Results of A Nationwide Cohort Study

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**Aims:** Prolonged therapy using nucleos(t)ide analogs (NUC) is

inevitable in patients with chronic hepatitis B infection (CHB). The long-term impact of NUC therapy on the development of Parkinson disease (PD) in patients with CHB has not been studied.

**Methods:** The study population comprised the National Health Insurance Service claims database from January 1, 2013, to December 31, 2013, only included treatment naïve CHB patients and those without previously diagnosed with neurodegenerative disease. Participants were followed from the index date until either the diagnosis of PD or the study's conclusion on December 31, 2021. The primary outcome was the incidence of PD, compared between the group with initiated NUC therapy at cohort entry and the group without NUC therapy.

**Results:** Patients receiving NUC therapy (n=18,365) tended to be younger and more male, with a lower prevalence of comorbidities but a higher prevalence of cirrhosis (23.3% vs. 6.7%) compared to patients without NUC therapy (n=212,820). During the study period, a total of 1,646 patients were diagnosed with PD. In a fully adjusted competing risk model, 3 years of follow-up (HR 0.61; 95% CI 0.39–0.97) showed statistical significance. In the PS-matched cohort of 18,365 pairs, cumulative incidences of 2 to 4 years of follow-up groups showed statistically lower HR in NUC treated group than untreated group. In adjusted models including PS-matched analysis, there was no statistically significant difference between the treated and untreated group in cumulative incidence of PD at the beginning and end of follow-up.

**Conclusions:** In CHB patients, NUC therapy is likely to affect PD development differently over cumulative time. Further analysis of PD incidence and NUC effects over time is ongoing.

**Keywords:** Chronic Hepatitis B virus, Nucelos(T)Ide analogs, Parkinson disease, Association

## PE-06

### Epidemiological Insights into Hepatitis B through Blood Samples from the 2020 Korea National Health and Nutrition Examination Survey

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**Aims:** In the WHO criteria for hepatitis elimination, the treatment rate for Hepatitis B is calculated based on the number of patients requiring treatment. Due to limitations in domestic data for estimating this patient population, our study aims to examine the distribution and characteristics of Hepatitis B Virus (HBV) infection in Korea.

**Methods:** A total of 137 blood samples, which were positive for HBV surface antigen from participants of the Korea National Health and Nutrition Examination Survey (KNHANES) and stored at the National Biobank of Korea in 2020, were analyzed.

**Results:** The analysis of the blood samples revealed detectable HBV DNA levels in 62% (85 out of 137) of cases. Among those with detectable HBV DNA, 35 males (58.3%) and 50 females (64.9%) were found to be positive. The prevalence of detectable HBV DNA was highest among individuals aged 10 to 39 years and it gradually decreased with increasing age (81.3% for ages 10-39, 30.0% for ages 70 and above). HBV DNA levels were categorized into five groups, alongside measurements of AST, ALT, and the FIB-4 index. The study also recorded antiviral treatment status and diagnoses of cirrhosis or hepatocellular carcinoma. Twelve individuals were receiving hepatitis B treatment. According to domestic medical reimbursement criteria, 17 individuals (12.4%) required antiviral therapy, with a treatment rate of 70.6%. FIB-4 indexes over 3.25, indicative of significant fibrosis, and elevated AST or ALT levels, suggesting liver damage, were more common in participants with undetectable HBV DNA and those with levels between $10^5$ and $10^8$ IU/ml.

**Conclusions:** In the 2020 KNHANES blood sample analysis, about 12% of patients needed hepatitis B treatment, achieving a 70% treatment rate. Elevated AST, ALT, and FIB-4 index levels were notably higher in individuals with either undetectable HBV DNA or levels between $10^5$ and $10^8$ IU/ml.

**Keywords:** Viral hepatitis, Hepatitis B, Elimination, Epidemiology

| | HBV DNA(IU/ml) | | | | | p-value |
|---|---|---|---|---|---|---|
| | not-detect | <2000 | 2000-$10^5$ | $10^5$-$10^8$ | >$10^8$ | |
| Total (%) | 52(37.9) | 50(36.5) | 19(13.9) | 10(7.3) | 6(4.4) | |
| Male (%) | 25(41.7) | 25(41.7) | 3(5.0) | 4(6.7) | 3(5.0) | 0.117 |
| Female (%) | 27(35.1) | 25(32.5) | 16(20.8) | 6(7.8) | 3(3.9) | |
| Age ± SD | 61.02±12.02 | 54.44±11.23 | 54.68±13.04 | 48.20±11.27 | 44.17±19.36 | 0.001 |
| Diagnosed with Hepatitis B | 11(21.1) | 7(14.0) | 1(5.3) | 1(10.0) | 0(0.0) | 0.007 |
| Hepatitis B Treatment | 10(19.2) | 2(4.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0.170 |
| Diagnosed with Cirrhosis | 5(9.6) | 1(2.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0.004 |
| Diagnosed with HCC | 4(7.7) | 0(0.0) | 0(0.0) | 0(0.0) | 0(0.0) | 0.003 |
| FIB-4 <1.45 | 19(36.5) | 29(58.0) | 13(68.4) | 4(40.0) | 3(50.0) | |
| FIB-4 1.45-3.25 | 24(46.2) | 20(40.0) | 6(31.6) | 3(30.0) | 2(33.3) | 0.030 |
| FIB-4 >3.25 | 9(17.3) | 1(2.0) | 0(0.0) | 3(30.0) | 1(16.7) | |
| AST >80 U/L (%) | 2(3.8) | 0(0.0) | 0(0.0) | 1(10.0) | 0(0.0) | 0.268 |
| AST >40 U/L (%) | 4(7.7) | 4(8.0) | 1(5.3) | 5(50.0) | 1(16.7) | 0.016 |
| ALT >80 U/L (%) | 2(3.8) | 0(0.0) | 0(0.0) | 1(10.0) | 0(0.0) | 0.268 |
| ALT >40 U/L (%) | 4(7.7) | 5(10.0) | 1(5.3) | 4(40.0) | 2(33.3) | 0.016 |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; SD, standard deviation.

## PE-07

### Tenofovir Is Associated with a Better Prognosis for Hepatitis B Virus-Related Hepatocellular Carcinoma Than Entecavir

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**Aims:** Whether tenofovir or entecavir has different effects on the prevention of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) in secondary and tertiary preventive settings remains controversial. This study was aimed to compare the long-term prognosis of HCC between tenofovir and entecavir in patients with chronic hepatitis B (CHB).

**Methods:** CHB patients who were diagnosed with HCC between November 2008 and December 2018 and were treated with either entecavir or tenofovir (n=3,056) at a tertiary center in Korea were included. The effect of tenofovir vs. entecavir on the prognosis of HBV-related HCC was compared by multivariable-adjusted Cox and propensity score (PS)-matched analyses. Various predefined subgroup analyses were performed.

**Results:** During a median follow-up period of 3.0 years, entecavir-treated patients (n=3,469) had a mortality rate of 41.2%, whereas tenofovir-treated patients (n=3,056) had a mortality rate of 34.6%. Overall survival (OS) was better in tenofovir-treated patients compared with entecavir-treated patients (adjusted hazard ratio [aHR], 0.77; 95% confidence interval [CI], 0.71–0.84, $P<0.001$). The difference in OS probability between the two groups became more pronounced over time. The magnitude of the risk difference in OS after 2 years of HCC diagnosis (HR, 0.50; 95% CI, 0.42–0.60, $P<0.001$) was more prominent than that within 2 years (HR, 0.88; 95% CI, 0.80–0.96, $P=0.02$), which were consistently observed in the PS-matched analysis. In all subgroups, except for those with advanced terminal stage HCC or those with compromised underlying liver function whose life expectancy is shorter, tenofovir was associated with better OS compared to entecavir.

**Conclusions:** In patients with HBV-related HCC, tenofovir showed a better prognosis than entecavir, particularly among those with extended survival. This should be considered when determining the most suitable treatment strategy for patients with HBV-related HCC.

**Keywords:** Liver cancer, Nucleotide analogue, Overall survival, Recurrence-free survival

## PE-08

### Genomic Landscape of Non-Hodgkin Lymphoma Patients with Current or Past Hepatitis B Virus Infections

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**Aims:** As hepatitis B virus (HBV) infection is a risk factor for non-Hodgkin lymphoma (NHL), we aimed to assess the effect of current or past HBV infections on the development of NHL.

**Methods:** Patients who were diagnosed with NHL and underwent targeted next-generation sequencing (NGS) for NHL tissue at Seoul National University Hospital between 2019 and 2022 were consecutively enrolled. Targeted NGS was performed for 166 NHL-related genes to detect single nucleotide variant (SNV). Current and past HBV infections were defined by a positive HBV surface antigen (HBsAg) and a positive HBV core antibody (HBcAb) with a negative HBsAg, respectively. The incidence of SNV was compared among three groups.

**Results:** A total of 252 patients were included for analysis. The incidence of *MYD88* (control vs. current HBV infection vs. past HBV infection: 14.0% vs. 34.8% vs. 30.0%; $P=0.005$), *PIM1* (16.3% vs. 34.8% vs. 29.0%; $P=0.03$), and *MYC* (3.1% vs. 8.7% vs. 12.0%; $P=0.03$) gene mutation was significantly higher in the current or past HBV infection group compared to the control group. On the other hand, the current HBV infection group showed significantly higher incidence of *ATM* (4.7% vs. 13.0% vs. 0%; $P=0.004$), *BCL10* (3.9% vs. 17.4% vs. 6.0%; $P=0.046$), and *BIRC3* (0.8% vs. 13.0% vs. 0%; $P=0.003$) gene mutation than the other two groups.

**Conclusions:** Although current or past HBV infections share some of the gene mutations associated with the development of NHL, current HBV infection exhibited other distinct gene mutations.

**Keywords:** Chronic hepatitis B, Lymphoma, Targeted NGS

## PE-09

### A Multicenter Observational Study to Compare the Effects of Drug Convenience on Safety and Efficacy of Entecavir Tablet and ODT (Orally Disintegrating Tablet) in Patients with Chronic Hepatitis B

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**Aims:** Drug compliance is recognized as an important factor in that long-term continuous drug treatment is required for the treatment of chronic hepatitis B. The purpose of this study is to compare the effectiveness of drug compliance, safety, and efficacy on two formulations (Tablet and ODT) of Entecavir in chronic hepatitis B patients.

**Methods:** This study is a non-interventional, multicenter, observational study targeting patients with chronic hepatitis B who received Entecavir for more than 6 months, maximum 12 months. We analyzed adverse events that occurred during the entire treatment period, medication compliance and changes in HBV_DNA levels at 3, 6 and 12 months compared to baseline.

**Results:** A total number of 350 patients at 17 sites were enrolled, and 240 and 110 subjects participated in Entecavir tablet and ODT groups, respectively. Most of adverse events reported in this study were already noted in the precautions for Entecavir use, and no specific information of concern were observed. There was no statistical difference between the drug adverse reaction ratio of tablets and ODTs, 1.25% and 2.73%, respectively. As a result of the drug convenience evaluation, more than 60% of the study subjects responded that Entecavir ODT is more convenient to take than the existing drugs. HBV DNA change at 3, 6 and 12 months compared to baseline showed a statistically significant decrease in both groups, and no statistical difference was observed between the administered groups. However, statistically significant decrease was observed in the Entecavir ODT subjects (-2.79 ±1.85, *P*=0.0113) compared to the Entecavir tablet subjects (-1.26±2.34) at 3 months.

**Conclusions:** Although there are limitations in this observational study that cannot meet the same conditions between comparison groups, the advantage of the study results can be they reflect real world practice. The safety results were similar to those previously approved for both Entecavir tablets and ODT (Orally Disintegrating Tablet), and no adverse events of concern were observed. It was confirmed that HBV DNA was significantly reduced in chronic hepatitis B patients receiving Entecavir. In addition, Entecavir ODT is more convenient to take than Entecavir tablet, and is considered to be a safe and useful treatment for chronic hepatitis B patients.

**Keywords:** Chronic hepatitis B, Entecavir

## PE-10

## Risk of Hepatocellular Carcinoma after Curative Treatment When Switching from Tenofovir Disoproxil Fumarate or Entecavir to Tenofovir Alafenamide: A Real-World Multicenter Cohort Study

**Hyunjae Shin**[1], Seung Up Kim[2], Byeong Geun Song[3], Youngsu Park[1], Yunmi Ko[1], Jeayeon Park[1], Moon Haeng Hur[1], Yun Bin Lee[1], Eun Ju Cho[1], Jeong-Hoon Lee[1], Su Jong Yu[1], Jung-Hwan Yoon[1], Dong Hyun Sinn[3], Yoon Jun Kim[1]

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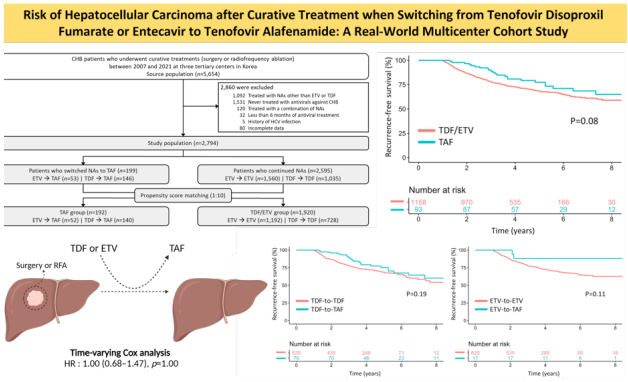
**Aims:** Antiviral treatment reduces the risk of developing hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). However, there is a lack of high-quality evidence regarding the preventive effects of TAF on HCC. We evaluated the impact of TAF use after curative treatment on HCC recurrence.

**Methods:** Patients who underwent surgery or radiofrequency ablation as a curative treatment for HCC were selected. Those patients who continued antiviral treatment with NAs (entecavir [ETV] or tenofovir disoproxil fumarate [TDF]) or switched to TAF were included. The primary outcome was HCC recurrence, and the time-varying effect of NA use on HCC recurrence was analyzed using various statistical methods.

**Results:** Among 2,794 consecutive patients with CHB who received curative treatment for HCC, 199 subsequently switched from ETV or TDF to TAF. After a median of 3.0 years, 1,303 patients (46.6%) experienced HCC recurrence. After propensity score matching (ratio 1:10), switching to TAF was not associated with an increased HCC recurrence (hazard ratio [HR], 1.00 [95% CI, 0.68–1.47]; *P*=1.00) by time-varying Cox analysis. Switching to TAF was not associated with HCC recurrence in subgroups of NA (HR, 1.06 [95% CI, 0.67–1.67]; *P*=0.81 for TDF, and 1.09 [95% CI, 0.51–2.33]; *P*=0.82 for ETV). Kaplan-Meier analysis showed comparable HCC recurrence-free survival between patients who switched to TAF and those who continued with their NA (*P*=0.08). Time-varying Cox analyses in various subgroups confirmed the primary findings.

**Conclusions:** TAF is as effective as TDF and ETV in preventing HCC recurrence after curative treatment.

**Keywords:** Entecavir, Tenofovir alafenamide, Liver cancer, Recurrence, Time-varying effects




## PE-11

### An Artificial Intelligence Model Utilizing Computed Tomography Auto-Segmentation to Predict Hepatocellular Carcinoma in Patients with Chronic Hepatitis B

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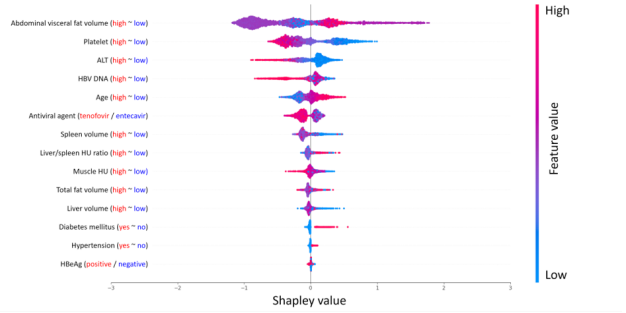
**Aims:** Artificial intelligence (AI) has recently shown promising potential for predicting hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). We aimed to develop an AI-based HCC prediction model by utilizing features extracted from the abdominal computed tomography (CT) images.

**Methods:** An AI prediction model employing a gradient-boosting machine (GBM) algorithm was developed utilizing six variables extracted by DeepFore®, a deep learning-based CT autosegmentation software (i.e., volumes of abdominal visceral fat, total fat, spleen, and liver; liver-to-spleen Hounsfield Unit [HU] ratio; and muscle HU) as well as eight clinical variables. The derivation and internal validation cohorts included 5,585 patients at five tertiary centers in Korea. External validation was conducted on an independently established cohort from two tertiary centers in Korea, comprising 2,883 patients.

**Results:** The derivation cohort was randomly divided into the training and internal validation sets at a 3:1 ratio. Our model, DeepFore, demonstrated strong predictive performance, with a c-index of 0.91 and good calibration function in the internal validation cohort ($P$=0.78 by the Hosmer-Lemeshow test). In the external validation cohort, DeepFore showed a significantly better discrimination function compared to previous models including PLAN-B, PAGE-B, modified PAGE-B, and CU-HCC (c-index, 0.89 vs. 0.65—0.78; all $P$<0.001) and maintained a good calibration function ($P$=0.42 by the Hosmer-Lemeshow test). The stratification into four groups, according to the calculated risk probability of the GBM algorithm, demonstrated the 10-year cumulative HCC incidence of 0.0%, 0.4%, 16.0%, and 46.2% in the minimal-, low-, intermediate-, and high-risk groups, respectively.

**Conclusions:** This AI prediction model, integrating GBM and deep learning-based auto-segmentation of CT images, offers significantly enhanced performance in predicting HCC risk among patients with CHB compared to previous models.

**Keywords:** Hepatic steatosis, Deep learning, Visceral fat, Myosteatosis, Segmentation




## PE-12

### The Changes in Plasma HBV-RNA Levels in The Patients with Chronic Hepatitis B Are Treated with Tenofovir Alafenamide (TAF)

Ha Linh[1], Le Quoc Tuan[1], Dinh Cong Tiep[1], Dinh Cong Dang[1]

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**Aims:** Each year, about 0.5% of chronic hepatitis B virus will develop liver cancer (HCC). In Vietnam, in 2017, more than 51,000 of people with cirrhosis, more than 14,000 people with hepatocellular cancer and more than 32,000 of people died. Plasma HBV-DNA concentration is an important for Antiviral treatment, monitoring and evaluation. It plays a role in predicting complications of cirrhosis and HCC.

**Aims:** Determine changes in plasma HBV-RNA levels in the patients with chronic hepatitis B are treated with Tenofovir

Alafenamide (TAF) and related factors.

**Methods:** Prospective descriptive study including 126 patients with chronic hepatitis B are treated with TAF from May 2018 to November 2022. RNA extraction procedure from plasma samples: According to the instructions of the QIAamp Viral Mini Kit (Qiagen, Germany).

**Results:** Plasma HBV-RNA concentration decreased rapidly from the time before treatment to after 6 months of treatment, then decreased slowly from after 6 months to after 12 months of treatment (reduction level was 0.39 $log_{10}$copies/mL/month vs. 0.08 $log_{10}$copies/mL/month, respectively $P<0.05$).

Plasma HBV-RNA concentration decreased more slowly than plasma HBV-DNA concentration was statistically significant in after 6 months of treatment (reduction: 0.39 $log_{10}$copies/mL/month vs. 1.03 $log_{10}$copies/mL/month, respectively, $P<0.05$).

In HBeAg-positive patients, pre-treatment plasma HBV-RNA levels have quite good prognostic value for virologic response after 6 months and 12 months of treatment.

Pre-treatment plasma HBV-RNA concentration is an independent prognostic factor for virologic response after 6 months and 12 months of treatment in the group of patients with positive HBeAg. But this prognosis is not significant in the group of HBeAg negative patients.

**Conclusions:** The results show the good potential of the plasma HBV-RNA marker to become a routine test with prognostic significance in clinical practice.

**Keywords:** Plasma HBV-RNA concentration, Chronic hepatitis B, Tenofovir alafenamide (TAF)

## PE-13

### Survey on the Change of HBcrAg in Patients with Chronic Hepatitis B before and after Treatment with Tenofovir Disoproxil Fumarate 300mg

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**Aims:** This study aimed to assess the change in HBcrAg levels in patients with chronic hepatitis B before and after treatment with Tenofovir disoproxil fumarate 300mg.

**Methods:** A cross-sectional descriptive study was conducted on 101 patients with hepatitis B at the Gastroenterology-Hepatobiliary Center, Bach Mai Hospital, from October 2020 to June 2022.

**Results:** The overall serum HBcrAg concentration showed a gradual decrease throughout treatment, reducing from an initial level of 5,94±1,36 logU/ml to 5,50±1,47 logU/ml after 3 months; 5,04±1,40 logU/ml after 6 months; and 4,92±1,34 logU/ml after 12 months. The difference in serum HBcrAg levels at 3, 6, and 12 months compared to baseline was statistically significant ($P<0.0001$).

In the HBeAg-negative chronic hepatitis group, HBcrAg concentration decreased from 5,22±1,14 logU/ml initially to 4,13 ±1,13 logU/ml after 3 months; 3,85±1,28 logU/ml after 6 months; and 3,76±1,20 logU/ml after 12 months. The difference in serum HBcrAg levels at 3, 6, and 12 months compared to baseline was also statistically significant ($P<0.05$). In the HBeAg-positive chronic hepatitis group, HBcrAg concentration decreased from 7,13±0,68 logU/ml to 6,46±0,71 logU/ml after 3 months; 5,90±0,64 logU/ml after 6 months and 5,65± 0,81 logU/ml after 12 months. The difference in serum HBcrAg levels at 3, 6, and 12 months compared to baseline was statistically significant ($P<0.0001$).

There was no significant difference in the reduction of HBcrAg levels between the HBeAg-negative and HBeAg-positive chronic hepatitis B groups ($P>0.05$).

**Conclusions:** The HBcrAg biomarker should be considered for routine clinical use in managing, monitoring, and predicting outcomes for patients with chronic hepatitis B.

**Keywords:** Hbcrag, Hepatitis B, Tenofovir disoproxil fumarate, Bach MAI hospital

## PE-14

### Impact of Antiretroviral Therapy on Liver Enzymes in HIV Patients in Western Regional Hospital, Nepal: A Pre-Post Study

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School of Health and Allied Sciences, Pokhara University, Nepal

**Aims:** Antiretroviral therapy (ART) has been a remarkable achievement in treating HIV disease, but it may also exacerbate liver disease. Monitoring the viral load and CD4 counts of HIV patients is crucial in evaluating the outcome of ART. This study aimed to assess the level of liver enzymes in HIV patients, taking into consideration the effect of comorbidities and different drug therapies.

**Methods:** A pre-post study was conducted on 250 HIV patients at the Western Regional Hospital, an ART center of Nepal, before and after the ART. Laboratory variables, ART use, viral load and CD4 count were obtained at baseline and over 18 months of the period. Various statistical tests were used to analyze based on the nature of data.

**Results:** Among 250 patients, 120 (48%) were males and 130 (52%) were females with a median age of 40. ART was initiated to 44 (17.6%), 45 (18.0%), 160 (64%) and 1 (0.4%) patients of clinical stage I, II, III and IV as categorized by WHO respectively.

Statistical significance ($P$<0.05) was found for the reduction of viral load, increase in CD4 count and as well as for elevation of liver enzymes after receiving ART whereas statistical insignificance ($P$>0.05) was observed with various comorbidities and as well as with difference in therapy either efavirenz or nevirapine among drugs.

**Conclusions:** It was observed that the elevation of the liver enzyme occurs with antiretroviral therapy though comorbidities associated with HIV and efavirenz or nevirapine based therapy were observed to not affect the elevation of liver enzymes.

**Keywords:** ART, HIV, Liver enzyme, Comorbidities, NEPAL

## PE-15

### Post-Vaccination Immunity against Hepatitis B among between the Ages 10 to 35 Years

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**Aims:** Hepatitis B infection remains a significant global healthcare challenge, particularly prevalent in developing regions. Mongolia implemented vaccination against hepatitis B (HepB) in 1991, resulting in a notable decrease in hepatitis B virus (HBV) infections and associated mortality among the vaccinated generation. Despite numerous studies conducted since the initiation of the HepB immunization program in Mongolia, long-term immunity remains unexplored in our region.

**Methods:** This cross-sectional study was conducted between January 2022 and December 2023, involving individuals aged 10 to 35 years in Eastern province Mongolia who had received HepB vaccination according to the national program. A total of 380 individuals were randomly selected, and data were collected using a structured questionnaire. Blood samples were obtained, and serum titers of hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc) were determined using a two-step sandwich chemiluminescent enzyme immunoassay. Additionally, the age-specific geometric mean of anti-HBs was estimated.

**Results:** Overall, 98.5% of participants reported receiving HepB vaccination as infants. The majority exhibited inadequate anti-HBs titers, while 19.8% had anti-HBs levels > 10 mIU/mL, of whom 6.1% demonstrated immunity induced by HBV infection. Approximately 5 % of children aged 10-19 years and an average of 8.2 % of young adults tested serologically positive for HBsAg. The geometric mean anti-HBs titer declined with age, ranging from an average of 39.2 mIU/mL in 10-year-old children to 13.9 IU/mL in 27-year-old adults ($P$<0.001).

**Conclusions:** In Mongolia, a minority of individuals aged 10 - 35 years exhibit immunity to HBV, with the geometric mean titer of anti-HBs declining with age. To achieve sustained protection against HBV, revaccination in adulthood may be warranted.

**Keywords:** Hepatitis B, Post-Vaccination immunity, Anti-HBS, HBSAG

## PE-16

### DNA-Guided Hepatitis B Diagnosis, Viral Load Is Essential, but Not Sufficient

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**Aims:** An infection with the hepatitis B virus (HBV) affects 350 million individuals globally and is a global public health concern. Chronic hepatitis B (CHB) patients have a higher chance of hepatocellular cancer, hepatic decompensation, and liver cirrhosis. Preserving an undetectable viral load lowers the consequences associated with chronic infections. The HBV infection cannot be completely cured by medication. The current generation of pharmaceuticals is costly, and prone to side effects.

**Methods:** Following valid consent, patients were tested for hepatitis B using the fast kit HBsAg at the central diagnostic laboratory and research center. Following this, samples were processed for viral load using the TruePCR HBV Viral Load Kit, which was run in the Bio-Rad CFX96.

**Results:** Of the 130 patients, 40 percent were men and 60 percent were women. Merely 20% have a sigmoid curve, indicating that the HBV viral load exceeds 2.5 IU/mL. The mean number of copies/mL for those who tested positive for the virus is 1,12000. By examining the dilution series of the 4th WHO international standard for hepatitis B virus for nucleic acid amplification techniques, the analytical sensitivity for HBV of the TRUEPCR HBV Viral load kit was ascertained, and this was validated by WHO Multiplex Material.

**Conclusions:** The current recommendations aim to bring clinical practice uniformity. However, there is still debate regarding the best course of action for asymptomatic CHB patients who test positive for hepatitis B antigen and have a viral load of less than 2.5 IU/mL, as well as the appropriate viral load cut-off value.

**Keywords:** HBV, PCR, WHO

## PE-17

### The Relationship between miR-146a, Platelet to Lymphocyte Ratio (PLR) and Liver Fibrosis in Hepatitis B

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**Aims:** This study aims to determine the relationship between miR-146a, Platelet to Lymphocyte Ratio (PLR) and liver fibrosis in Hepatitis B

**Methods:** This research was conducted cross-sectionally at the Internal Medicine Polyclinic, Gastroenterohepatology Department, RSUD Dr. Moewardi in naive hepatitis B patients aged more than 30 years. All patients had agreed to informed consent and had blood tests and miR-146a tests. Liver fibrosis examination using elastography. The correlation test uses the Spearman rank test with a *P* value < 0.05

**Results:** The mean age of patients was 49±11 years with the majority of patients being men (n: 17, 66%). The results of the correlation test between miR-146a and liver fibrosis values showed that the correlation coefficient was r = 0.639 and *P*=0.001. The results of the correlation test between PLR and liver fibrosis values showed that the correlation coefficient was r = -0.455 and *P*=0.020.

**Conclusions:** This study has proven a significant relationship between the variables miR-146a and PLR on liver fibrosis in hepatitis B

**Keywords:** MIR-146A, Platelet to lymphocyte ratio (PLR), Liver fibrosis, Hepatitis B

## HCV, Basic

### PE-01

### Interleukin-18 rs187238 Gene Polymorphism with Risk of Chronic Hepatitis C: An-Updated Meta-Analysis

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Department of Internal Medicine, St. Carolus Hospital, Indonesia

**Aims:** World Health Organization (WHO) estimates around 71 million people have chronic hepatitis C virus (HCV) infection. Around 60–70 out of 100 patients with HCV infection will develop chronic liver disease, a major cause of liver cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation worldwide. Pathogenesis of liver damage in chronic HCV are still not fully understood. Interleukin-18 (IL-18) is a cytokine which regulates T cell activation and proliferation. Genetic variation affecting protein structure of IL-18 may lead to immune dysfunction, inflammatory tissue damage, and potentially contributing to the development of diverse chronic liver diseases. Several studies discovered the association between IL-18 rs 187238 gene polymorphism and risk of chronic hepatitis C, however, published results showed indeterminate results. This meta-analysis aimed to determine association between Interleukin-18 promoter -137 G/C gene polymorphism (rs187238) and chronic hepatitis c susceptibility.

**Methods:** This meta-analysis followed the PRISMA guidelines. The literatures were taken from Pubmed and Google Scholar, with June 2021 as the latest edition that was computed, and it is limited to English only. A total of 6 studies were included in this review. A Review Manager 5.4 was utilized to analyze the data.

**Results:** There were 6 studies incorporated to analysis.IL-18 rs 187238 gene polymorphism was associated with an increase of Chronic Hepatitis C (C vs G, OR 95%CI = 1.16 [1.03-1.30] *P*=0.01) and a decrease of Chronic Hepatitis C (G vs C, OR 95%CI = 0.87 [0.77-0.97] *P*=0.01; GG vs GC + CC, OR 95%CI =0.81 [0.70-0.94] *P*=0.006; GC vs GG + CC, OR 95%CI =1.20 [1.03-1.39] *P*=0.02))

**Conclusions:** There was association between IL-18 rs 187238 gene polymorphism and Chronic Hepatitis C.

**Keywords:** Chronic hepatitis C, Gene polymorphisms, IL-18 RS 187238

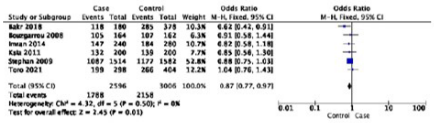

**Fig 1.** Forest plot of association between IL-18 rs187238 and Chronic Hepatitis C G vs C

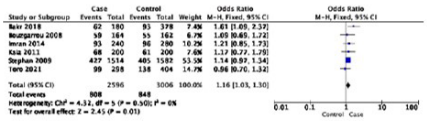

**Fig 2.** Forest plot of association between IL-18 rs187238 and Chronic Hepatitis C C vs G

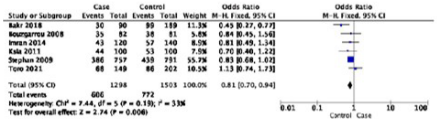

**Fig 3.** Forest plot of association between IL-18 rs187238 and Chronic Hepatitis C GG vs GC + CC

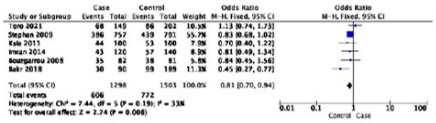

**Fig 4.** Forest plot of association between IL-18 rs187238 and Chronic Hepatitis C GC vs GG + CC

### PE-02

### Risk of Extrahepatic Cancers among Patients with Chronic Hepatitis C Virus in Korea: A Population-Based Retrospective Cohort Study Using National Health Insurance Service Claim Data, 2002-2022

**Yoon Park,** Moran Ki

Department of Cancer Control and Population Health, Graduate School of

Cancer Science and Policy, National Cancer Center, Korea

**Aims:** The burden of hepatitis C virus (HCV) may not be limited to liver. The relevant studies conducted from other countries were controversial and domestic studies are still lacking. Therefore, we aimed to examine the potential relationship between chronic HCV infection and the risk of extrahepatic cancers other than liver in a Korean population.

**Methods:** We evaluated the National Health Insurance Service claim data collected in Korea from 2002 to 2022. A total of 3,304,219 subjects (217,436 HCV and 3,086,783 non-HCV subjects) aged 20-89 without any history of cancer were identified as study population and were followed up December 31, 2022. The endpoint was occurrence of any extrahepatic cancer or death, whichever comes first. Time-to-event analyses were performed using Cox proportional hazards models.

**Results:** After adjusting for age, sex, comorbidities (including HCV × comorbid disease interaction terms), and death as competing risk, adjusted hazard ratios (aHRs) for incident non-hepatic cancers were significantly higher in chronic HCV patients compared to controls without HCV infection. In specific, the cancer risk was higher for gallbladder or biliary tract [aHR: 1.86, 95% confidence interval (CI): 1.28-2.70], pancreas [aHR: 2.20, 95% CI: 1.74-2.79], kidney [aHR: 1.74, 95% CI: 1.08-2.80], and thyroid [aHR: 1.65, 95% CI: 1.33-2.05]. For hematopoietic malignancies, HCV patients had a higher risk of Non-Hodgkin lymphoma [aHR: 1.58, 95% CI: 0.98-2.55], leukemia [aHR: 2.64, 95% CI: 1.59-4.37], and Hodgkin lymphoma [aHR: 6.99, 95% CI: 2.31-21.10], but this has a limitation of marginal significance or wide range of confidence intervals due to small number of events occurred.

**Conclusions:** It demonstrated that HCV infection is associated with an increased risk of several extrahepatic cancers as well as liver cancer in Koreans. This may support the notion of HCV as a multifaceted systemic disease that needs to be diagnosed and treated early before disease severity progresses.

**Keywords:** Hepatitis, Extrahepatic cancer, Korea, Epidemiology

## PE-03

### A Multilevel Analysis of Factors Affecting the Prevalence of Hepatitis C Virus

**Hwa Young Choi**, Dahye Paik, Moran Ki

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**Aims:** Previous research has primarily focused on individual-level factors influencing the prevalence of hepatitis C virus (HCV). This study addressed the limitations of previous research by simultaneously considering both individual-level factors and regional-level factors to identify the factors affecting the prevalence of HCV in South Korea.

**Methods:** The participants were selected through 5% stratified sampling of National Health Insurance Service (NHIS) data based on sex, age, region (city or county), and health insurance quintile for the years 2005, 2010, 2015, and 2020. Factors related to HCV prevalence were defined as individual-level factors (sex, age, health insurance quintile), and regional(city/town)-level factors (HCV prevalence rate, regional deprivation index, unmet medical needs rate, high-risk alcohol consumption rate).

Individual-level factors and the prevalence of HCV were calculated using NHIS data, while the rates of unmet medical needs and high-risk drinking were derived from Korea Community Health Survey data. Also, the Regional Deprivation Index was computed by integrating 9 socioeconomic indicators from the Population and Housing Census surveys conducted by Statistics Korea, using the sum of Z-scores method. To assess the reliability of the calculated Regional Deprivation Index, it was compared with previously published deprivation indices for correlation.

A Multilevel logistic regression analysis was conducted to examine four different models: Null (model 1), individual-level (model 2), regional-level (model 3), and combined individual and regional-level (model 4) models. The multi-level analysis calculated measures of fit for each model, as well as the proportion of variance explained by region, assessed through the Intraclass Correlation Coefficient (ICC). Furthermore, the Percentage Change in Variation (PVC) for each level model was calculated, along with the Odds Ratios (OR) for each level.

**Results:** The correlation between the Regional Deprivation Index calculated in this study and the previously published deprivation index (Sources: Busan Metropolitan City Public Health and Medical Support Group) was found to be very high (correlation coefficients: 0.989 in 2005, 0.967 in 2010, 0.982 in 2015, and 0.979 in 2020).

In the 2020 Multilevel analysis results, the ICC for model 1 to model 4 ranged from a minimum of 0.26 to a maximum of 0.63, all exceeding 0.1. This suggests a significant difference in HCV prevalence rates across regions, confirming the appropriateness of multilevel analysis. For each model, the PVC showed that compared to the base model (model 1), there was a 43.2% increase in variation at the individual level (model 2), a 69.1% increase in variation at the regional level (model 3), and a 75.4% change in variation in the combined individual and regional-level model (model 4).

In model 4, which adjusted for both individual and regional levels, the odds ratios for factors related to HCV prevalence, including age, health insurance quintile, Regional Deprivation Index, and HCV prevalence rate by region, were significantly high. Similar trends were observed in the multi-level analysis

results for the remaining three years (2005, 2010, 2015), showing consistency with the findings from 2020.

**Conclusions:** Both individual-level factors and regional-level factors have been found to influence the prevalence of HCV. Specifically, it has been observed that regional-level factors exert a significantly greater impact on HCV prevalence than individual-level factors. Consequently, proactive HCV prevention policies and early screening are needed for groups with higher regional-level risk factors.

**Keywords:** Hepatitis C virus, Prevalence, Multilevel analysis, Regionalsocioeconomic status

## PE-04

### Trends in Prevalence and Survival Rates among Hepatitis C Patients and Substance Users in South Korea, 2002-2023

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Department of Cancer Control and Population Health, National Cancer Center Graduate School of Cancer Science and Policy, Goyang, Korea

**Aims:** In recent years, there has been a noticeable trend of an increasing number of patients in South Korea seeking treatment for drug use. Drug use stands as a prominent risk factor for hepatitis C virus (HCV) infection. Consequently, this study aims to investigate the prevalence changes among three groups: drug use, HCV and individuals with both HCV and drug use. Additionally, it seeks to assess the survival rates within each group and evaluate associated factors.

**Methods:** The study utilized National Health Insurance Service (NHIS) data from South Korea spanning the years 2002 to 2023. The study subjects were identified using ICD-10 diagnostic codes, specifically targeting individuals diagnosed with acute or chronic HCV (ICD-10 codes: B17.1, B18.2) and drug users. The criteria for drug users included diagnoses such as Mental and behavioral disorders due to psychoactive substance use (F10-F19), Poisoning by narcotics and psychodysleptics (T40), Poisoning by antiepileptic, sedative-hypnotic, and antiparkinsonism drugs (T42), Poisoning by other psychotropic drugs not elsewhere classified (T43), Poisoning and toxic effects of antiepileptic, sedative-hypnotic, antiparkinsonism, and psychotropic drugs of undetermined intent (Y11), Poisoning and toxic effects of narcotics and hallucinogens of undetermined intent (Y12), and Poisoning and toxic effects of other drugs acting on the autonomic nervous system (Y13).

The prevalence rates for the three groups HCV patients, drug use, and individuals with both HCV and drug use were calculated annually from 2002 to 2023, adjusting for sex and age. Using Cox proportional hazards regression, we calculated sex and age-adjusted survival rates for three groups.

**Results:** During the observation period (from 2002 to 2023), there were 831,972 cases of HCV (1.65%), 1,511,743 cases of drug use (2.99%), and 54,722 cases of both HCV and drug use (0.11%) confirmed. Adjusted for age and sex, the prevalence rates showed a decreasing trend for HCV, from 161.6 (/100,000) in 2002 to 112.2 (/100,000) in 2023. However, for drug user, the rates increased from 132.4 (/100,000) in 2002 to 386.9 (/100,000) in 2023, and for the group with both HCV and drug use, the rates increased from 1.23 (/100,000) in 2002 to 2.10 per 100,000 in 2023.

Over the 22-year observation period, the sex and age adjusted survival rates were as follows: for those solely infected with HCV, it was 85.2% (with a 5-year survival rate of 97.3% and a 10-year survival rate of 94.7%); for those solely engaged in drug use, it was 75.5% (with a 5-year survival rate of 95.0% and a 10-year survival rate of 90.1%); for the group with both HCV and drug use, it was 71.6% (with a 5-year survival rate of 96.3% and a 10-year survival rate of 90.1%). Notably, the survival rates fell even further when drug use was included.

**Conclusions:** Over the past 22 years, the prevalence of HCV in South Korea has shown a decreasing trend, while the prevalence of drug use has been increasing. It has been observed that the survival rates significantly decrease when drug use is involved. Therefore, proactive intervention policies targeting both HCV and drug use, especially for high-risk groups with both conditions, are necessary along with prevention policies for HCV and drug use.

**Keywords:** Hepatitis C virus, Substance users, Survival, Big data

## PE-05

### The Impact of Effect of Increased Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) on Bilirubin (BIL) in Hepatitis C Patients

**Devi Yulia Rahmi**[1], Muhammad Irzaq[2]

[1]Department of Management, Universitas Andalas, [2]Department of Music Education, Alumnus Padang State University, Indonesia

**Aims:** The hepatitis C virus is the cause of hepatitis C, which is an inflammation of the liver. An estimated 50 million people worldwide suffer from a chronic hepatitis C virus infection, and 1.0 million new cases are reported annually (WHO, 2024). Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Bilirubin (BIL) are one of the productions of the liver, where if liver damage occurs, there will be abnormalities in the results of liver enzymes and bilirubin (Aleya dan Berawi, 2014). This study aims to examine the effect of increasing ALT and AST on bilirubin.

**Methods:** This research is a quantitative study using secondary data from patients suffering from Hepatitis C. The data source is from UCI Machine Learning. The data was processed with multiple regression analysis to answer the research objectives

using SPSS tools.

**Results:** The regression analysis's findings indicate that ALT and AST have an impact on the rise in bilirubin. The analysis's findings also demonstrate that, unlike ALT, which has no significant effect on bilirubin, AST has a significant effect (*P*-value 0.05, $\beta$=0.169). ALT and AST have respective VIF and Tolerance values of 0.704 and 1.420, so there is no multicollinearity between them. The study's findings are consistent with Aleya and Berawi (2014), which demonstrate a relationship between ALT, AST, and bilirubin.

**Conclusions:** According to the study's findings, AST significantly affected bilirubin levels in those with hepatitis C. ALT, on the other hand, correlated although not significantly.

**Keywords:** Hepatitis C, Alanine aminotransferase, Aspartate aminotransferase, Bilirubin

**Coefficients[a]**

| Model | | Unstandardized Coefficients B | Unstandardized Coefficients Std. Error | Standardized Coefficients Beta | t | Sig. | 95.0% Confidence Interval for B Lower Bound | 95.0% Confidence Interval for B Upper Bound | Correlations Zero-order | Correlations Partial | Correlations Part | Collinearity Statistics Tolerance | Collinearity Statistics VIF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | (Constant) | 6.620 | 4.176 | | 1.585 | .132 | -2.233 | 15.474 | | | | | |
| | ALT | -.172 | .194 | -.176 | -.886 | .389 | -.584 | .240 | .272 | -.216 | -.148 | .704 | 1.420 |
| | AST | .169 | .041 | .825 | 4.143 | .001 | .083 | .256 | .729 | .719 | .692 | .704 | 1.420 |

a. Dependent Variable: BIL

## HCV, Clinical

### PE-01

### Association Between Hepatitis C, Autoimmune Hepatitis and Insulin Resistance, Results from NHANES (National Health and Nutrition Examination Survey)

Javad Alizargar

Kashan University, Iran

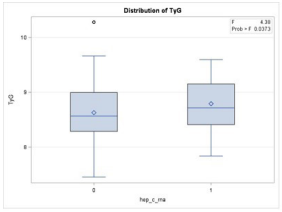
**Aims:** One of the pathogenic characteristics in individuals with HCV infection is insulin resistance, which frequently triggers the onset of type -2 diabetes. Insulin resistance is a significant factor in the emergence of numerous HCV infection-related problems. Hepatitis C increases insulin resistance, which in turn causes interferon resistance, the advancement of steatosis, and fibrosis. Increased insulin resistance is frequently associated with chronic liver disease. In this study we are trying to evaluate the status of insulin resistance calculated by a new marker, TyG (triglyceride glucose index) in National Health and Nutrition Examination Survey database in hepatitis C and autoimmune hepatitis patients. Viral hepatitis will be also compared with autoimmune hepatitis regarding the insulin resistance.

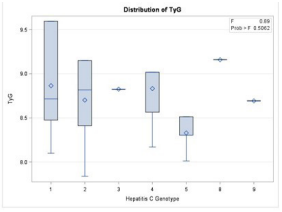
**Methods:** The National Health and Nutrition Examination Survey (NHANES) database served as the source for our data extraction. Following the application of inclusion and exclusion criteria, we focused on 283 individuals for this study, comprising 67 individuals with positive diagnoses of HCV and autoimmune hepatitis. From the database, we extracted demographic characteristics, hepatitis C infection status determined by RNA testing, as well as the genotypes of hepatitis C and autoimmune hepatitis status. Our analysis employed ANOVA, Spearman's rank correlation, and logistic regression techniques, chosen due to the non-normal distribution of the data.

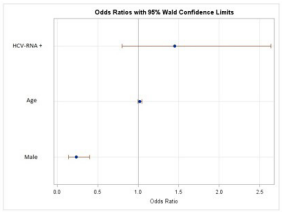
**Results:** insulin resistance is higher in hepatitis C patients confirmed with hepatitis C RNA (HCV-RNA), but not different between different Hepatitis C genotypes. Correlation analysis with Spearman's rank correlation showed no correlation between hepatitis C infection and insulin resistance. Although increasing the risk of infection, after controlling for age and gender, insulin resistance cannot be associated with hepatitis C infection (OR=1.451, CI=0.798-2.638). Compared to the viral hepatitis, autoimmune hepatitis patients have higher insulin resistance and insulin resistance is highly associated with autoimmune hepatitis (OR=11.06, CI=2.163-56.551).

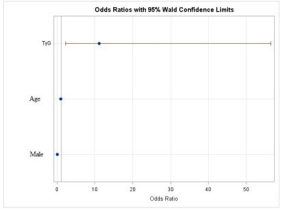
**Conclusions:** Hepatitis C patients have high insulin resistance levels but Hepatitis C infection is not independently associated high insulin resistance. On the other hand, Insulin resistance is highly and independently associated with autoimmune hepatitis.

**Keywords:** HCV, Metabolic syndrome, Hyperlipidemia, Insulin resistance




### PE-02

### Glecaprevir/Pibrentasvir Improves Fibrosis after SVR and during Long-Term Follow-Up

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**Aims:** Chronic hepatitis C (CHC) has been a significant contributor to advanced liver diseases, such as liver cirrhosis and hepatocellular carcinoma (HCC). The advent of direct-acting antiviral agents (DAAs), particularly pangenotypic DAAs like glecaprevir/pibrentasvir and sofosbuvir/velpatasvir, has revolutionized CHC treatment. Fibrosis plays a crucial role in disease progression post sustained virologic response (SVR). This study focuses on analyzing fibrosis improvement after SVR in patients treated with glecaprevir/pibrentasvir.

**Methods:** This single-center retrospective cohort study reviewed patients undergoing glecaprevir/pibrentasvir treatment. SVR evaluation was conducted 12 weeks post-treatment by checking HCV RNA. Fibrosis assessment occurred through fibroscan before treatment, at the SVR time point, and annually thereafter.

**Results:** Out of 264 patients treated with glecaprevir/pibrentasvir, with an average age of 59.2 years and a female dominance of 79.8%, 31.1%, 66.7%, 1.5%, and 0.8% had genotypes 1, 2, 3, and 6, respectively. Sixty-one patients had liver cirrhosis, and 237 were treatment-naïve. A remarkable 98.5% of patients achieved SVR, with only 5 patients diagnosed with HCC during the follow-up period. Liver stiffness decreased from 6.3 kPa to 5.6 kPa at SVR ($P$=0.0004). After a long-term follow-up of at least 1 year, liver stiffness further decreased from 7.1 kPa to 5.0 kPa ($P$<0.0001).

**Conclusions:** Glecaprevir/pibrentasvir not only proved effective in treating CHC but also demonstrated significant improvement in liver fibrosis over the long term.

**Keywords:** Chronic hepatitis C, Fibrosis, SVR, Glecaprevir/pibrentasvir

## PE-03

## Efficacy and Safety of Locally Developed and Imported Direct-Acting Antiviral Agents for Hepatitis C in China-A Systematic Review, Meta-Analysis

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**Aims:** Locally developed direct-acting antiviral agents (DAAs) have the advantage of lower price compared with the imported ones, but lower market share, and the treatment rate of hepatitis C in China is far below the global target. This study aims to generate comparative efficacy and safety evidence of locally developed and imported DAAs to promote hepatitis C treatment in China.

**Methods:** We systematically reviewed the efficacy and safety evidence of 5 locally developed and 6 imported DAAs held valid registration number in China as of January 2024, and performed meta-analyses, subgroup analyses and meta-regressions.

**Results:** 19 randomized controlled trials (RCTs) and 82 single-arm trials (SATs) were included in the analyses. The synthesis analyses of RCTs and SATs (Table 1-2) and meta-regressions of SATs (Table 3) all demonstrated no statistically significant difference in sustained virological response (SVR12), relapse, virological breakthrough and SAEs between locally developed and imported DAAs, but higher adverse events (AEs) of the former than that of latter. The multiple meta-regression of SATs adjusted for the race of patients revealed that the AEs rate of locally developed DAAs was 33.7% higher than that of imported ones (0.337, [95% CI: 0.188, 0.486], $P$<0.001) (Table 3). Genotype subgroup difference was identified for the SAEs rate ($P$-for-interaction=0.005, $I^2$=73.06%) that SAEs rate of locally developed genotype-specific DAAs was higher than that of imported ones, but no statistically significant difference was found in the pan-genotype subgroup (Table 4).

**Table 1:** Synthesis analyses of evidence generated by RCTs: locally developed vs imported DAAs

| Outcome measure | Control | Origin of DAA | No. of included studies | Experimental group | Control group | Heterogeneity | | RD (95% CI) | $P$-value |
|---|---|---|---|---|---|---|---|---|---|
| | | | | No. of events/sample size | | $I^2$(%) | $P$ | | |
| AEs | PEG-IFN +RBV | Total | 4 | 363/455 | 344/393 | | | | |
| | | Locally developed | 1 | 90/93 | 42/44 | / | / | 0.01 (-0.06, 0.08) | **<0.01** |
| | | Imported | 3 | 273/362 | 302/349 | 0.00 | 0.52 | -0.11 (-0.16, -0.07) | |
| | Placebo | Total | 11 | 2157/3067 | 857/1249 | | | | |
| | | Locally developed | 1 | 298/318 | 84/106 | / | / | 0.14 (0.06, 0.23) | **<0.01** |
| | | Imported | 10 | 1859/2749 | 773/1143 | 0.00 | 0.55 | 0.004 (-0.03, 0.04) | |
| SAEs | PEG-IFN +RBV | Total | 4 | 15/455 | 4/392 | | | | |
| | | Locally developed | 1 | 8/93 | 1/43 | / | / | 0.06 (-0.008, 0.14) | 0.09 |
| | | Imported | 3 | 7/362 | 3/349 | / | 0.99 | 0.0005 (-0.001, 0.001) | |
| | Placebo | Total | 13 | 98/3381 | 54/1372 | | | | |
| | | Locally developed | 1 | 7/318 | 5/106 | / | / | -0.03 (-0.07, 0.02) | 0.20 |
| | | Imported | 12 | 91/3063 | 49/1266 | 43.46 | 0.03 | 0.005 (-0.008, 0.02) | |

**Notes:** RCTs=randomized controlled trials; PEG-IFN+RBV=pegylated interferon and ribavirin; DAAs=direct-acting antiviral agents; RD=risk difference; CI=confidence interval; SVR12=HCV sustained virologic response, which is undetectable HCV RNA in the blood 12 weeks after the end of treatment; AEs=any adverse events; SAEs=serious adverse events; $P$-value for test of group difference; Bold means statistically significant.

**Table 2:** Synthesis analyses of evidence generated by SATs: locally developed vs imported DAAs

| Outcome measure | Origin of DAA | No. of included studies | No. of events/sample size | Heterogeneity | | ES (95% CI) | $P$-value |
|---|---|---|---|---|---|---|---|
| | | | | $I^2$(%) | $P$ | | |
| SVR12 | Total | 82 | 11831/12988 | | | | |
| | Locally developed | 7 | 1335/1369 | 79.01 | 0.00 | 0.97 (0.95, 0.99) | 0.21 |
| | Imported | 75 | 10496/11619 | 94.90 | 0.00 | 0.96 (0.94, 0.98) | |
| Relapse | Total | 71 | 285/9445 | | | | |
| | Locally developed | 7 | 28/1369 | 69.52 | 0.00 | 0.02 (0.01, 0.04) | 0.65 |
| | Imported | 64 | 257/8076 | 79.67 | 0.00 | 0.02 (0.01, 0.03) | |
| Virological breakthrough | Total | 54 | 27/7007 | | | | |
| | Locally developed | 7 | 13/1369 | 79.00 | 0.00007 | 0.003 (<1E-09, 0.02) | 0.51 |
| | Imported | 47 | 14/5638 | 0.00 | 0.98 | 0.0000002 (<1E-09, 0.0006) | |
| AEs | Total | 63 | 5632/8330 | | | | |
| | Locally developed | 7 | 1150/1369 | 96.01 | 0.00 | 0.93 (0.85, 0.99) | **0.00002** |
| | Imported | 56 | 4482/6961 | 95.29 | 0.00 | 0.69 (0.64, 0.74) | |
| SAEs | Total | 71 | 284/8120 | | | | |
| | Locally developed | 7 | 63/1369 | 34.75 | 0.16 | 0.04 (0.03, 0.06) | 0.12 |
| | Imported | 64 | 221/6751 | 73.74 | 0.00 | 0.03 (0.02, 0.03) | |

**Notes:** SATs=single-arm trials; DAAs=direct-acting antiviral agents; ES=effect size; CI=confidence interval; SVR12=HCV sustained virologic response, which is undetectable HCV RNA in the blood 12 weeks after the end of treatment; $P$-value for test of group difference.

**Table 3:** Adjusted multiple meta-regression of SATs for AEs between locally developed and imported DAAs

| Outcome measure | Variable | Coefficient | 95% CI | $P$ |
|---|---|---|---|---|
| AEs | Origin of DAAs | | | |
| | Imported (Ref.) | | | |
| | Locally developed | 0.337 | 0.188, 0.486 | **<0.001** |
| | Race | | | |
| | Asian (Ref.) | | | |
| | White and black | 0.185 | 0.080, 0.291 | **0.001** |
| | Unknown | -0.036 | -0.202, 0.130 | 0.67 |
| | No. of included studies=63; $I^2$=66.74%; Adjusted $R^2$=35.39% | | | |

**Notes:** SATs=single-arm trials; CI=confidence interval; Ref.=reference; AEs=any adverse events; Bold means statistically significant.

**Table 4:** Subgroup analyses of SATs for SAEs: locally developed vs imported DAAs

| Outcome measure | Subgroup | Origin of DAA | No. of included studies | No. of events/sample size | Heterogeneity | | ES (95% CI) | $P$-value |
|---|---|---|---|---|---|---|---|---|
| | | | | | $I^2$(%) | $P$ | | |
| SAEs | Pan-genotypic | Yes | 37 | 207/4770 | | | | |
| | | Locally developed | 2 | 37/697 | / | / | 0.05 (0.04, 0.07) | 0.42 |
| | | Imported | 35 | 170/4073 | 80.42 | 0.00 | 0.04 (0.02, 0.05) | |
| | | No | 34 | 77/3350 | | | | |
| | | Locally developed | 5 | 26/672 | 0.00 | 0.82 | 0.04 (0.02, 0.05) | **0.007** |
| | | Imported | 29 | 51/2678 | 41.85 | 0.01 | 0.01 (0.005, 0.02) | |
| | | Subgroup effect: P for interaction =0.005, $I^2$=73.06% | | | | | | |

**Notes:** SATs=single-arm trials; DAAs=direct-acting antiviral agents; ES=effect size; CI=confidence interval; SAEs=serious adverse events; $P$-value for test of group difference; Bold means statistically significant; No heterogeneity is reported in case that the No. of trials≤3.

**Conclusions:** Existing evidence do not demonstrate statistically

significant differences in efficacy between locally developed and imported DAAs, but slightly inferior safety of the former than the latter, especially among the genotype-specific DAAs. There is a need to improve the post-market surveillance and strengthening the monitoring of DAA treatment. Locally developed pan-genotype DAAs should play a more important role in increasing treatment rate of hepatitis C.

**Keywords:** Direct-acting antiviral agents, Hepatitis C, Efficacy, safety

## PE-04

### Prognosis after Sustained Virologic Response of Elderly Chronic Hepatitis C Patients Treated with Direct-Acting Antivirals

Jeong Han Kim[1], Jae Hyun Yoon[2], Jung Hee Kim[3], Sung Eun Kim[4], Ji Won Park[4], Gi-Ae Kim[5], Yewan Park[5], Seong Kyun Na[6], Hyo Young Lee[6], Young-Sun Lee[7]

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**Aims:** Direct-acting antiviral (DAA) therapy can cure chronic hepatitis C (CHC), and DAA was introduced to Korea in 2016. A good prognosis is expected in patients who achieved sustained virologic response (SVR) after DAA treatment. However, information about the prognosis of Korean elderly CHC patients who achieved SVR after DAA treatment is still limited. We aimed to investigate the prognosis of these patients.

**Methods:** This is a multicenter prospective observational study. The CHC patients who over 65 years old and achieved SVR after DAA treatment were enrolled and final follow-up date was June 2023. The primary end-point was hepatocellular carcinoma (HCC) occurrence. Recurrence or reinfection and decompensation were the secondary end-point. At last one time in a year, we checked about this end-point.

**Results:** Total 466 patients were included in this analysis and mean follow-up duration was 35.2 months. Male was 182 patients (39.1%) and median age was 73 years. Genotypes were 1 (208, 44.6%), 2 (256, 54.9%), and 3 (2, 0.4%). Significant alcohol intake prevalence was 27 (5.8%) and cirrhosis was 1188 (40.3%). Mean Child-Pugh score and AFP level were 5.1 and 11.5 ng/mL. HCC occurrence cases were 29 patients (6.2%) for up to 6 years. HCC patients had male predominance (65.5% vs. 37.3%, $P$=0.003), high cirrhosis prevalence (75.9% vs. 38.0%, $P$<0.001), higher AFP level (7.0 ng/mL vs. 3.4 ng/mL, $P$=0.003), higher APRI (0.7 vs. 0.5, $P$=0.008) and FIB-4 (4.5 vs. 3.3, $P$=0.008). Cox regression analysis showed male ($P$=0.029) and cirrhosis ($P$=0.047) were significant risk factors for HCC occurrence.

**Conclusions:** The prognosis of elderly CHC patients achieved SVR after DAA treatment was generally good. However, HCC risk was not completely removed especially in patients with male and cirrhosis patients. Therefore, regular follow-up surveillance is still warranted.

**Keywords:** Hepatitis C, Direct-acting antiviral, Sustained virologic response, Hepatocellular carcinoma

## PE-05

### Prognosis after Sustained Virologic Response of Chronic Hepatitis C Patients with Cirrhosis Treated with Direct-Acting Antiviral Treatment

Jeong Han Kim[1], Jae Hyun Yoon[2], Jung Hee Kim[3], Sung Eun Kim[4], Tae Hyung Kim[4], Gi-Ae Kim[5], Yewan Park[5], Seong Kyun Na[6], Hyo Young Lee[6], Young-Sun Lee[7]

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**Aims:** Direct-acting antiviral (DAA) therapy can cure chronic hepatitis C (CHC), and DAA was introduced to Korea in 2016. A good prognosis is expected in patients who achieved sustained virologic response (SVR) after DAA treatment. However, information about the prognosis of Korean CHC related liver cirrhosis (LC) patients who achieved SVR after DAA treatment is still limited. We aimed to investigate the prognosis of these patients.

**Methods:** This is a multicenter prospective observational study. The CHC related LC patients achieved SVR after DAA treatment were enrolled and final follow-up date was June 2023. The primary end-point was hepatocellular carcinoma (HCC) occurrence. Recurrence or reinfection and decompensation were the secondary end-point. At last one time in a year, we checked about this end-point.

**Results:** Total 386 patients were included in this analysis and mean follow-up duration was 38.9 months. Male was 189 patients (49.0%) and median age was 64 years. Genotypes were 1 (197, 51.1%), 2 (187, 48.4%), and 3 (2, 0.5%). Significant alcohol intake prevalence was 72 (18.7%). Mean Child-Pugh score and AFP level were 5.2 and 12.8 ng/mL. HCC occurrence cases were 34 patients (8.8%) for up to 5 years. HCC patients had older

age (69 years vs. 64 years, *P*=0.070), male predominance (64.7% vs. 47.4%, *P*=0.072), higher AFP level (7.5 ng/mL vs. 5.1 ng/mL, *P*=0.017), higher APRI (1.1 vs. 0.8, *P*=0.012) and FIB-4 (5.4 vs. 4.1, *P*=0.014). Cox regression analysis showed male (*P*=0.045) and AFP over 6.93 (*P*=0.014) were significant risk factors for HCC occurrence. Recurrence or reinfection occurred in 2 patients (0.5%) at 3 and 31 months after SVR each. New decompensation occurred in 8 patients (2.1%) and 4 among them were related with HCC occurrence.

**Conclusions:** The prognosis of LC patients achieved SVR after DAA treatment was generally good. However, HCC risk was not completely removed especially in patients with male and high AFP level. Furthermore, HCC occurrence can lead to decompensation. Recurrence or reinfection is also possible. Therefore, regular follow-up surveillance is still warranted.

**Keywords:** Hepatitis C, Direct-acting antiviral, Sustained virologic response, Hepatocellular carcinoma

## PE-06

### Assessing Liver Fibrosis in Patients with Chronic Hepatitis C Genotype 6 Treated with Ledvir

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**Aims:** Hepatitis C virus (HCV) is an important health problem globally. If left untreated, there is a risk of progression to cirrhosis, hepatocellular carcinoma and death.

**Aims:** Assessing liver fibrosis (LF) in patients with HCV treated with Ledvir.

**Methods:** The prospective cohort study was conducted on 54 patients with HCV genotype 6 who were treated with Ledvir (Ledipasvir/Sofosbuvir 90mg/400 mg) orally once a day for 12 weeks at Cam Khe Clinic from 4/2019 to 12/2023. LF was evaluated using the METAVIR scoring system, by Fibroscan. Quantification of HCV RNA using HCV RNA real-time PCR method. Evaluate treatment response at week 4 after starting treatment, week 12 and 24 after end of treatment (EOT).

**Results:** Virologic response rate at 4 weeks of treatment was 96.3% and sustained virological response at 12 weeks was 98.1%. LF from 11.6 kPa before treatment, to 10.1 kPa at EOT, 9.3 kPa at week 12 after EOT and 8.2 kPa at week 24 after EOT. The proportion of F4 patients before treatment was 25.9%, at EOT was 18.5% and week 24 after EOT was 14.8%. F0-F1 group at the time before treatment was 37.0%, and increased to 55.6% at EOT and 74.1% at week 24 after EOT. Factors related to LF response are: overweight, initial fibrosis and AST activity (*P*<0.01). Side effects of the drug include: nausea and headache.

**Conclusions:** The level of LF improvement gradually increased in patients with HCV treated with Ledvir over time: EOT, week 12 after EOT and week 24 after EOT.

**Keywords:** Response, liver fibrosis, Chronic hepatitis C virus, Genotype 6,, LEDVIR

## PE-07

### Real-World Data with Pangenotypic Direct-Acting Antivirals: Preliminary Results of the SVR10K Study

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**Aims:** A previous real world data analysis demonstrated high effectiveness of sofosbuvir/velpatasvir (SOF/VEL) in > 6,000 HCV patients from 12 clinical cohorts across Australia, Canada, Europe & USA. Expanding this research initiative to include even more patients from additional geographical areas will allow to show SOF/VEL effectiveness across multiple diverse populations & the evaluation of HCV patient characteristics across Western countries, Asia, Middle Eastern and Latin-American regions.

**Methods:** This real-world analysis includes patients ≥ 18 years treated with SOF/VEL without RBV for 12 weeks, as decided by the treating HCP, from 7 sites across Hong Kong, Mexico, Sweden, Spain, Taiwan, and the United Arab Emirates. Age, sex, treatment experienced (TE), cirrhosis stage (no decompensated included), genotype, coinfections, time to treatment initiation (TTI) from HCV diagnosis, and SVR (4/12/24) were analyzed.

**Results:** Overall, 4,679 patients were included, 51% of them from Asian countries. Median age was 56.9 [IQR 46-66], where males 59%, and age > 50 years in 68%. Genotype 3 was present in 25%, F4 21%, TE 5%, while HIV, HBV and HDV coinfection was reported in 4.7%, 4.3%, and 0.1%, respectively. The TTI was available in 74%, with 17% having ≤ 30 days. In terms of effectiveness, SVR was achieved in 98.4% of the treated population, 99% for Asian countries.

**Conclusions:** Results on treatment effectiveness in these new geographies did not differ from real world studies of patients in the Western countries, reinforcing that HCV treatment guidelines are globally applicable, and supporting the efficacy of pDAA therapy.

**Keywords:** Sofsbuvir/pelvastapir, HCV, DAA

## PE-08

### Long-Term Safety and Efficacy of Sofosbuvir-Based Direct-Acting Antivirals in Pediatric Patients with Hepatitis C Virus

**Sungshin Kwon**[1], Daniel H. Leung[2], Suzanne Whitworth[3], Jessica Wen4, Giuseppe Indolfi[5], Karen Murray[6], Philip Rosenthal[7], Chuan-Hao Lin[8], Wikrom Karnsakul[9], Sanjay Bansal[10], Jonathan R. Honegger[11], William Balistreri[12], Kathy Schwarz[13], Winita Hardikar[14], Regino Gonzales-Peralta[15]

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**Aims:** DAAs have shown high sustained virologic response (SVR) rates and favorable safety profiles in children, but data describing long-term outcomes are limited. Herein, we describe final follow-up data from study GS-US-334-1113 (NCT02510300) describing virologic outcomes and effects on growth and sexual development in children with chronic HCV infection.

**Methods:** Children with chronic HCV infection who received sofosbuvir (SOF)+RBV, ledipasvir (LDV)/SOF±RBV, SOF/velpatasvir (VEL), or SOF/VEL/voxilaprevir (VOX) in prior clinical trials were eligible to enroll in this 5-year registry study. Every 6 to 12 months, we assessed the durability of SVR by measuring HCV RNA, and we evaluated the effects of DAAs on growth and sexual development by measuring weight, height, and body mass index (BMI) percentiles and z-scores and Tanner pubertal stage.

**Results:** A total of 461 patients were enrolled between October 2015 and June 2021; 20% were treated with SOF+RBV, 42% with LDV/SOF±RBV, 34% with SOF/VEL, and 4% with SOF/VEL/VOX in parent trials. Among 426 patients with ≥ 1 post-baseline measurement, 58% were female, 80% were White. At enrollment, the median age (range) was 12 (3–18) years, and the mean (SD) weight, height, and BMI z-scores were 0.2 (1.23), −0.2 (1.05), and 0.4 (1.12), respectively. The median (range) follow-up was 193 (9–325) weeks. All but 2 patients achieved SVR in parent trials, and 100% of these patients maintained SVR throughout the registry study. Treatment with SOF-based DAAs had little impact on growth at week 240, and the mean changes (SD) in z-scores for weight, height, and BMI were 0.1 (0.71), 0.0 (0.67), and 0.1 (0.70), respectively. DAA treatment did not impact sexual development as assessed by Tanner stage.

**Conclusions:** HCV treatment with SOF-based regimens resulted in durable SVR in children and had no impact on growth or sexual development up to 5 years posttreatment.

**Keywords:** HCV, Pediatric, DAA, Sofosfovir/velpatasvir

## PE-09

### Improved Linkage of Care of Chronic Hepatitis C among People Who Use Drugs (PWUDs) with On-Site-Treatment Program: A Prospective, Multicenter Study

**Gwang Hyeon Choi**[1], Min Kyung Park[1], Young-Hoon Cheon[2], Do Hoon Kwon[3], Sung Nam Jo[4], Og-Jin Jang[5,6], Eun Sun Jang[1], Sook-Hyang Jeong[1]

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**Aims:** There are no reports of the effectiveness of on-site treatment of hepatitis C in PWUD (people who use drugs) in South Korea. Therefore, this study aimed to investigate the treatment rate of an on-site-treatment group compared to referral to a tertiary hospital for anti-HCV therapy, and factors related to treatment in patients with PWUDs.

**Methods:** A total of 33 PWUDs (median age 54 years, 90.9% male, and intravenous drug user 97%) with positive anti-HCV and HCV RNA were prospectively enrolled in 4 hospitals from August 2022 to December 2023. For them, blood tests including complete blood cell count and liver panel, and questionnaires related to socioeconomic, psychiatric and risk factors for HCV infection were conducted. One site provided on-site HCV treatment under remote consultation of a hepatologist (on-site treatment group), and the other 3 sites provided information on the need for HCV treatment and information for visiting a tertiary hospital (referral group).

**Results:** Among 33 PWUDs, the overall treatment rate was only 51.5% (17/33). Seventeen patients (51.5%) were in the on-site-treatment group and 16 patients were in the referral group. The on-site treatment group showed a significantly higher median age (55 vs. 50, $P$=0.002) and a relatively higher proportion of Medicaid (76.5% vs. 43.8, $P$=0.101) than the education group. The treatment rate of the on-site treatment group was significantly higher than that of the referral group (88.2% vs.

12.5%, *P*<0.001).

In the multivariate logistic regression analysis, the on-site program was the only significant factor for HCV treatment (RR 62.256, 95% CI 5.811 – 128.654, *P*=0.001).

**Conclusions:** The HCV treatment rate in the PWUD-HCV patient population is 57.6% far below the target for HCV elimination. The on-site treatment program operating by cooperative supervision is an effective strategy to improve the linkage-of-care for HCV.

**Keywords:** HCV, PWUD, Linkage of care, Treatment

# Alcoholic Liver Disease

## PE-01

### Comparison of the Effects of Medical Addiction Therapy on Liver Function in Alcohol Use Disorder: Retrospective Cohort Study

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**Aims:** Alcohol abstinence is crucial in the management and prognosis of alcohol-associated liver disease (ALD). Naltrexone and acamprosate have been proved effective as medical addiction therapy drugs for alcohol use disorders (AUD): better rates of abstinence and lowered rates of binge drinking. However, it is still uncertain whether these addiction therapy can induce better outcomes in patients with ALD. Therefore, we conducted a study to investigate the effects of medication addiction therapy, especially naltrexone and acamprosate, on liver function in patients with ALD.

**Methods:** In this retrospective analysis, 1221 patients with AUD causing ALD who had either received treatment with naltrexone (n = 469) or acamprosate (n = 121), or who had not received any medication for medical addiction therapy as a control group (n = 631) were evaluated. In each group, ALT and PLT levels were taken and examined at the time of AUD diagnosis, shortly before starting treatment, and at the conclusion of follow-up. The comparison of numerical values among the three groups was conducted using one-way analysis of variance (ANOVA).

**Results:** There was no significant difference among the groups in terms of initial ALT levels. Regarding initial PLT levels, except for between the control and naltrexone groups, there was no significant difference observed among the groups. There was no significant difference among the groups in terms of changes in ALT (*P*=0.3930) and PLT levels (*P*=0.6689) at the end of follow-up.

**Conclusions:** It is not certain that medical addiction therapy for alcohol use disorder is able to significantly affect liver function in ALD. Further research is warranted to prospectively validate our results in various stages of ALD.

**Keywords:** Alcohol use disorder, Alcoholic liver disease, Medical addiction therapy

## PE-02

### The Impact of Psychiatric Intervention on Outcomes in Patients with Alcoholic Liver Disease: A Retrospective Cohort Study

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**Aims:** Alcohol consumption is a major global concern leading to significant social and economic losses, yet its consumption remains high. Alcohol is a major cause of chronic liver disease. However, the co-occurrence of psychiatric conditions in patients with alcoholic liver disease and its impact on survival have not been adequately addressed.

**Methods:** To investigate the medical utilization related to psychiatric problems in patients with alcoholic liver disease, we utilized data from the National Health Insurance Service–National Sample Cohort in Korea between 2002 and 2019. We defined psychiatric intervention as being claimed for outpatient clinics more than twice or hospitalized for psychiatric diseases such as depression, bipolar disorder, and anxiety. We further examined death and suicide attempts between those with and without psychiatric intervention.

**Results:** Among total number of 46,340 patients who were enrolled, 37,155 were male (80.1%). 7,527 patients received psychiatric intervention. Baseline characteristics demonstrated that patients who received the intervention were older (55.60 ±13.70 years vs 49.52±12.92 years), had a higher prevalence of females (23.9 % vs 19.03%), and had more comorbidities (Charlson comorbidity index; 2.65±2.12 vs 2.21±1.58) than patients without psychiatric intervention. After adjustment, patients in the psychiatric intervention group exhibited a higher incidence of suicide attempts (adjusted HR: 3.343, 95% CI: 2.298 - 4.862) and death (adjusted HR: 1.568, 95% CI: 1.448 - 1.669) compared to their counterparts. Factors such as male sex and low socioeconomic status were also found to be associated with suicide attempts.

**Conclusions:** This study underscores the importance of addressing psychiatric approaches, with a special focus on suicide attempts in patients with alcoholic liver disease.

**Keywords:** Alcoholic liver disease, Psychiatric intervention

# Autoimmune Liver Disease

## PE-01

### Discordance between Biochemical Response and Histological Remission in Patients with Autoimmune Hepatitis

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**Aims:** In autoimmune hepatitis (AIH), normal levels of transaminases and IgG define biochemical remission and are considered surrogate markers for histological remission. This study aimed to assess whether a biochemical response is a reliable surrogate marker for predicting histological remission in patients with autoimmune hepatitis.

**Methods:** We studied 8 patients (median age at diagnosis 63 years; 62.5% female) with AIH, who received immunosuppressive treatment and underwent a follow-up liver biopsy more than 2 years after the initial liver biopsy. Sustained biochemical response was defined as maintaining normal levels of ALT and IgG for six months prior to the follow-up liver biopsy.

**Results:** All eight patients showed a biochemical response within one year of immunosuppressive therapy, and six of them exhibited a sustained biochemical response at the time of follow-up liver biopsy. The two patients who did not show a sustained biochemical response had modified Hepatitis Activity Index (mHAI) scores of 6 and 12, respectively, indicating moderate to high histological activity. Of the six patients who demonstrated a sustained biochemical response, only two showed histological remission. Despite having a sustained biochemical response, the remaining four patients exhibited histological activity; among them, two had mHAI scores of 9 and 10, indicating high histological activity. These two patients, unlike the other four, had continuously rising serum gamma-glutamyl transferase (GGT) levels measured at three-month intervals prior to the follow-up liver biposy.

**Conclusions:** A biochemical response may not be a reliable surrogate marker for histological remission. There is a need to identify noninvasive biomarkers that can predict histological remission in patients with AIH.

**Keywords:** Autoimmune hepatitis, Biochemical response, Histological remission

## PE-02

### Retrospetic Analysis of Autoimmune Hepatitis and Autoimmune Hepatitis-Primary Biliary Cirrhosis Overlap Syndrome in a Tertiary Hospital

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**Aims:** Overlap syndrome of autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC) (AIH-PBC overlap syndrome) is a rare disease that has not been clearly characterized in Korean patients. This study investigated the clinical features of autoimmune hepatitis and AIH-PBC overlap syndrome in a tertiary hospital.

**Methods:** This retrospective cohort study included 307 consecutive patients who were diagnosed as AIH (n=261) or AIH-PBC overlap syndrome (n=46) based on the Paris and the International Autoimmune Hepatitis Group (IAIHG) criteria from 2008 to 2020. We compared the clinical features of these two groups retrospectively, including their biochemical characteristics, treatments, responses, and clinical outcomes.

**Results:** The AIH-PBC overlap syndrome patients exhibited biochemical characteristics of both AIH and PBC, and showed a similar response to ursodeoxycholic acid (UDCA) monotherapy as for the PBC patients. Relapse occured 37 out of 307 in autoimmune hepatitis and 13 out of 46 in overlap SD patients.

Ther risk factors for associated with autoimmune hepatitis relapses were total bilirubin(> 1.5 mg/dL), alanine aminotransferse, IgG at initial time ($P$=0.037, 0.043, 0.039) in multivariate logistic regression. The other hand, the risk factors for relapse of overlap syndrome were age at diagnosis of the disease (>=50 years). UDCA and steroid combiation therapy ($P$=0.041, 0.024).

Liver cirrhosis developed more rapidly in AIH-PBC overlap syndrome patients than in AIH patients group ($P$=0.037).

**Conclusions:** The AIH-PBC overlap syndrome patients exhibited a worse prognosis and liver cirrhosis developed more rapidly in AIH-PBC overlap syndrome patients group.

**Keywords:** Autoimmune hepatitis, Overlap syndrome, Relapse, Prognosis

## PE-03

### Associations of Antinuclear Antibody with Mitochondrial Antibody and Smooth Muscle Antibody in Autoimmune Liver Diseases

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**Aims:** Autoimmune liver diseases (ALD) are immune-mediated

chronic liver diseases with clinical characteristics, the major disease entitis like autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC). We aimed to determine the significance of antinuclear antibodies (ANA) patterns in patients with ALD. We check associations of ANA with anti-smooth muscle antibodies (ASMA) and anti-mitochondrial antibodies (AMA).

**Methods:** ANA staining patterns were identified by HEp-2 cells with patients serum. ASMA and AMA were identified by rats tissue with patients serum. We retrospectively reviewed 902 patients were sent to our laboratory from 2022 till 2023. These patients were from division of Rheumatology and Gastroenterology in the hospital.

**Results:** Among 902 cases, 36 patients were detected ASMA positive. These ASMA positive cases, that ANA with low titer and almost were negative. From ASMA positive cases, there were 24 (66.7%) female and 12 (33.3%) male. The mean age of presentation was 52.3 years. Further analysis, according to the ANA ICAP classification, the ANA manifestations were AC1, AC4/5, and AC15~20. Among 902 cases, 30 patients were detected AMA positive. These AMA positive cases, there were 25 (80.6%) female and 6 (19.4%) male. The mean age of presentation was 61.1 years. We found these cases with high titer cytoplasmic fluorescence pattern (between 1:640~ 1:2560). It has been shown that cytoplasmic staining, including AC21, AC11/12, and AC15~20. In particular, AC21 showed extremely high correlation with PBC.

**Conclusions:** When autoimmune hepatitis was suspected, ASMA must be combined with ANA for interpretation. It some timely had no special characteristics for ALD, and must rely on other clinical data. It`s important to check cytoplasmic ANA patterns for ALD, even when nuclear ANA patterns are negative. And PBC patients are highly association with the positive ANA, unlike the nonspecific ANA in ASMA, especially, the ANA manifestations were AC21.

**Keywords:** Autoimmune liver disease, Mitochondrial antibody, Smooth muscle antibody

## Cell Biology and Molecular Biology

### PE-01

### Exploring CD47 as a Prognostic Marker for Pancreatic Cancer and Its Association with Adverse Clinicopathologic Features

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**Aims:** Pancreatic Adenocarcinoma (PDAC) is one of the dreaded malignancies having a five-year survival rate as low as 2% in advanced cases. It is estimated that by 2040, a 61.7% increase is expected globally. Despite it being deadly, we lack good predictors of prognosis which can help in the specific management of patients. The dense tumor microenvironment containing immune cells plays a vital role in the progression and invasiveness of PDAC. CD47 (Cluster of Differentiation 47) has a "don't eat me signal" to macrophages through the SIRP $\alpha$ receptor, contributing to escape immune surveillance of cancer cells, leading to the growth and invasiveness of cancer.

**Methods:** We have obtained pancreatic cancer microarray sections from 104 patients diagnosed in Hanyang Hospital from 2008 to 2023. Immunohistochemical staining with CD47 antibody was done. Data analysis was done using R Studio version 4.2.3.

**Results:** In this study elevated CD47 expression (56%) was correlated significantly with disease-free survival ($P$=0.007). It was also linked to lower overall survival ($P$=0.09). Multivariate analysis identified high CD47 expression as an independent factor affecting survival.

**Conclusions:** Elevated CD47 expression in Pancreatic Adenocarcinoma signals advanced disease and independently forecasts worse survival. This highlights CD47's dual role as a crucial prognostic marker and a potential therapeutic target, particularly in advanced PDAC stages.

**Keywords:** CD47, Pancreatic Adenocarcinoma, Survival

### PE-02

### Human PAH MRNA in vivo Screening for the Development of Phenylketonuria Treatment

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**Aims:** Phenylketonuria(PKU) is an autosomal recessive disorder caused by point mutations in the phenylalanine hydroxylase(PAH) gene. Phenylalanine accumulated in the brain causes brain dysfunction, but there is no fundamental treatment strategy. mRNA therapy allows for faster treatment than gene editing and does not cause permanent changes to the genome. Lipid NanoParticle(LNP) is a highly biocompatible vehicle and stably delivers substances. Here, we suggest a fundamental solution through an mRNA-based therapeutic approach.

**Methods:** We delivered mRNA encoding human Pah(hPah) encapsulated in LNP to PKU disease model mice. LNP and hPAH

mRNA were provided by mCureX and contain hPah and FLAG sequences. The total number of mice is 8, divided into vehicle group(n=3), 1 time injection group(n=3), and 2 times injection group(n=2). Proteins were extracted by mouse liver tissue with RIPA buffer including a cocktail of protease inhibitors. FLAG protein was detected through western blot to confirm the synthesis of hPAH protein. The levels of phenylalanine (Phe) and tyrosine (Tyr) in plasma were confirmed by amino acid analysis.

**Results:** There was no significant difference between 1 time injection and 2 times injection. However, FLAG protein was confirmed in all mice delivered with mRNA. PKU disease model mice showed lower Phe levels than the vehicle group. Additionally, all mice in the treated group showed higher Tyr levels compared to the vehicle group.

**Conclusions:** We demonstrated that hPAH mRNA can produce hPAH in the PKU mice model. The hPAH produced in this way converts Phe to Tyr, suggesting that it can be applied to the treatment of phenylketonuria.

**Keywords:** Phenylketonuria, Messengerrna, Phenylalanine hydroxylase

## PE-03

### Heat-Inactivated Bacteria: Potential Anti-Cancer Agents Against Liver, Pancreatic, and Gallbladder Cancer Cell Lines

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**Aims:** Cancers of the gastrointestinal tract pose significant global health challenges, with bacterial infections being recognized as one of the contributing factors in cancer development. The human gastrointestinal tract harbors a vast array of microorganisms collectively known as gut microbiota, which maintain a symbiotic relationship with the host. In this study, we aimed to investigate the effects of heat-killed bacteria on three cancer cell lines: HepG2 (liver), SMAD4 (pancreatic), and OCUG-1 (gallbladder).

**Methods:** Five bacterial strains, including Enterococcus faecalis, Staphylococcus hominis, Salmonella typhi, Escherichia coli, and Pseudomonas aeruginosa, were selected for analysis. The bacteria were subjected to thermal inactivation to ensure preservation of surface proteins. Different concentrations (0.01, 0.1, 0.5, and 1 mg/ml) of heat-inactivated bacterial solutions were prepared and evaluated for their effects on the viability of HepG2, SMAD4, and OCUG-1 cell lines using the MTT assay.

**Results:** After 48 hours of treatment, the MTT assay revealed that heat-killed bacterial solutions induced proliferation of stomach, colon, and gallbladder cancer cell lines. Specifically, the highest cell viability in OCUG-1 cells was observed in samples treated with S. hominis, while S. typhi-treated samples exhibited the highest viability in SMAD4 cells.

**Conclusions:** The findings suggest that bacterial infections may exacerbate cancer progression, and different bacterial species may have varying effects on specific cancerous tissues. This underscores the complex interplay between the gut microbiota and gastrointestinal cancers, highlighting the need for further research in this area.

**Keywords:** Microorganisms, Heat-killed bacteria, Cancel cell lines

## PE-04

### A Modern Approach for Transplanting Glucose-Sensitive Cells That Produce Insulin

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**Aims:** In patients with diabetes mellitus (DM), pancreatic $\beta$-cell deficiency occurs or develops, and their replacement by functionally complete cells producing insulin is the only possible way to cure this disease. The procedure for transplanting pancreatic cells can not be considered a standard intervention because of two main problems: 1. The need for lifelong immunosuppression; 2. The lack of the possibility of pancreas removal from donors with preserved cardiac activity and ascertained death of the brain. Currently, the only possible way to cure patients with diabetes is to transplant the pancreas or its cells, which is a very effective way to achieve and maintain long-term physiological control of blood glucose levels, but due to various risks (rejection) associated with performing a surgical procedure, this method is rarely used. In contrast, transplanting the islets of the pancreas requires minimal invasive surgery, as it is performed as part of a percutaneous intervention-through the portal vein, under the capsule of the spleen, kidney and liver, into the abdominal cavity, etc. A functioning transplant in a patient with diabetes can eliminate episodes of hypoglycemia, correct the level of glycated hemoglobin (HbA1c), reduce or completely eliminate the risk of secondary complications associated with the disease and, in the most optimal cases, allows you to achieve independence from insulin.

**Methods:** In the Republican Scientific and Specialized Center of Hepatopancreatobiliary Surgery, the Ministry of Health of the Republic of Uzbekistan has developed an effective method of surgical treatment of DM by free implantation of islet cells of the pancreas cultures and introduced into clinical practice. Xenotransplantation was performed by 186 DM patients aged 13 to 59 years. Of these, 106 were transplanted in newborn lambs, 80 from piglets. Transplantation of allogeneic islet cells of the pancreas was carried out in the following variants: under the

anterior sheet of the vagina of the rectus abdominis; under the capsule of the spleen; under the aponeurosis of the rectus abdominis muscle; round ligament of the liver; subcutaneously.

**Results:** The therapeutic effect of transplanted islet cells of pancreas in DM patients was assessed by the dynamics of the symptoms of diabetes. Disease of blood, serum, the need for exogenous insulin, the manifestation of macro- and microangiopathy. The dynamics of clinical manifestations of diabetes was studied separately in patients who received insulin before transplantation in a dose of less than or more than 40 units.

| Terms of the study after transplant, month | Blood sugar, mmol / l | P | Percentage to baseline | Endogenous insulin mcked / ml | P |
|---|---|---|---|---|---|
| Initial data | 10,9±0,40 | - | 100,0 | 1,4±0,30 | - |
| | 10,9±0,54 | - | 100,0 | 1,8±0,76 | - |
| 1 | 7,5±0,21 | <0,05 | 68,8 | 16,3±0,51 | <0,05 |
| | 7,9±0,41 | <0,05 | 73,4 | 13,5±0,84 | <0,05 |
| 3 | 7,6±0,41 | <0,05 | 69,7 | 14,6±0,80 | <0,05 |
| | 7,9±0,85 | <0,05 | 73,4 | 14,4±2,22 | <0,05 |
| 6 | 7,0±0,25 | <0,05 | 64,2 | 22,1±1,3 | <0,05 |
| | 7,3±0,41 | <0,05 | 66,9 | 13,8±1,34 | <0,05 |
| 9 | 7,4±0,30 | <0,05 | 67,8 | 14,6±0,42 | <0,05 |
| | 8,1±0,53 | <0,05 | 74,3 | 13,3±0,85 | <0,05 |
| 12 | 8,2±0,57 | <0,05 | 75,2 | 11,0±0,11 | <0,05 |
| | 8,9±0,50 | >,05 | 81,6 | 13,5±0,10 | <0,05 |

As the examination of patients with implants of the islet cells of pancreas showed, within 9 months after the transplantation practically all disappeared clinical manifestations of the diabetes itself and its complications. Only 3 patients showed mild complaints of dry mouth, sometimes pain in the limbs.

At 12 months after transplantation, the islet cells of pancreas of lambs and piglets decreased glycemia less. Transplantation of islet cells of pancreas also caused an increase in endogenous insulin. In patients receiving exogenous insulin before transplantation at a dose less than 40 units, the level of endogenous insulin was increased by 13.0-20.2 times and by 4.3-6.0 times, and in patients receiving exogenous insulin in a dose before transplantation more than 40 units, respectively in 5.7-6.4 and 3.8-6.2 times against the initial data.

Consequently, after the transplantation of islet cells of pancreas both lambs and pigs, it is possible to significantly reduce the dose of exogenous insulin administered to a patient with DM. So at 9 and 12 months after the transplant, the reduction in the dose of insulin received by the patients was statically unreliable. The need for exogenous insulin was more pronounced in recipients who received insulin at a dose of more than 40 units before the transplant.

Perhaps the future in the treatment of diabetes does not belong to the transplantation of the gland or its fragments, but to biotechnological methods.

**Conclusions:** Thus, summing up the clinical results of islet cell transplantation along with the achievements, we noted that the problem bears in itself many more questions that await their resolution. There are also difficulties in isolating islet cells, insufficient number of cadaveric pancreas and good immunological protection. In this connection, a great interest of sources for the production of healthy insulin-producing cells.

**Keywords:** Diabetes mellitus, Pancreatic B-cell, Insulin, Transplantation

## PE-05

### Therapeutic Potential of Moringa Oleifera Leaves Ethanolic Extract in Restoring Hepatic Enzyme Levels and Metabolic Functions in an Experimental Rat Model of Hypothyroidism

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**Aims:** The study aimed to explore the potential beneficial effects of Moringa oleifera leaf (MOL) extract on hepatic and metabolic parameters in male rats with experimental hypothyroidism. MOL is known to contain compounds like quercetin and chlorogenic acid, which possess antioxidant properties and can scavenge free radicals.

**Methods:** Forty-eight male Wistar rats were divided into four groups: Control (C), hypothyroid (H), control + MOL extract (C+M), and hypothyroid + MOL extract (H+M). Rats in the C group received no intervention, while those in the C+M and H+M groups received MOL extract pretreatment for four weeks. Subsequently, for six weeks, the H group received propylthiouracil in drinking water, while the C+M group received MOL extract, and the H+M group received both propylthiouracil and MOL extract.

**Results:** The results showed that the hypothyroid group exhibited elevated thyroid-stimulating hormone (TSH) levels and reduced thyroid hormone levels, along with significant alterations in liver enzymes, lipid profile, inflammatory markers, and apolipoprotein levels. Treatment with MOL extract resulted in a dose-dependent improvement in thyroid function, with notable increases in free T3 and free T4 levels and a decrease in TSH levels in the H+M group. Additionally, MOL extract treatment ameliorated hypercholesterolemia, reduced inflammation markers, suppressed oxidative stress, and prevented hepatic damage induced by thyroid hormone depletion.

**Conclusions:** In conclusion, MOL extract demonstrated therapeutic potential in restoring thyroid hormone levels and mitigating hepatic complications associated with hypothyroidism in the experimental rat model.

**Keywords:** Moringa oleifera leaf extracts, Hypothyroidism, Liver, Experimental rat model

## PE-06

### Organoid Technology as a Precise Prediction Platform of Systematic Treatment for Hepatocellular Carcinoma

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**Aims:** Hepatocellular carcinoma (HCC) stands as the foremost cause of cancer-related deaths on a global scale. Similar to other tumor types, HCC is marked by delayed diagnosis, poor prognosis, heterogeneity, and complexity. Despite the active prescription of numerous targeted drugs in both front-line and second-line settings, the current medications for HCC exhibit limited efficacy. Additionally, the varying sensitivity of individual HCC patients to approved targeted drugs leads to unfavorable prognoses.

**Methods:** There is an urgent need for an advanced *in vitro* model system that can 1) faithfully mirror *in vivo* tumor characteristics, 2) provide accurate drug efficacy assessments closely aligned with clinical outcomes, and 3) enable rapid decision-making for the personalized prescription of the most effective drugs.

**Results:** In this study, we provide an overview of the current HCC medication landscape and highlight its unmet clinical needs. We also present a comparative analysis of diverse *in vitro* models for assessing drug efficacy in HCC, including organoid technology.

**Conclusions:** we introduce a novel organoid-based *in vitro* model designed to expedite the personalized prescription of HCC medications, thereby enhancing the effectiveness of HCC treatment.

**Keywords:** Hepatocellular carcinoma, Organoids, Drug efficacy

## PE-07

### Codon Usage and Possible Involvement of Genes Associated with Liver Cancer

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**Aims:** Among all malignancies, liver cancer has a relatively high prevalence and is one of the leading causes of mortality globally. One important feature of cancer cells is their enhanced ability to proliferate, necessitating higher amounts of protein synthesis. Codons in the mRNA coding sequence are translated into a chain of amino acids to produce a polypeptide during the process of protein synthesis. When synonymous codons for every amino acid are not used at random in the coding sequences of genes, codon use bias, or CUB, results.

**Methods:** We utilized bioinformatic techniques to examine the molecular patterns, compositional characteristics, codon usage, and codon usage bias trend of the genes linked to liver cancer since no research has been published yet.

**Results:** The examination of base composition revealed that the genes associated with liver cancer were GC-rich. Additionally, at the third codon position, G/C ending codons were more favored than A/T ending ones. There were few genes linked to liver cancer in the CUB. Correspondence analysis suggested that natural selection and other variables could potentially have an impact on CUB in addition to base restrictions. Furthermore, correlation analysis results showed that transcripts of the genes linked to liver cancer released free energy in a significant way due to the presence of CUB and different GC contents.

We have highlighted tumor type-specific signatures of codon and codon pair usage based on CUB data. When creating tailored cancer treatments, it is important to take into account the varied changes in codon usage patterns that were found in paired data.

**Conclusions:** These recoded genes may be added to the human body to maximize gene expression levels and support liver cancer treatment regimens through the use of cutting-edge gene editing technologies like CRISPR/Cas or any other gene augmentation technology.

**Keywords:** Codon bias, Diagnosis, Therapeutics, Codon usage

## PE-08

### Liver Biopsy Results for Diagnosis and Differential Diagnosis of Liver Disorders: A Retrospective Study at Intermed Hospital, Mongolia

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**Aims:** Liver biopsy remains a crucial method for detecting changes in liver structure, including fibrosis, cirrhosis, and parenchymal disorders, despite the availability of various serological tests. Percutaneous liver biopsy, a minimally invasive outpatient procedure, offers accessibility and diagnostic accuracy.

**Methods:** A retrospective analysis of liver biopsy results conducted at Intermed Hospital's Gastroenterology-Endoscopy Center and Radiology Department from 2016 to May 2023 was

performed.

**Results:** The study encompassed 114 liver biopsy cases with an average age of 45.07±14.15 years, with female participants comprising 57.9%. Liver analysis primarily aimed at determining fibrosis (9.6%), distinguishing parenchymal disorders (70.2%), and diagnosing liver cancer (20.2%). The most prevalent parenchymal disorders included fatty liver (25%), primary biliary cholangitis (17.5%), and autoimmune hepatitis (22.5%). Liver tissue analysis conducted for the differential diagnosis of liver lesions revealed metastatic tumors in 11 cases (47.8%), primary liver tumors in 2 cases (8%), hemangioma in 2 cases (8%), focal nodular hyperplasia in 2 cases (8%), and adenoma in 1 case (4%). Autoimmune disorders were predominant in males, particularly primary biliary cholangitis (15.1%) and autoimmune hepatitis (21.2%).

**Conclusions:** Liver biopsy remains indispensable for diagnosing and differentially diagnosing liver disorders, offering valuable insights into disease management and treatment outcomes.

**Keywords:** Liver biopsy, Liver fibrosis, Liver parenchymal disorders, Liver cancer

# Genetic

## PE-01

### Protein-Centric Omics Analysis Reveals Circulating Complements Linked to Non-Viral Liver Diseases as Potential Therapeutic Targets

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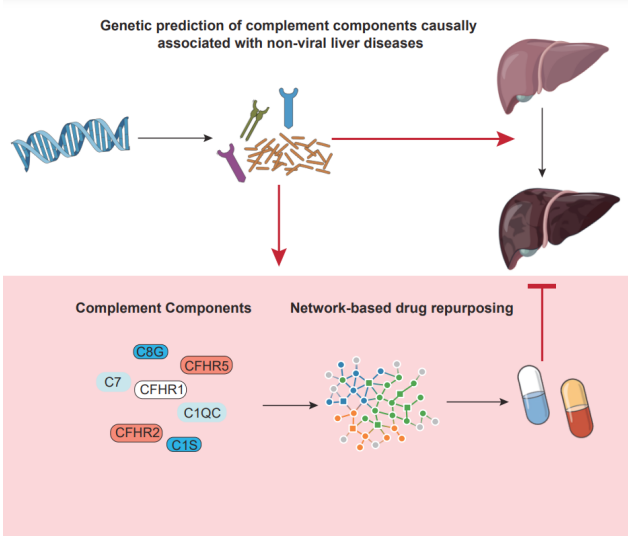
**Aims:** To evaluate the causal correlation between complement components and non-viral liver diseases and their potential use as druggable targets.

**Methods:** We conducted Mendelian randomization (MR) to assess the causal role of circulating complements in the risk of non-viral liver diseases. A complement-centric protein interaction network was constructed to explore biological functions and identify potential therapeutic options.

**Results:** In the MR analysis, genetically predicted levels of complement C1q C chain (C1QC) were positively associated with the risk of autoimmune hepatitis (odds ratio 1.125, 95% confidence interval 1.018–1.244), while complement factor H-related protein 5 (CFHR5) was positively associated with the risk of primary sclerosing cholangitis (PSC;1.193, 1.048–1.357). On the other hand, CFHR1 (0.621, 0.497–0.776) and CFHR2 (0.824, 0.703–0.965) were inversely associated with the risk of alcohol-related cirrhosis. There were also significant inverse associations between C8 gamma chain (C8G) and PSC (0.832, 0.707–0.979), as well as the risk of metabolic dysfunction-associated steatotic liver disease (1.167, 1.036–1.314). Additionally, C1S (0.111, 0.018–0.672), C7 (1.631, 1.190–2.236), and CFHR2 (1.279, 1.059–1.546) were significantly associated with the risk of hepatocellular carcinoma. Proteins from the complement regulatory networks and various liver disease related proteins share common biological processes. Furthermore, potential therapeutic drugs for various liver diseases were identified through drug repurposing based on the complement regulatory network.

**Conclusions:** Our study suggests that certain complement components, including C1S, C1QC, CFHR1, CFHR2, CFHR5, C7, and C8G, might play a role in non-viral liver diseases and could be potential targets for drug development.

**Keywords:** Mendelian randomization analysis, Complement-system proteins, Drug repositioning




## PE-02

### Massively Parallel Reporter Assay for Fine-Mapping of NAFLD-Specific Expression Quantitative Trait Locus (NAFLD-eQTL)

Hyungtai Sim, Murim Choi

Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Republic of Korea

**Aims:** Massively Parallel Reporter Assay (MPRA) is a high-throughput approach that allows simultaneous determination of regulatory effects from thousands of non-coding sequences. To investigate the regulatory activity of NAFLD-specific expression quantitative trait loci (eQTL), we selected 160

NAFLD- and 23 Liver-eQTL variants from NAFLD-eQTL for MPRA analysis.

**Methods:** A total of 7,500 candidate sequences were synthesized and cloned into a reporter construct. The resulting library was transfected into HepG2 cells and the cells were subsequently treated with oleic acid/palmitic acid, thapsigargin, and vehicle to model fatty-liver associated stress. After sample collection, mRNA was extracted, and 3′ tags were sequenced to determine which candidate elements carried regulatory effects and allelic enhancer activity.

**Results:** Comparing tags from library and mRNA revealed that more than 60% of the tested sequences have activity as enhancers. To validate the MPRA signals, we utilized ENCODE cCRE data and sequence-based prediction models, which showed a marginal enrichment in sequences with regulatory activity. This difference in enrichment may be attributed to the distinct nature of MPRA and other regulatory activity prediction models.

**Conclusions:** Integrative analysis for MPRA signals will be investigated for fine-mapping NAFLD-eQTL signals and find non-coding variants for regulating NAFLD-related traits.

**Keywords:** MPRA, EQTL, NAFLD

## Drug and Toxic Injury

### PE-01

### Double-Edged Sword? A Bibliometric Look at Antiretrovirals and Liver Injury in HIV Patients (2018-2024)

**Willy Febri**[1], Raiyan Fairozi[2]

[1]Department of Civil Engineering, Universitas Muhammadiyah Palangka Raya, Indonesia; [2]Department of Polyclinic, Quality Assurance of Central Kalimantan, Indonesia

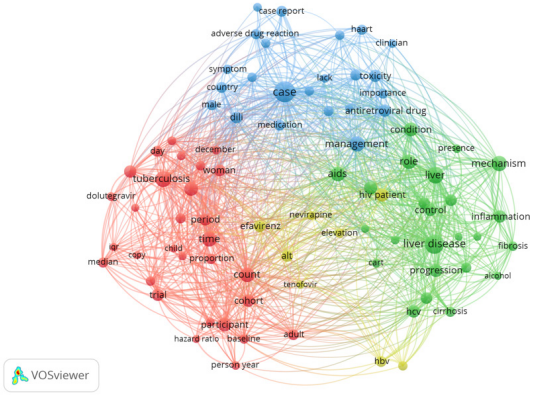
**Aims:** Antiretroviral therapy (ART) has revolutionized the treatment of HIV/AIDS, significantly improving patient outcomes and reducing mortality rates. However, concerns have been raised regarding potential adverse effects of ART on the liver, including hepatotoxicity and liver injury. This study aims to conduct a comprehensive bibliometric analysis using Scopus data from 2018 to 2024 to evaluate the relationship between antiretroviral drugs and liver injury in HIV patients.

**Methods:** This study employs a bibliometric framework to comprehensively delve into the ART effect toward liver injury. A meticulous mapping analysis was conducted leveraging VOSviewer software for visualization and scopus for data acquisition. Keywords related to HIV, antiretroviral therapy, liver injury, and hepatotoxicity were used to retrieve pertinent literature. The search string was designed to capture relevant articles published between 2018 and 2024.

**Results:** The analysis revealed a substantial increase in the number of publications addressing the relationship between antiretroviral therapy and liver injury in HIV patients during the specified period, indicating increasing research interest. The co-occurrence keywords analysis of 4 cluster encompassed time, liver diseases, case, and HIV Patient. Chronic administration of immunosuppressive drugs can lead to liver disease, particularly in individuals co-infected with HIV. Hepatotropic viruses induced hepatitis progress faster and cause more liver-related health problems. Treatment with antiretroviral therapy has extended life expectancy, but liver disease induced by HBV and CV causes significant AIDS-related deaths. Recent studies explore accelerated fibrosis and disease progression.

**Conclusions:** This study depicted valuable insights into the research landscape surrounding antiretroviral effects on liver injury in HIV patients. The findings underscore the importance of continued monitoring and research to optimize the safety and efficacy of antiretroviral therapy. Future studies should focus on elucidating the underlying mechanisms of liver injury, identifying biomarkers for early detection, and developing strategies to minimize hepatotoxicity while maximizing the therapeutic benefits of ART for HIV patients.

**Keywords:** Antiretroviral therapy (ART), Liver injury, HIV, Hepatotoxicity




### PE-02

### Development of CA19-9-Targeting Chimeric Antigen Receptor-Expressing Cytotoxic Cells for the Treatment of Cholangiocarcinoma

**Deok Hwa Seo**[1], Pil Soo Sung[2]

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**Aims:** The glycan carbohydrate antigen 19-9 (CA19-9) is one of the most important and widely used biomarkers cholangiocarcinoma. However, therapies specifically directed against CA19-9 remain insufficient. Here, we have developed chimeric antigen receptor (CAR) targeting CA19-9.

**Methods:** Peripheral blood mononuclear cells (PBMCs) from adult healthy donors were isolated using Ficoll-Hypaque density gradient centrifugation. For preparation of non-viral, gene specific targeted chimeric antigen receptor (CAR) cells from PBMCs, the procedure was conducted following the manufacturer's instructions using a Femtobiomed CELLSHOT system.

**Results:** Two days after electroporation of PBMCs, expression of eGFP was observed in T cells and NK cells. The proportion of CD3-CD56+ natural killer (NK) cells in the culture was 12.5%, while CD3+ CD4+ T cells accounted for 46.1%, and CD3+ CD8+ T cells accounted for 41.2%. CA19-9 CAR engineered cytotoxic cells and untransduced cells co-cultured with CA19-9 expressing cell (Capan-2). The CCK-8 analysis revealed that the cell number significantly decreased in CA19-9 expressing cell treated CA19-9 CAR engineered cytotoxic cells compared to untransduced cells.

**Conclusions:** In our study, we demonstrated that CA19-9 targeting CAR expressing cytotoxic cells exhibited killing of CA19-9 expressing cancer cells. Here, we have developed chimeric antigen receptor (CAR)- expression cytotoxic cells targeting CA19-9.

**Keywords:** Chimeric antigen receptor, CA19-9, Electroporation, Cholangiocarcinoma

## PE-03

### Risk of Dyslipidemia and Cardiovascular Events in Chronic Hepatitis B Patients Taking Tenofovir Alafenamide: A National Wide Data Analysis

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[1]Department of internal medicine, Soonchunhyang University school of medicine, [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital

**Aims:** Tenofovir alafenamide fumarate (TAF) is known to be associated with hyperlipidemia. Despite many small-scale studies, evidence remains scarce. This study aims to assess the safety of tenofovir alafenamide fumarate regarding hyperlipidemia and cardiovascular diseases using a national cohort.

**Methods:** We conducted a retrospective analysis of claims data from the Health Insurance Review and Assessment Service over five years. Incidence rates of hyperlipidemia and major adverse cardiovascular events (MACE) were compared using 1:1 propensity score matching between TAF and tenofovir disoproxil fumarate (TDF) users. MACE was defined as the occurrence of ischemic heart disease, myocardial infarction, stroke, or percutaneous coronary intervention.

**Results:** The incidence of hyperlipidemia among TAF users was 21.53 per 1,000 person-years, compared to 10.15 among TDF users. The incidence rate ratio (IRR) was 2.12 (95% CI 1.92 - 2.35), indicating a higher incidence in TAF users compared to TDF users ($P<0.001$). After adjusting for other factors, Cox regression analysis showed TAF was significantly associated with hyperlipidemia compared to TDF (hazard ratio [HR] 1.83, 95% CI 1.66 - 2.02, $P<0.001$). The incidence of MACE was 2.26 per 1,000 person-years for both TDF and TAF users, with an IRR of 1.00 (95% CI 0.77 - 1.28), showing no significant difference between the groups ($P=0.978$). Cox regression analysis for MACE yielded an HR of 1.02 (95% CI 0.78 - 1.33), indicating no disparity between the groups ($P=0.906$).

**Conclusions:** TAF is associated with a higher incidence of hyperlipidemia than TDF. Although the incidence of MACE in the TAF group has not been significantly higher compared to the TDF group, long-term outcome results are warranted.

**Keywords:** Insurance claims data, Tenofovir disoproxil fumarate (TDF), Tenofovir alafenamide fumarate (TAF), Chronic hepatitis B

## PE-04

### Liver and Kidney Injury from Ethylene Glycol/Diethylene Glycol-Contaminated Cough Syrups in Children: A Literature Review

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**Aims:** Around 200 children in Indonesia perished in a public health emergency in 2022 as a result of cough syrups tainted with ethylene glycol (EG) and diethylene glycol (DEG). These industrial solvents are extremely hazardous and can seriously harm internal organs, especially the kidneys and liver. The purpose of this review was to examine the effects of cough syrups contaminated with EG/DEG on drug and toxic harm, with a particular emphasis on liver damage.

**Methods:** Prominent research works from the 2010–2023 publication window were found by searching the PubMed, EBSCO, and Web of Science databases. Acute kidney damage (AKI), liver function indicators in children under the age of eighteen, and studies on EG/DEG included.

**Results:** Twelve studies with proven occurrences of EG/DEG poisoning from tainted cough syrups were found during the study. AKI and EG/DEG exposure were shown to be significantly correlated in all investigations, with a pooled prevalence of 87.5% (95% CI: 82.3-91.7%). Furthermore, increased liver enzymes in afflicted children were identified in 4 (33.3%) of the

trials. Elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were the most often detected abnormalities, with reported prevalences of 21.4% (95% CI: 8.6-40.7%) and 28.6% (95% CI: 14.3-28.2%). The majority of patients had mild to moderate increases in liver enzymes that resolved with supportive therapy, but the severity of liver impairment varied.

**Conclusions:** This research reveals that infants who cough up EG/DEG-contaminated cough syrups can have liver dysfunction in addition to AKI, with an incidence of raised liver enzymes surpassing 20%. The terrible events that occurred in Indonesia highlight how crucial strict regulations and quality control procedures are to averting such incidents. In order to mitigate liver damage in the aftermath of such poisoning instances and to clarify the long-term effects of EG/DEG consumption on liver function, more study is required.

**Keywords:** Ethylene glycol/diethylene glycol, Cough syrup contamination, Liver injury, Children

## PE-05

### Parenteral Nutrition-Induced Liver Function Complications: Incidence, Risk Factors, and Prognosis

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Department of Internal Medicine, Gastroenterology and Hepatology, Soonchunhyang University School of Medicine, Bucheon, Korea

**Aims:** Parenteral Nutrition-Associated Liver Disease (PNALD) represents a significant complication in individuals undergoing parenteral nutrition. This study aims to explore the incidence, risk factors, and outcomes associated with PNALD, including abnormal liver function tests, in patients receiving parenteral nutrition.

**Methods:** A retrospective analysis of 500 patients receiving parenteral nutrition at a tertiary medical center between December 2022 and February 2023 investigated baseline characteristics, abnormal liver function test incidence and timing, risk factors for PNALD, and PNALD prognosis using logistic regression.

**Results:** The study, involving patients with a mean age of 68.7 years, reported a 24.4% incidence of abnormal liver function tests and an 8.2% incidence of PNALD. Risk factors for abnormal liver function tests included liver disease (odds ratio [OR] 2.064, 95% confidence interval [CI] 1.224-3.479), infection (OR 1.654, 95% CI 1.075-2.546), parenteral nutrition (PN) duration (OR 1.035, 95% CI 1.014-1.056), and PN calories (OR 1.001, 95% CI 1.000-1.002). Significant PNALD risk factors comprised liver disease (OR 3.623, 95% CI 1.670-7.858), lung disease (OR 3.648, 95% CI 1.615-8.240), recent surgery (OR 3.719, 95% CI 1.645-8.407), PN duration (OR 1.041, 95% CI 1.016-1.068), total cholesterol (OR 1.005, 95% CI 1.000-1.010), and HDL (OR 1.012, 95% CI 1.001-1.023). The majority of PNALD cases (85.3%) showed improvement with PN modification or cessation.

**Conclusions:** The study underscores that abnormal liver function tests and PNALD risks can emerge with short-term PN use. Identifying and addressing patient-specific risk factors are vital for predicting and preventing PNALD onset.

**Keywords:** Parenteral nutrition, Parenteral nutrition-associated liver disease, Liver injury, Abnormal liver function test

## PE-06

### Pharmacovigilance Study on Potential Interaction Aspects of Use in Inhibiting Covid-19 Virus in Indonesia

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**Aims:** Only clinical trials were being conducted to treat COVID-19 at the last time, and there was no known cure. Antiviral medication therapy is administered as a substitute to stop virus-transmitting infected cells. As a result, medication safety and the possibility of adverse drug reactions (ADRs) must be taken into consideration when managing treatment. The therapeutic process may be hampered by unfavorable incidents that could arise—actual or hypothetical. Pharmaceutical vigilance research is one strategy to lessen this. This study aims to determine the characteristics of patients and the potential for drug interactions in COVID-19 patients at Hospital X in Indonesia and to determine the pharmacovigilance of drugs used as therapeutic drugs for COVID-19 disease obtained in journals.

**Methods:** The research method used uses qualitative data and is described descriptively. The materials used are research Results: published in national and international scientific journals and secondary data through medical records of COVID-19 patients hospitalized X from March to December 2020 in Indonesia.

**Results:** Based on the study, the results showed that the 30 patients with COVID-19 were dominated by men (60%) and aged between 46 to 55 years (50%). Data on potential drug interactions showed that 28 out of 30 patients had the potential to experience drug interactions with severe (9.23%), moderate (74.62%), and mild (16.15%) categories. Drugs that are widely used in the treatment of COVID-19 disease include Hydroxychloroquine, Chloroquine, Remdesivir, Azithromycin, Tocilizumab, Lopinavir/Ritonavir, Darunavir/Cobicistat, Ribavirin, Umifenovir, and Ceftriaxone. The most common side effects include cardiac disorders, such as QT interval prolongation, gastrointestinal disorders, elevated transaminase enzymes, liver failure, acute renal failure, decreased hearing, and hepato-

biliary disorders.

**Conclusions:** It can be concluded that the drugs used in the use of COVID-19 therapy cause various unwanted side effects so that monitoring before and after therapy is needed such as ECG monitoring, monitoring IL-6 levels, and checking laboratory results in monitoring efforts.

**Keywords:** COVID-19 virus, Interaction aspects, Pharmacovigilance

## PE-07

### Unveiling the Concealed Risks of Using Bajakah Kalalawit Leaves (Uncaria gambir Roxb.) through Toxicity Tests on Liver

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[1]Department of Biology, Universitas Palangka Raya, Indonesia, [2]Department of Pharmacy, Universitas Palangka Raya, Indonesia, [3]Department of Biology, Universitas Palangka Raya, Indonesia

**Aims:** Bajakah Kalalawit is a well-known endemic plant of Kalimantan in Indonesia. Since the spread of information on the efficacy of Bajakah Kalalawit as an anti-inflammatory, antidiabetic and even anticancer, the number of people who use it has also increased. People drink Bajakah Kalalawit leaves periodically with a relatively long period of time to increase endurance. This study aims to determine the level of toxicity of Bajakah Kalalawit leaves on liver histopathology of mice that are given oral injection.

**Methods:** The research conducted was experimental in the laboratory using mice. Bajakah leaf extract was made using reflux technique, then given orally to mice at a dose of 4 treatment groups such as 0 mg / kg (control), 52.5 mg / kg, 105 mg / kg and 210 mg / kg every day for 30 days. Furthermore, the histological structure of the mice liver was examined.

**Results:** Based on the observation of the histopathological images of the liver in mice, the microscopic picture of liver tissue in the control treatment group looks normal, the cells are dominated by normal cells with clearly visible nuclei and round shape. In contrast to the control, the use of Bajakah Kalalawit leaf extract in doses of 52.5 mg/kg, 105 mg/kg and 210 mg/kg orally for 30 days showed a toxic effect on the liver of mice characterized by necrosis and hydropic degeneration. Necrosis is the death of liver cells causing hepatocytes can not return to normal form.

**Conclusions:** The use of Bajakah at doses of more than 52.5 mg/kg for 30 days can cause liver cell damage. The right dose is needed for the use of Bajakah over a long period of time. In addition, more modern processing is needed so that Bajakah can be widely used without causing adverse side effects.

**Keywords:** Bajakah kalalawit, Liver, Histopathology, Necrosis

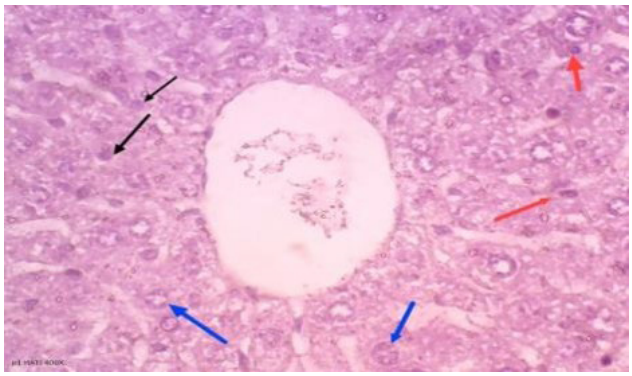

**Figure 1.** Liver Hispatology of Mice treated with 52.5 mg dose for 30 days (black arrows indicate normal cells; red arrows indicate necrosis; blue arrows indicate hydropsis degeneration).

# Liver Cirrhosis, Portal Hypertension with Cx. Basic

## PE-01

### Childhood Non-Hodgkin Lymphoma (NHL) and Myeloproliferative Neoplasm with Buddh Chiari syndrome: A Rare Presentation

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Department of Hemat-Oncology and Bone Marrow Transplant, India

**Aims:** Budd Chiari syndrome is a very rare disease caused by an obstruction of the hepatic veins. Myeloproliferative neoplasm (MPNs) is defined as clonal disorders of the hematopoietic stem cell in which an exaggerated production of terminally differentiated myeloid cells occurs. Classical, Philadelphia negative MPNs that is polycythemia vera, essential thrombocytopenia and primary myelofibrosis, exhibit propensity towards the development of thrombotic complications that can occur in unusual sites e.g. Portal, splanchnic or hepatic veins, the placenta or cerebral sinuses. Prothrombotic hematological disorders, in particular MPNs, are identified in a significant proportion of patients with Budd Chiari syndrome. Here, we present a rare case of Budd Chiari syndrome with MPN managed by a multidisciplinary team of experts.

An 8-year-old female was diagnosed with Budd Chiari syndrome. She complained of fever, weight loss and abdominal swelling and was evaluated and diagnosed as T-cell lymphoma.

**Methods:** Her investigations revealed hemoglobin- 12.6g/dl, total leukocyte count- 14.06/ $mm^3$ platelet count-5,37,000/ microliter with ANA- negative and normal high-performance liquid chromatography/electrophoresis. Iron profile and viral markers were normal.

Her flow cytometry revealed CD3, CD5, CD52, CD2- bright positive, CD7, CD4, CD95- moderate positive, CD8- dim positive. Her immunophenotyping findings were consistent with T-cell Prolymphocytic Leukemia, a subtype of NHL. Bone marrow aspiration were normal. CT-abdomen showed hepatomegaly with hetero-dense parenchyma and enlarged splenomegaly and ascites.

**Results:** Her hypercoagulable parameters were normal along with the absence of lupus anticoagulant. Thrombophilic work-up revealed a JAK-2 positive mutation with methylenetetrahydrofolate reductase (MTHFR) gene mutation. She was started on an anti-coagulant, blood thinner, and hydroxyurea. Her liver USG revealed enlarged liver with obliterated IVC for which IVC and hepatic vein stenting was done.

**Conclusions:** Childhood disease with MPNS is rare and by identifying the proper cause appropriate management can be done. Although rare, in childhood associated with Budd Chiari syndrome and other thrombotic complications at rare sites, we should rule out MPNs.

**Keywords:** Budd chiarl, MPN, NHL, JAK-2

# Liver Cirrhosis, Portal Hypertension with Cx. Clinical

## PE-01

### Predictive Performance Concerning Distinct SMI Cut-Offs of Sarcopenia for Mortality among Cirrhosis

**Chao Sun**, Han Wang

Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, China

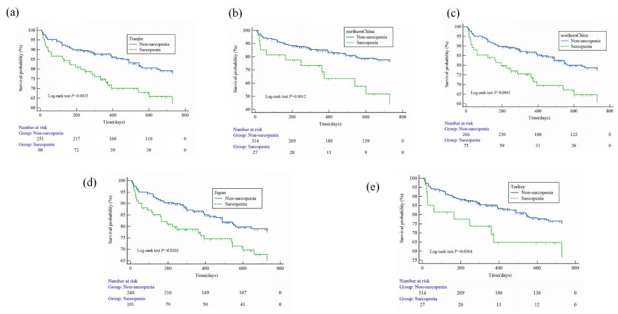
**Aims:** Although the clinical relevance of sarcopenia has been verified in the context of cirrhosis, there are insufficient data concerning cut-offs of CT-demarcated skeletal muscle index (SMI) in different ethnicities. We aimed to clarify the predictive performance of distinct SMI values-defined sarcopenia for prognostication among cirrhosis.

**Methods:** We prospectively enrolled 341 inpatients due to cirrhosis-associated acute deterioration. A wealth of cut-offs concerning SMI (TJ, northernChina, southernChina, Japan and Turkey criteria) were testified to determine 2-year all-cause mortality according to Kaplan-Meier survival curve with log-rank test and multivariate Cox regression.

**Results:** Sarcopenia was present in 26.4%, 7.9%, 22%, 29.6% and 7.9%, respectively, according to TJ, northernChina, southernChina, Japan and Turkey criteria. Survival curve showed significant differences between patients with and without sarcopenia defined by all criteria (*P* for log-rank test < 0.05). Univariate Cox regression indicated age, BMI, CTP class, MELD-Na, creatinine, total bilirubin, sodium, albumin and sarcopenia were significantly associated with long-term mortality. Further multivariate Cox regression by adjusting age, BMI and MELD-Na revealed that northernChina-defined sarcopenia was independently associated with mortality (HR = 1.99, *P*=0.0431), while TJ criteria-defined sarcopenia exhibited marginally significant association (HR = 1.62, *P*=0.0595). Moreover, sarcopenia defined by northernChina (HR = 1.93, *P*=0.0453), TJ (HR = 1.73, *P*=0.0280), and southernChina criteria (HR = 1.73, *P*=0.0368) was significantly associated with mortality by adjusting age, BMI and CTP class.

**Conclusions:** Our findings provide strong evidence to develop continent-based SMI cut-offs to identify sarcopenic cirrhotic patients, considering its prognostic importance.

**Keywords:** Sarcopenia, Liver cirrhosis, Skeletal muscle index, Mortality, Cut-offs




## PE-02

### Zinc Deficiency in Patients with Chronic Liver Disease: Single Center Study

**Lkhagvasuren Batbaatar**, Doljinsuren Enkhbayar, Nyam Biziya

Department of Biomedical Engineering, Mongolian University of Science and Technology, Dornod Medical Center, Choibalsan, Mongolia

**Aims:** This study aimed to assess the prevalence of serum zinc deficiency among patients with chronic liver disease (CLD) in clinical practice and examine its association with clinical characteristics.

**Methods:** We analyzed 397 patients with CLD, including 195 with liver cirrhosis, admitted to Dornod Medical Center in 2023-2024.

**Results:** Zinc deficiency (< 60 μg/dL) was found in 38.1% of patients, with 54.8% prevalence among those with liver cirrhosis. Including marginal deficiency (< 80 μg/dL), 80.8% of patients were affected, with 89.5% among cirrhosis cases. Serum zinc levels correlated most strongly with serum albumin levels, with 92.3% of patients with albumin.

**Conclusions:** Zinc deficiency is prevalent in CLD patients, particularly in those with liver cirrhosis. Regular monitoring of serum zinc levels, especially in cirrhosis patients, is recommended.

**Keywords:** Chronic liver disease (CLD), Zinc deficiency, Liver Cirrhosis

## PE-03

### Sarcopenia and Sarcopenic Obesity in Liver Cirrhosis in the Kazakh Population. Experience of the National Research Oncology Center

Khalima Malgazdarova, Marzhan Zhanasbaeva, Aybar Agynbay, Jakipov Murat, Ilyas Sagyndykov

National Research Oncology Center, Kazakhstan

**Aims:** Sarcopenia and sarcopenic obesity are frequent complications in cirrhotic patients and associated with a poor prognosis. We for the first time assessed the frequency of sarcopenia and sarcopenic obesity in patients with liver cirrhosis among the kazakh population.

**Methods:** Data of patients who came to our clinic with a diagnosis of liver cirrhosis in the period from 2021-2022. The assessment was carried out according to the results of computed tomography scans, using the skeletal muscle indices of the third lumbar vertebra (SMI).

**Results:** A total of 44 patients with liver cirrhosis were enrolled. Cirrhosis etiology was hepatitis C virus in 12 patients (27%), hepatitis B+D in 8 (18%), cryptogenic in 5 (11%), hepatitis B virus in 3 (7%), hepatitis B+C in 2 (5%), autoimmune hepatitis in 5 (11%), primary biliary cholangitis 5 (11%), alcohol in 3 (7%), primary sclerosing cholangitis in 1 (2%). Sarcopenia was present in 30 patients (68%), 10 had sarcopenic obesity (23%). Patients with sarcopenia were more often women (73%), mean age was 58 years, mean BMI 24.4, SMI 52.4 $cm^2/m^2$, mean albumin 35.1 g/l, bilirubin 45 umol/l, INR 1.2 and maximum levels MELD Na 26, Child-Pugh 8, hepatic encephalopathy was observed in 36%, esophageal varices in 76%, ascites in 43%.Patients with sarcopenic obesity were more often women (60%), mean age 52 years, mean BMI 27.7, SMI L3 48.5, bilirubin 25.3, albumin 28.9, INR 1.3, MELD Na 16, Child-Pugh 9. They had esophageal varices in 70%, hepatic encephalopathy in 70%, ascites in 60%. Bleeding from esophageal varices in both cases developed in 30% of patients.

**Conclusions:** Sarcopenia and sarcopenic obesity were common in patients with cirrhosis among the kazakh population treated at our center, and older age, female patients, and normal BMI were associated with an increased risk of developing sarcopenia in patients with cirrhosis.

**Keywords:** Sarcopenia, Cirrhosis, Sarcopenic obesity, Skeletal muscle indices

## PE-04

### Endoscopic Prophylaxis and Treatment of Portal-Genesis Oesophageal Haemorrhage

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**Aims:** To evaluate the treatment efficacy of pneumatic endoscopic band ligation of bleeding esophageal varices (EV).

**Methods:** The experience of applying pneumatic endoscopic ligation treatment in the patients managed at the General Surgery Unit of the Almaty City Emergency Hospital during 2020–2024 was analyzed. Endoscopic ligation is a modern minimally invasive and less traumatic intervention used to markedly reduce mortality and improve quality of life in patients with portal hypertension syndrome. Th e evidence on 76 patients following endoscopic EV ligation was summarized. Th e patient age ranged from 15 to 71 years (mean 46.26 years); 40 men (52.6 %) and 36 women (47.4 %) were included. Among the 76 patients, portal hypertension was caused by viral cirrhosis in 38, hepatitis B in 5, delta agent hepatitis B in 18, hepatitis C in 13, a hepatitis B–C combination in 1 and a delta agent hepatitis B — hepatitis C combination in 1 patient. In 21 patients, cirrhosis was of unknown aetiology. A portal vein malformation was observed in 13 people of whom 4 had it combined with thrombosis.

**Results:** A total of 94 ligation procedures were performed in 76 patients with grade II–III OV. Some patients needed to undergo the procedure several times, 18 patients had 2 sessions. Two cases required 3 and 4 sessions each. Moderate oesophageal soreness was reported in 32 patients for 1–6 days following the ligation. No complications were registered during the operation. In early postoperative period, 2 patients developed recurrent bleeding, with haemostasis reachieved by a repeated vein ligation below bleeding.

**Conclusions:** Hence, small invasiveness and minor traumatism coupled with high efficiency and lesser complications render endoscopic ligation the method of choice in primary and secondary prophylaxis and treatment of OV. Endoscopic ligation improves the patient's quality of life, allows an extra time for conservative treatment and longer period to liver transplantation.

**Keywords:** Oesophageal and gastric varices, Oesophageal bleedin, Pneumatic band ligato, Portal hypertension

## PE-05

### Synchronous Splenectomy and Hepatectomy in the Management of Hepatocellular Carcinoma with Liver Cirrhosis and Hypersplenism: Assessing Indications and Outcomes

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**Aims:** Hepatocellular carcinoma (HCC) often presents concomitantly with liver cirrhosis and hypersplenism, posing challenges in treatment strategies. Synchronous splenectomy and hepatectomy have emerged as a potential approach, yet indications for its utilization remain to be clearly defined.

**Methods:** A retrospective analysis was conducted on 10 patients (9 males, 1 female; mean age 56.9±8.9 years) who underwent synchronous splenectomy and hepatectomy for HCC with cirrhosis and hypersplenism. Preoperative parameters including Total Bilirubin, Prothrombin, and Platelet counts were assessed, along with Child-Pugh classification. Surgical procedures, complications (graded using Clavien-Dindo classification), and postoperative outcomes were analyzed.

**Results:** Of the 10 patients, 9 were classified as Child-Pugh A and 1 as Child-Pugh B preoperatively. Majority (7/10) underwent major hepatectomy. The postoperative course showed a reduction in Total Bilirubin (16.63±18.03 micromol/lit), stabilizing Prothrombin levels (70.7±14.9), and a significant increase in Platelet counts (275.7±139.05 G/l). Complication rate was low, with one patient experiencing a grade IVb complication, while the rest had complications ranging from 0 to II. Two patients experienced recurrence at 11 and 13 months post-surgery, while the remaining seven showed no signs of recurrence to date.

**Conclusions:** Synchronous splenectomy and hepatectomy in the treatment of HCC with liver cirrhosis and hypersplenism demonstrate promising outcomes in terms of postoperative liver function and platelet counts. Despite the need for careful patient selection and meticulous surgical technique, this approach offers a viable option in selected cases. Further studies are warranted to refine indications and optimize patient selection for improved outcomes.

**Keywords:** Hepatectomy, Splenectomy, Hypersplenism, Liver cirrhosis

## PE-06

### Combine Surgery and Interventional Radiologic Method to Achieve Curative Treatment for Patients with HCC and Clinically Significal Portal Hypertension

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Department of Liver - GI Surgery and Oncology, National Hospital of Tropical Diseases, Vietnam

**Aims:** Clinically significant portal hypertension (CSPH) has been identified as an important prognostic factor in patients with HCC, and remains a relative contraindication for liver resection.

Liver transplantation is the treatment of choice but still out of question with many patients.

We combine some surgeries and interventional radiologic method to achieve curative treatment.

**Methods:** We report of 3 patients:

Case 1: Fundectomy and Periesophagogastric Devascularization combined with Hepatectomy for Patient with HCC and Isolated gastric varices (IGOV 1), hypersplenism.

Case 2: Distal Splenorenal Shunt combined with Hepatectomy for patient with HCC and reccurenced Esophageal Varices Bleeding.

Case 3: Saphenoperitoneal Shunt Surgery combine with Intermittent Hepatic Vein Balloon Occlusion During Radiofrequency Ablation for patient with HCC and refractory ascites.

**Results:** 3 patients have recovered well with no complications.

**Conclusions:** Combination different methods of surgery and IR could be achieve curative treatment for selected patients with HCC and portal hypertension.

**Keywords:** Portal hypertension, HCC

## PE-07

### The Experience of Using a Modified Endoscopic Ligator for The Treatment of Bleeding from Esophageal Varicose Veins

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**Aims:** To evaluate the effectiveness of endoscopic ligation with the modified ligator for prevention and treatment of bleeding from varicose esophageal veins.

**Methods:** It is analyzed the experience of application and introduction of the endoscopic treatment with modified ligator of the patients treated at the Department of General Surgery of the State Institution "Clinical hospital of the Presidential and Governmental Affairs Department of the Kyrgyz Republic" in 2019–2020.Total procedures of endoscopic ligation by the modified ligator were performed to 31 patients with previously diagnosed with the diagnosis of "Varicose veins of the esophagus of the II–III degree".

**Results:** After endoscopic ligation of varicose veins outside the esophagus in all cases the patients had no pain syndrome in the esophageal projection. In 7 cases there was moderate hyperthermia up to 37.8°C. There were no complications during the operation, and there were no early and late complications in the form of recurrent bleeding. The degree of varicose veins eradication in the esophagus was estimated 1 month after the procedure. There were no varicose veins in 27 patients out of 31 patients on control esophagoscopy 3–4 weeks after EL, in 3

of them "Varicose veins of the esophagus of the I degree" was detected, and in 1 case – "Varicose veins of the esophagus of the II degree". The maximum follow-up period of the patients with no progressing varicosity after the performed endoscopic ligation of esophageal varicose veins with a modified ligator was 1 year.

It should be concluded that endoscopic hemostasis with the modified ligator is not less effective in the prevention and treatment of variceal bleeding than ligators of other manufacturers.

**Conclusions:** Endoscopic ligation is a highly effective method in the prevention and treatment of bleeding from esophageal varices in patients with complications of portal hypertension syndrome, which can reduce mortality by 2 times.

However, this procedure using a modified ligator still requires additional development of the execution technique.

**Keywords:** Modified endoscopic ligator, Varicose veins, Liver cirrohsis, Portal hypertansion

## PE-08

### Fecal Calprotectin as a Potential Non-Invasive Diagnostic Biomarker for Hepatic Encephalopathy: A Meta-Analysis

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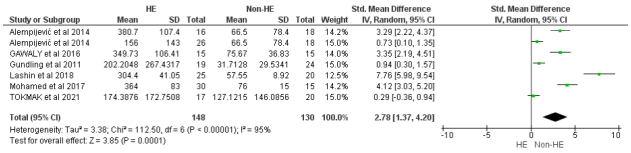
**Aims:** Given that patients may exhibit mild cognitive impairment, diagnosing hepatic encephalopathy (HE) remains a clinical challenge. Early detection of HE is crucial because effective treatment lowers morbidity and mortality. Expectedly, there is the need of non-invasive readily available biomarker for the diagnosis of HE. One such biomarker is fecal calprotectin which is the established marker of intestinal inflammation. Among cirrhotic patients with ascites, intestinal inflammation brought on by bacterial translocation and overgrowth is one of the main pathophysiological processes of HE. Accordingly, diagnostic potential of fecal calprotectin for HE was evaluated in this meta-analysis.

**Methods:** From the inception to January 2024, the Pubmed, Google Scholar, and Embase were searched for studies that assessed fecal calprotecin of cirrhotic patients with and without HE. Results comprised the standardized mean difference (SMD) in the fecal calprotectin of the two groups with a 95% Confidence Interval (CI). According to the heterogeneity, the fecal calprotectin values were analyzed using the Revman 5.1 program using either a fixed or random effect.

**Results:** The meta-analysis included six studies with 278 cirrhotic patients of which 148 had HE and 130 did not have HE. The analysis revealed a significantly higher fecal calprotectin in HE patients as compared to non-HE patients (SMD: 2.78, CI: 1.37-4.20, $I^2$=95%, *P* value =0.0001). Expectedly, fecal calprotectin was significantly higher in cirrhotic individuals as compared to healthy controls among the included studies (SMD: 1.80, CI: 1.07-2.53, $I^2$=88%, *P* value =0.00001). Furthermore, the fecal calprotectin level increased with the increasing grading of HE according to West Haven Criteria.

**Conclusions:** Fecal calprotectin may be considered as a non-invasive reliable diagnostic marker for HE. Fecal calprotectin level can potentially be used for grading of HE. Fecal calprotectin level can guide the treatment of HE as well.

**Keywords:** Hepatic encephalopathy, Fecal calprotectin, Liver cirrhosis




## PE-09

### The Value of Platelet-Albumin-Bilirubin Score in Predicting Early Rebleeding and In-Hospital Mortality in Cirrhotic Patients with Acute Variceal Bleeding

Le Thi Thu Hien[1], Hoang Thanh Phuong[3], Luong Thi Dao[3], Pham Như Quynh[1]

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**Aims:** The albumin, bilirubin, platelet level was validated as a prognostic indicator in patients with cirrhosis. Incorporating the platelet-albumin-bilirubin (PALBI) score may improve validity in predicting outcome of acute variceal bleeding in patients with cirrhosis.

To determine the value of platelet-albumin-bilirubin (PALBI) score in predicting early rebleeding and in-hospital mortality in cirrhotic patients with acute variceal bleeding (AVB).

**Methods:** A cross-sectional descriptive study carried out on cirrhotic patients with AVB in Thai Nguyen Nation Hospital since January 2023 to February 2024. Child Turcotte Pugh (CTP) class, and PALBI scores were calculated on admission, and were correlated to the outcome of variceal bleeding. Areas under the receiving-operator characteristic curve (AUROC) were calculated for survival and rebleeding.

**Results:** Mean age was 53.8 years; male (73.2%), CTP-A (6.5%), CTP-B (31.3%), CTP-C (62.2%), PALBI-1 (19.8%), PALBI-2 (17.2%), and PALBI-3 (63%). PALBI score had a good prognostic power in in-hospital mortality (AUROC = 0.83; 95%CI: 0.7-0.93, *P*<0.01), at the cut-off value of - 1.65 had a sensitivity of 85.9% and a specificity of 65.1%; has good value in predicting early

rebleeding (AUROC = 0.76, 95%CI: 0.61-0.86, *P*<0.01), at the cut-off value of - 1.51 has a sensitivity of 61.0 % and specificity 86.1%.

**Conclusions:** PALBI score has a significant perfomance in the prognosis of early rebleeding and in-hospital mortality in cirrhotic patients with AVB.

**Keywords:** Palbi scale, Gastrointestinal bleeding, Esophageal varices, Cirrhosis

## PE-10

### A Report of Lesions of Liver in Autopsy

**Harshita Dubey**, Amar Ranjan, Shuvrajyoti Mondal

All India Institute of Medical Sciences, New Delhi, India

**Aims:** Lesions of the liver cause significant morbidity and mortality even without causing significant signs & symptoms. A liver biopsy may not give the exact picture. An autopsy study may be a better choice.

**Methods:** A retrospective analysis of the histopathological findings of autopsy cases was done during the years 2017–20. Only those cases were selected that showed positive histopathological findings in the heart, lung, liver, spleen, kidney, and brain. A total of 70 cases were taken. The age group was between 4 days and 77 years. Males and females were 52 and 18, respectively. Out of a total 70 cases, 41 showed significant lesions in the liver, which were analyzed.

**Results:** The most common lesion was a moderate-to-severe degree of hepatic steatosis, which showed foci of cirrhosis 14/70 (20%). Grossly, most of the cases were mixed types of cirrhosis; macronodular & micronodular. The next prominent group of diseases was cirrhosis (9/70), 12.8%. Other common diseases were chronic hepatitis & granuloma, 4/70 (5.7%) each. Cardiac cirrhosis was seen in 2/70 cases. Nonalcoholic hepatic steatosis was seen in a case of an 11-month-old male baby who presented with umbilical granuloma on gross examination, and his lung also showed pneumonic features. Other conditions, such as hydatid cyst, metastasis from primary cancer of unknown origin, and acute inflammatory cell infiltration in chronic hepatitis, were seen in 1/70 cases.

**Conclusions:** Histopathological examination of postmortem specimens is conducted at limited centers in our country. This diminishes the opportunity of medical professionals to learn about liver pathology.

**Keywords:** Liver biopsy, Liver diseases, Autopsy

**Table 1.** Lesions of liver in autopsy

| S. No | Disease | number | % |
|---|---|---|---|
| 1 | Moderate to severe degree of Hepatic steatosis progressing to cirrhosis | 14 | 20 |
| 2 | Chronic hepatitis with cirrhosis | 9 | 12.8 |
| 3 | Chronic hepatitis | 4 | 5.7 |
| 4 | Granuloma | 4 | 5.7 |
| 5 | Cardiac cirrhosis | 2 | 2.8 |
| | Nonalcoholic hepatic steatosis | 1 | 1.4 |
| 6 | Hydatid cyst | 1 | 1.4 |
| 7 | Acute on chronic hepatitis | 1 | 1.4 |
| 8 | metastasis | | |
| 9 | Focal degeneration | 1 | 1.4 |
| 10 | | 1 | 1.4 |
| 11 | Necrotic liver | 1 | 1.4 |
| 12 | | 1 | 1.4 |
| 13 | Chronic hepatitis with vascular degeneration | 1 | 1.4 |
| 14 | Hepatic steatosis mild | 29 | 41.4 |
| 15 | Total | 70 | |

# Liver Failure, Acute

## PE-01

### Exploring Self-Efficacy Levels Among Chronic Liver Disease Patients in Indonesia: Implications for Healthcare Support and Intervention

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**Aims:** Chronic liver diseases are prevalent worldwide and pose significant health risks. While medical care traditionally focuses on physical well-being, there's a growing recognition of the importance of addressing patients' emotional and social needs, especially as chronic diseases become more common in developed nations. This research aimed to explore the levels of self-efficacy among chronic liver disease patients in Indonesia, recognizing the significance of self-belief in managing such conditions.

**Methods:** This research employed a cross-sectional design and involved 100 chronic liver disease patients from general hospitals using the Chronic Disease Self-Efficacy Scales Indonesian version.

**Results:** The study found that the majority of participants reported moderate self-efficacy (57.8%), followed by high self-efficacy (37.2%). The prevalence of moderate self-efficacy can be attributed to the challenging symptoms experienced by individuals with chronic liver disease, such as chronic fatigue, abdominal discomfort, swelling, itchiness, nausea, vomiting, and loss of appetite, all of which can impact their confidence in managing their condition. To support these patients effectively, healthcare professionals should focus on fostering positive activities and improving coping skills to enhance their self-efficacy.

**Conclusions:** In conclusion, this study sheds light on the levels of self-efficacy among chronic liver disease patients in Indonesia. The findings reveal a predominance of moderate self-efficacy among participants, likely influenced by the challenging symptoms associated with the condition. Given the crucial role of self-efficacy in managing chronic diseases, healthcare professionals should prioritize interventions aimed at strengthening patients' belief in their ability to cope and manage their condition effectively. Strategies such as engaging in positive activities and enhancing coping skills can empower patients and contribute to better disease management outcomes. Moreover, future research could explore additional factors influencing self-efficacy in this population and evaluate the effectiveness of tailored interventions in improving patients' overall well-being and treatment adherence.

**Keywords:** Chronic liver disease, Self-efficacy, Healthcare intervention, Symptom management

## PE-02

### Analysis of Conformational Changes in The Aromatic Residue Binding Site of FXa Using Molecular Simulations

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**Aims:** Cirrhosis, an irreversible stage of liver fibrosis, significantly impacts hemostasis due to diminished liver synthetic function. Patients with cirrhosis face heightened bleeding risk, particularly gastrointestinal bleeding and coagulopathy. Human coagulation factor X (FX) is a vital enzyme in blood clotting, regulated by intricate proteolytic events. FXa, the activated form, interacts with factor Va, leading to prothrombin activation. Understanding FXa's conformational dynamics is crucial. Molecular dynamics simulations, an invaluable tool, offer insights into FXa's structural flexibility. This study focuses on analyzing conformational changes in the aromatic residue binding site of FXa through a 30-ns simulation, shedding light on its functional mechanism.

**Methods:** Selected PDB entries 1c5m (open FXa) and 3cen (closed FXa) for MD simulations. GROMACS with GROMOS96 force field analyzed RMSD, gating distance, and hydrogen bonds over 30 ns. Systems neutralized, short MD runs performed in explicit SPC water boxes. MD simulations used PME for electrostatic interactions and LCPO for SASA calculations, saving coordinates every 1 ps.

**Results:** Molecular simulations of FXa's aromatic binding site reveal notable conformational changes. RMSD analysis indicates greater flexibility in Tyr-99 of the closed system (0.18 vs 0.12). The gating distance, separating Tyr-99 and Phe-174, is significantly larger in the open system (9.23–11.33Å) than the closed system (4.69–6.35Å), allowing diverse substrate entry. Ligand-deleted closed system simulations show a dynamic transition from a gating distance of 4.70Å to 10.65Å after 6 ns. Distinct gating distances affect solvent-accessible surface area (SASA), highlighting varied structural environments in open and closed FXa states. Hydrogen bond analysis emphasizes a more extensive network in the closed state, particularly the Ile-176-NH and Phe-174-O bond with a notable 91.7% lifetime, crucial for maintaining the closed conformation relevant to hemostasis.

**Conclusions:** 30-ns MD simulations uncover FXa's aryl-binding site dynamics. The open state, with a larger gating distance, suits variable-size substrates and exhibits a larger hydrophobic SASA. The ligand-induced closed state displays a tailored, smaller S4 pocket for specific substrates, highlighting FXa's crucial role in blood coagulation regulation.

**Keywords:** FXA conformation, Molecular dynamics simulations, Aromatic binding site, Gating distance

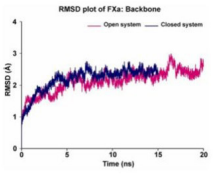


Fig 1. RMSD time course for backbone atoms of the serine protease domain of the two different conformations of FXa

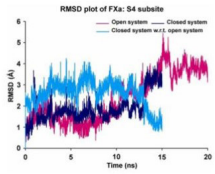


Fig 2. RMSD time course for all-atoms of S4 subsite (Tyr-99, Phe-174 and Trp-215) of the two different conformations of FXa

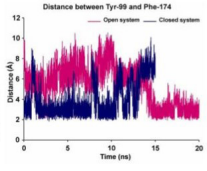


Fig 3. Conformational transitions in the S4 binding site shown by the distance spanned by the two gating residues (Tyr-99 and Phe-174) in the two different conformations of FXa

## PE-03

### Formulating the Degenertive Changes Are Associated with Acute Infective Viral Hepatitis Patients

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[1]Department of Dentistry, CHC, Siyana, Bulandsehar, U.P, India, [2]Department of Biochemistry, RDMC, Banda, U.P, India

**Aims:** Liver is the only organ that possesses the enormous capability of regeneration in human. Since the liver has considerable functional reserve and as a consequence, simple liver function tests like serum albumin and bilirubin concentrations are insensitive indicators of liver diseases. The results obtained from biochemical tests are not frequently specific, as they show the fundamental pathological processes common to various diseased conditions, and provide limited diagnostic information. Therefore, tests reflecting liver cell damage particularly in monitoring the activities of certain hepatic enzymes in serum or plasma are often superior in this regard. Liver disease is accompanied by an increased production of free radicals. Hepatocyte membranes are quite rich in PUFA, which are susceptible to attack by free radicals.

**Methods:** This study was performed on blood samples from 30 patients of age group ranging from 20 to 60 years with acute infective hepatitis sent for investigations to diagnostic clinical laboratory at RDMC, Banda, U.P. Patients with other diseases such as Diabetes Mellitus, Cardiovascular Diseases, Hypertension and kidney diseases were excluded from the study. Healthy voluntary blood donors (HVBD) attending the blood bank of our hospital served as the control group. Thirty venous samples from the patients with AIH and 30 samples collected from HVBD which served as the control group out of which 15 males and 15 females (for both the groups) were analyzed.

**TABLE I**
**COMPARATIVE ACCOUNT OF ROUTINE LIVER FUNCTION PROFILE BETWEEN CONTROLS AND PATIENTS GROUP**

| PARAMETER | CONTROL (N=30) MEAN ± SD | PATIENTS (N=30) MEAN ± SD |
|---|---|---|
| Total bilirubin (mg/dl) | 0.75 ± 0.12 | 8.00 ± 5.00** |
| Direct bilirubin (mg/dl) | 0.25 ±0.07 | 3.40 ± 0.50** |
| Indirect bilirubin (mg/dl) | 0.70 ±0.20 | 5.10 ± 1.50** |
| Total Protein (g/dl) | 7.80 ± 1.50 | 8.00 ± 1.20^ |
| Albumin (g/dl) | 3.00 ±0.50 | 3.98 ± 0.40* |
| SGOT (AST) (IU/L) | 30.60 ± 6.60 | 400.10 ± 98.50** |
| SGPT (ALT) (IU/L) | 24.66 ± 6.50 | 370.50 ± 97.98** |
| ALP (IU/L) | 80.10 ± 20.00 | 110.22 ± 32.18^ |

^Not significant
*P < 0.01
**P <0.001
n= Number of samples

**TABLE II**
**COMPARISON OF TOTAL BILIRUBIN, MDA LEVEL, SOD AND CATALASE ACTIVITIES IN ACUTE INFECTIVE HEPATITIS PATIENTS AND CONTROLS**

| PARAMETER | CONTROL (N=30) MEAN ± SD | PATIENTS (N=30) MEAN ± SD |
|---|---|---|
| Total bilirubin (mg/dl) | 0.70 ± 0.10 | 8.00 ± 4.00 ** |
| SOD (Units/gm Hb) | 4050.10 ± 798.10 | 2000.30 ± 330.60* |
| CAT (Units/gm Hb) | 6000.80 ± 1132.27 | 2642.54 ± 510.10* |
| MDA (nmol/dl) | 130.35 ± 34.00 | 710.20 ± 12.50** |

*P < 0.01
**P <0.001
n= Number of samples

**Results:** Patients with AIH showed significantly higher levels of serum Bilirubin and enzymes, namely, SGOT and SGPT as compared to that in the control group ($P$<0.001). The noticeable point here is that the serum total bilirubin values in the patient group ranged from 2.4 to 19.3 mg% and the direct bilirubin from 0.5 to 8.6 mg%. The correlation between Serum Bilirubin and Serum MDA was significantly positive.

**Conclusions:** Bilirubin *in vivo* as a potent-anti-oxidant, anti-mutagen, anti-compliment and an endogenous tissue protector. The increased serum bilirubin levels could be looked as a compensatory/retaliatory phenomenon in response to cellular per-oxidative changes. The same happening is true for all the enzymatic parameters except that for ALP. Antioxidant enzymes such as SOD, catalaze and glutathione peroxidase are enzymes that remove $O_2$ and $H_2O_2$ from tissues. SOD activity is especially important for antioxidant defense.

**Keywords:** Hepatitis, Antioxidant, MDA, Catalase

# Liver, Infectious Disease

## PE-01

### Prevalence and Associated Factors of Liver Disease in Indonesia: Analysis from the Indonesia Family Life Survey

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**Aims:** Liver disease is a significant health concern globally, and understanding its prevalence and associated factors is crucial for effective prevention and management strategies. This study examines the prevalence and associated factors of liver disease in Indonesia.

**Methods:** This study included 22,797 individuals who met specified inclusion and exclusion criteria. Bivariate and multivariate analyses, including logistic regression, were conducted to explore the relationships between liver disease and various risk factors, including demographics, lifestyle, behavior, psychosocial factors, comorbidities, and insurance status.

**Results:** The prevalence of liver disease in the study population was found to be 1.1%. Participants had a mean age of 38.71 ±16.2 years, with 55.5% being male. Most participants were employed (81.1%), married (76.9%), and identified as Javanese or Balinese (67%). Comorbidities such as hypertension (11.2%), dyslipidemia (4.1%), diabetes mellitus (1.9%), and heart disease (1.4%) were prevalent among the study population. Multivariate analysis revealed several significant associations between liver disease and comorbid conditions (diabetes, dyslipidemia), stress, lack of physical activity, male gender, economic status, ethnicity, low education, inadequate fruit and vegetable consumption, fat intake, and soda consumption.

**Conclusions:** This study highlights the relatively low but still significant prevalence of liver disease in Indonesia and identifies various risk factors associated with its occurrence. Understanding these factors can inform targeted interventions and public health policies aimed at reducing the burden of liver disease in the Indonesian population.

**Keywords:** Liver disease, Prevalence, Risk factor

## PE-02

### Seroprevalence of Hepatitis A, E, and Human Immunodeficiency Virus in People Who Use Drugs in South Korea

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**Aims:** In South Korea, comprehensive data on the prevalence of viral infections such as hepatitis A virus (HAV), hepatitis E virus (HEV), and human immunodeficiency virus (HIV) among people who use drugs (PWUD) are scant. This study aims to explore the seroprevalence of these infections, with a particular focus on the susceptibility to non-parenteral viral hepatitis among PWUD.

**Methods:** A prospective multicenter cohort study was conducted from August 2022 to October 2023 at four drug rehabilitation centers, which collectively serve over 90% of PWUD in South Korea.

**Results:** Of the 318 PWUD screened for HAV, HEV, and HIV antibodies, 195 (61.3%) were positive for HAV IgG, 24 (7.6%) for HEV IgG, and 12 (3.8%) for HIV antibodies. HAV IgG positivity was highest in the 10s age group at 77.8%, decreasing to 35.4% in the 20s, 34.8% in the 30s, and 50% in the 40s. HEV IgG seroprevalence increased with age, showing 0% in the 10s, 3.1% in the 20s, 6.5% in the 30s, 4.7% in the 40s, 10.3% in the 50s, and 19.2% in the 60s. HIV seropositivity was most notable in the 30s at 15.2%, 4.6% in the 20s, and 3.1% in the 40s, with no cases observed in the 10s or those over 50. Among the 12 HIV-positive individuals, with an average age of 33.5±6.7 years, none had HBV or HCV co-infections. Notably, 33.3% lacked anti-HBs antibodies, 91.7% lacked anti-HEV IgG, and 58.3% lacked anti-HAV IgG.

**Conclusions:** No HBV or HCV co-infection was observed in HIV-positive PWUD in South Korea. However, a significant proportion remained susceptible to HAV or HEV infection, underlining the need for increased awareness and preventive measures against non-parenteral viral hepatitis among this population.

**Keywords:** Hepatitis A, Hepatitis E, Human immunodeficiency virus, People who use drugs

## PE-03

### Humanized Mice Efficiently Engrafted with Primary Human Hepatocytes Are Useful for Liver Disease Research

Hee Sun Byun[1], Eunhye Yu[1], Inseon Bak[1], Hee-Jeong Han[3], Young Sam Im[2], Sang-Min Kang[3], YongOu Kim[2], Dae-Yeul Yu[1], Kyeong-Won Yoo[1]

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**Aims:** Human liver chimeric mice are useful models of human hepatitis virus infection, including hepatitis B and C virus infections. Because hepatitis virus infection requires humanized mice with high chimerism, our study aimed to enhance engraftment effect in order to create a mouse model with human liver cells.

**Methods:** For the humanized liver mouse model, FAH knockout mice (NIG-FAH) were generated from immunodeficient mice (NOD/SCID-IL2Rg$^{-/-}$, NIG) using CRISPER-Cas9 technology. Fah-deficient mice progress mouse liver disorder only when the defensive drug 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) is withdrawn. Here we performed the retrorsine pretreatment to increase the effectiveness of liver transplantation. After transplanting human hepatocytes into mice, functionality of chimeric mice was analyzed human serum albumin(HSA) through ELISA in mouse serum and sequentially observed by IHC. Mice more than 12 weeks after transplantation were challenged with HBV and HCV.

**Results:** NOD/SCID-IL2Rg$^{-/-}$ (NIG) mouse have been reported to be excellent recipients of human xenografts and Fah knockout mice was generated into this background. The primary human hepatocytes (PHHs) engraftment into immunodeficient *fah*$^{-/-}$ mice has attempted in several groups with and without retrorsine treatment. Addition of retrorsine treatment enhanced the engraftment rate of human hepatocyte to more than 70% from at 12 weeks after transplantation. These mice were infected with HBV and HCV to confirm infectivity.

**Conclusions:** These data demonstrate that NIG-FAH humanized liver mouse can be used as an *in vivo* model for liver infectious diseases(HBV, HCV) and may become useful for studying human liver disease.

**Keywords:** Humanized liver mouse, Immune-deficient, Hepatitis virus infection, Primary human hepatocytes

## PE-04

### Identification of Cytotoxic CD4+ Population among CD69(-) Liver-Infiltrating T-Cells

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**Aims:** The $CD69^+$ tissue-resident T-cell population comprises a considerable proportion of intrahepatic T cells and provides an early, rapid adaptive immune response. However, the characteristics of $CD69^-$ populations and their role need to be elucidated.

**Methods:** We collected background liver tissues, which were obtained during hepatectomy in patients with various etiologies of chronic liver disease. Single-cell dissociation and flow cytometry were performed to analyze the liver-infiltrating T-cell population. Fatty changes and fibrosis grade were confirmed by histologic examinations.

**Results:** The $CD69^-$ subpopulation was more enriched in $CD4^+$ T cells compared to $CD8^+$ T cells. $CD69^-CD4^+$/$CD8^+$ T cells showed a similar activation phenotype but expressed PD-1 less, compared to the $CD69^+$ subpopulation. Interestingly, the $CD69^-$ subpopulation had more ex vivo expression of perforin and granzyme B, compared to the $CD69^+$ subpopulation among $CD4^+$ T cells. Perforin expression was less in the $CD69^-CD4^+$ T cells than in the $CD69^-$/$CD69^+CD8^+$ T cells, but in terms of granzyme B expression, $CD69^-CD4^+$ T cells were similar to $CD69^+CD8^+$ T cells, although $CD69^+CD8^+$ T cells had a more granzyme $B^+$ population than $CD69^-CD4^+$ T cells. $NKG2D^+$ and $CD56^+$ populations among $CD69^-CD4^+$ T cells had more perforin or granzyme B, suggesting they might be activated in an innate-like manner. The frequency of cytotoxic $CD69^-CD4^+$ T cells was positively correlated with the serum ALT level but was negatively correlated with liver fibrosis.

**Conclusions:** We have identified for the first time that cytotoxic $CD4^+$ T cells among liver-infiltrating T cells are mainly $CD69^-$ population, which can recirculate. This population might be associated with liver inflammation, which needs to be further validated.

**Keywords:** CD4 T cells, Cytotoxicity, CD69

## PE-05

### Unveiling the Silent Invader: A Case of Hydatid Disease in a Filipino Male Presenting as Abdominal Pain

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**Aims:** Echinococcal cysts, caused by the larval stage of the Echinococcus tapeworm, represent a rare but significant clinical entity within the realm of gastroenterology. These parasitic infections present diagnostic and therapeutic challenges due to their variable clinical manifestations and potential for severe complications.

**Methods:** This is a case of a 75 year old male with no comorbidities or maintenance medications, retired policeman, who used to live in a farm 50 years ago with backyard poultry, dogs and carabaos. Due to persistent epigastric pain, ultrasound was done 1 year ago which showed multiple liver cysts for which cyst aspiration done, no medications taken. Hepatic cysts showed brown, turbid fluid with scattered mononuclear and polymorphonuclear cell infiltrates negative for malignant cells. No medication was given and patient was only advised monitoring. On monitoring, noted continued enlargement of cysts despite repeated cyst aspiration. Patient then consulted our institution for which MRI Cholangiopancreatography without contrast was requested which revealed multiple complex hepatic and subcapsular cysts enlarging the liver, some with hemorrhagic components, with extra-hepatic and peritoneal and retroperitoneal lesions. Features in the MRCP were consistent with hydatid disease.

**Results:** Patient was started on albendazole 400mg 1 tablet twice a day and is ongoing treatment until now. Patient reports no recurrence of abdominal pain since medication started and was advised regular follow up.

**Conclusions:** This case highlights the importance of considering hydatid disease in the differential diagnosis of patients presenting with abdominal symptoms, particularly in regions endemic to the parasite. Regular monitoring of these patients is essential to assess treatment response, detect complications and prevent recurrence.

**Keywords:** Hydatid disease, Echinococcus, Tapeworm, Parasitic liver infection

## PE-06

### Method of Transfistulal Elimination of Cystobiliary Fistulas of the Residual Cavity after Echinococcectomy from the Liver

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**Aims:** Development of a method for endoscopic treatment of postoperative cystobiliary fistulas of the residual cavity after echinococcectomy from the liver.

**Methods:** The clinic has developed and applied a method of transfistula endoscopic elimination of cystobiliary fistulas in 13 patients after open echinococcectomy from the liver. Transfistula endovideoscopy of the residual liver cavity is used for functioning drainages of the residual liver cavity (CL4, CL5).

**Results:** In order to eliminate the biliary fistula, the minimum effective energy level for the coagulation mode (60-80 W) was used. Bile ducts larger than 0.3 mm in diameter were coagulated only when reliable contact was achieved between the electrode and the wall of the bile duct, and, for reliability, coagulation was carried out along the circumference of the duct. In order to avoid certain difficulties associated with coagulation, it is necessary to use the following techniques: the axis of the instrument is moved away from the zone of direction of the bile flow to detect the source of bile leakage; the instrument is retracted from the duct to be coagulated to the maximum possible distance, allowing coagulation to be carried out with the withdrawn loop. At the end of the intervention, it was considered advisable to conduct a final examination of the residual cavity with minimal irrigation pressure, so that no small fistulas remain visible. No complications were observed.

**Conclusions:** The developed endoscopic method for eliminating cystobiliary fistulas from the residual cavity is safe, minimally invasive, which helps prevent repeated surgical interventions and reduce postoperative bed days.

**Keywords:** Echinococcosis of the liver, Cystobiliary fistulas of the residual cavity, Endoscopic interventions,

## PE-07

### Sequence of Choosing Tactics for Minimally Invasive Treatment of Obstructional Jaundice of Parasitic Genesis

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**Aims:** Determination of the sequence of choice of tactics for minimally invasive treatment of obstructive jaundice of parasitic origin.

**Methods:** The study is based on an analysis of 470 patients with liver echinococcosis, operated on during the period 2007-2022. Liver echinococcosis, complicated by obstructive jaundice, was detected in 95 (20.2%) patients. There were 42.3% men, 57.7% women.

**Results:** 46 (48.4%) patients were hospitalized with a severe icteric form of the disease, a severe clinical picture caused by the formation of a cystobiliary fistula with segmental bile ducts - 28 (29.5%), with a mild course - 22.1%. Endoscopic papillosphincterotomy (EPST), as the first stage of the operation, was performed in 29 (30.5%) patients, including instrumental removal of fragments of the chitinous membrane and daughter cysts of echinococcus. For the purpose of simultaneous decompression of the residual cavity of the hydatid cyst and common bile duct after EPST, nasobiliary drainage was performed. Combined EPST and nasobiliary drainage was used in 11.6% patients. And in 3.1% patients with EC breakthrough into the bile ducts, with the development of parasitic obstructive jaundice, 2-stage minimally invasive interventions were undertaken. The first stage was primary EPST, the second - interventions using the modified PAIR method. In 66.3% patients who, for various reasons, could not eliminate biliary hypertension endoscopically, after appropriate preoperative preparation, traditional operations were performed in a delayed manner. Postoperative complications occurred in 8 (8.4%), deaths – in 3 (3.1%).

**Conclusions:** Staged combined minimally invasive tactics for the treatment of obstructive jaundice of parasitic origin help improve immediate results.

**Keywords:** Parasitic obstructive jaundice, Endoscopic papillosphincterotomy, Pair

## PE-08

### Minimally Invasive Treatment of Liver Echinococcosis, Subdiaphragmal Localization

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**Aims:** Improving the results of surgical treatment of liver echinococcosis, subphrenic localization.

**Methods:** A study of 64 patients with liver echinococcosis localized in the diaphragmatic surface of the VIII segment of the liver was analyzed, where 21 (32.8%) underwent puncture-drainage interventions under ultrasound control. There were 29 men (45.3%), women - 35 (54.7%). Suppuration of hydatid cysts (HC) was noted in 33.3% of patients.

**Results:** Drainage was necessarily performed through 3-4 cm of healthy liver parenchyma, which ensures tightness and prevents the leakage of echinococcal fluid into the free abdominal cavity. In the postoperative period, the average follow-up for the volume of the residual cavity was 21.8±6.7 months. (median 69%); range, 3-24.7 months). Cyst volumes that were

calculated in recent months ranged from 0.00 to 47.00 ml with an average of 21.11 ml. Among all patients, cysts decreased in volume by 76.2%. The average reduction in cyst volume at follow-up is 71.4%. The mean duration of catheterization among the 14 (66.7%) patients with uncomplicated EP was 18.1 days (mean, 3.93 days; range, 1–21 days). When the duration of catheterization in a group of patients with suppuration of a hydatid cyst (n=7) was 33.1 days. The average hospital stay for all patients was 2.3 days (range 1-5 days). The average length of hospitalization was 1.5 days for patients with an uncomplicated form receiving PAIR, 1.7 days for patients with suppurative HC.

**Conclusions:** One of the most effective methods of surgical treatment of liver echinococcosis, subdiaphragmatic localization, is minimally invasive interventions under ultrasound control.

**Keywords:** Subphrenic echinococcosis of the liver, Ultrasound-guided Interventions, Suppuration of a hydatid cyst

## PE-09

### Analysis of Socio-Economic and Mental Health Factors in Someone Affected by Liver Disease

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**Aims:** Liver disease is one of the diseases that often attacks the Indonesian population. This research analyzes the impact of smoking behavior, dietary behavior, mental health and socio-economic variables on liver patients in Indonesia.

**Methods:** This research uses quantitative analysis with a probit model. The number of respondents was 31,167 respondents with as many as 315 patients affected by the liver. data source from the Indonesia Family Life Survey 5.

**Results:** The results show that partially the behavioral variables of people who smoke, the depression variable, and a high level of education have a significant positive chance of increasing the occurrence of liver disease in them as indicated by a *P* value < 0.05. Meanwhile, people who already have a worsening health status will have an increased risk of developing liver disease. The variables BMI, eating frequency, income and age do not significantly influence the risk of liver disease as indicated by a *P* value>0.05.

**Conclusions:** Therefore, the Indonesian population must maintain health by not smoking, not being depressed, using higher education effectively, and maintaining health from an early age.

**Keywords:** Liver disease, Mental health, Smoking

## PE-10

### Pattern of Liver Function Tests Abnormality in Dengue Fever and Its Clinical Outcome

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**Aims:** Liver Function Test (LFT) used as screening and functional assessment of the liver; can help early recognition and prediction of Dengue fever (DF) severity in hospitalized patients. We aimed to assess the pattern of LFT in patients diagnosed as Dengue fever in our institute.

**Methods:** This is an analytical study which was conducted from July 10, 2023 to September 15, 2023, where seropositive dengue positive cases diagnosed by Rapid Immunochromatographic test were included. The severity of DF was graded into DF without warning signs (DFWS)/mild DF, dengue with warning signs, and severe DF (SDF) in compliance with the World Health Organization (WHO) criteria. Elevation in LFTs was co-related with good (survival or complication free stay) or bad outcome (death or complications).

**Results:** The mean age of the patients was 46.18±16.85 years which included 113 males and 65 females. Fifty five patients (30.89%) had mild elevation of aminotransferases (up to 2 fold increases), 108 patients (60.67%) had moderate increases (3 to 4 fold) and 15 patients (8.42%) had severe (4 fold increase). Other deranged LFT parameters included total bilirubin in 14.6% (N= 26), aspartate aminotransferase (AST) 79.21%(N= 141), alanine aminotransferase (ALT) 71.91%(N= 128), alkaline phosphatase (ALP) 12.92%(N= 23), albumin 37.64%(N= 67) and prothrombin time index (PTI) [international normalized ratio (INR) in 6.17% of the patients (N= 11). ALT was statistically higher in patients with septicemia, hepatic and renal failure (severe dengue fever), (*P*-value ≤ 0.05).

**Conclusions:** Serum bilirubin, AST, ALT and ALP were significantly higher in patients with SDF and non-survivors. While preferentially high AST may serve as an early indicator of dengue infection and high bilirubin, ALT and ALP may act as poor prognostic markers. Raised LFTs was associated with prolonged hospital stay and greater complications and mortality.

**Keywords:** Complication, Dengue fever, Liver function test, Septicemia

## PE-11

### Liver Enzymes Alterations in Laboratory Confirmed Bacteremic Adult Patients

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**Aims:** Liver enzymes are altered in many physiological and pathological events. Close observation of liver enzymes can help patient treatment and monitoring. This study aimed to observe an alteration in liver enzymes in laboratory-confirmed bacteremic adult patients.

**Methods:** It was a hospital-based descriptive study conducted in Manipal Teaching Hospital, Pokhara, Nepal. Suspected bacteremic patients were asked for blood cultures. Earliest Liver enzymes, aspartate aminotransferase(AST), alanine transaminase(ALT), and alkaline phosphatase(ALP) test reports of Patients with growth in blood culture were traced. The patients with known liver dysfunction were excluded. Blood cultures and identification of isolates were done by conventional microbiological methods. Liver function markers were estimated using Vitrous 4600 dry chemistry analyzer.

**Results:** From 151 laboratory-confirmed bacteremic patients, 12 different pathogens were isolated. The commonest organisms were *Staphylococcus aureus* (57, 37.74%), *Acinetobacter spp* (27, 17.88%), *Pseudomonas aeruginosa* (27, 17.88%) followed by *E coli* (19, 12.58%). The mean values of AST, ALT, and ALP were elevated and were 78.50 IU/L, 58.89 IU/L, and 127.25 IU/L respectively. AST and ALT mean values were elevated in patients with isolation of *Acinetobacter*, *E coli, Klebsiella*, MRSA, and MSSA, and remained normal in patients with isolation of *Citrobacter, Enterobacter, Enterococcus, Proteus*, *Pseudomonas*, and *Serratia* spp. Differently, the mean value of ALP was increased in patients with isolation of *Citrobacter, Enterobacter, E coli, Klebsiella*, and *MRSA*. These enzyme values were indifferent to the isolation of MDR and non-MDR isolates. Mean AST and ALT values were elevated in patients in Emergency, Critical care, Surgery, and Medicine wards but the mean ALP value was increased in patients from the Surgery ward and Emergency only.

**Conclusions:** Adult patients with bacteremia, usually have elevated liver enzymes and were found to be altered selectively in different organisms and wards. Correlation of these values with pathogens, and with wards could be important for comprehensive patient management.

**Keywords:** Bacteremia, Liver enzymes

## PE-12

### Harmfulness Effects of Pedalium Murex L. Extract in Liver and Kidney Histopathological Examination in Mus Musculus

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**Aims:** Pedalium murex L. or butterfly pea is more increasingly being consumed as traditional medicine though it contains secondary metabolites, which can be non-beneficial to its consumer. $LD_{50}$ and histopathological examination are used frequently in toxicity studies. Thus we aimed to determine the toxicity level of Pedalium murex L. extract and its effects on the liver and kidney in mice.

**Methods:** We carried out this analytical experimental study with from September 2021 to July 2022. Mice were categorised into five dose groups. They were treated with aquades, paracetamol-induced, and root extract at 500, 1000, and 2000 mg/kg BW orally for 14 consecutive days.

**Results:** Pedalium murex L. was classified as having very low toxicity (LD50 > 2000 mg/kg BW). We detected toxicity signs in mice such as lethargy and tremor in the group treated with more than 1000 mg/kg BW. Histopathological examinations showed leucocytes, vacuolation, and necrosis in the liver and kidneys of mice. There were significant differences in liver and kidney histopathological scores between the five study groups ($P<0.05$).

**Conclusions:** Pedalium murexes L. are safe to consume at a dosage of 500 and 1000 mg/kg BW since no mice died after being treated for 14 days. Liver and kidney damage appeared at 2000 mg/kg BW dosage in histopathological examination. Hence, its consumption at this dosage should be limited.

**Keywords:** MUS musculus, Pedalium murex L, Liver and kidney, Histopathological

## PE-13

### Urinary Tract Infection in Non-Hospitalized Patients with Cirrhosis and No Symptoms of Urinary Tract Infection: A Case Series Study

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**Aims:** Urinary tract infection (UTI) in patients with liver cirrhosis, even in the absence of symptoms, poses significant risks and can contribute to decompensation and increased mortality rates.

**Methods:** This case series study aimed to assess the prevalence of UTI among non-hospitalized cirrhotic patients attending a hepatology outpatient unit. From May 2023 to September 2023, a total of 82 cirrhotic patients underwent clinical evaluation and laboratory assessments, including urine analysis, urine culture, blood culture, and hepatic function tests.

**Results:** The mean age of the patients was 48 years, with 73% being male. Hepatitis B and delta virus were the primary etiological factors in 48% of cases, with the Child-Pugh B functional

class observed in 56% of cases. Despite lacking UTI symptoms, 5.9% of patients tested positive for UTI, predominantly caused by E. coli and Klebsiella pneumonia.

**Conclusions:** This study highlights a UTI prevalence of approximately 7% among non-hospitalized cirrhotic patients without UTI symptoms, underscoring the importance of routine screening for UTI in this population to mitigate associated risks.

**Keywords:** Urinary tract infection, Infections in cirrhotic, Liver parenchyma chronic disease

## PE-14

### Leishmania Donovani: CD2 Biased Immune Response Skews the SAG Mediated Therapy for a Predominant Th1 Response in Experimental Infection

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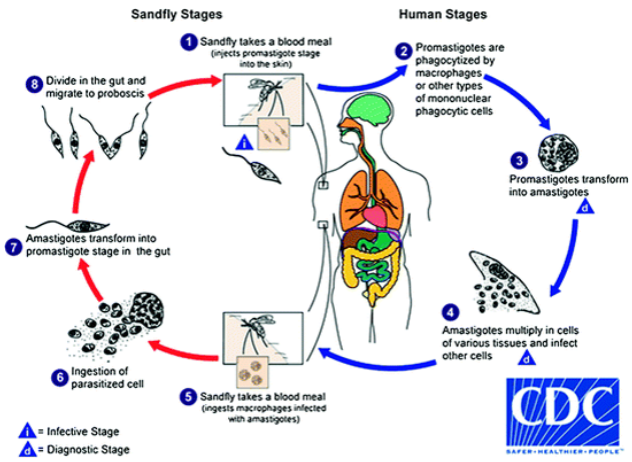
**Aims:** Visceral leishmaniasis is a macrophage associated disorder which leads to a profound decrease in the natural immunotherapeutic potential of the infected subjects to combat the disease. Visceral leishmaniasis is a macrophage associated disorder which leads to a profound decrease in the natural immunotherapeutic potential of the infected subjects to combat the disease. We have evaluated the effect of combining CD2 with conventional antimonial (sb) therapy in protection in BALB/c mice infected with either drug sensitive or resistant strain of Leishmania donovani with 3×10(7) parasites via-intra-cardiac route.

**Methods:** Mice were treated with anti CD2 adjunct SAG sub-cutaneously twice a week for 4 weeks. Assessment for measurement of weight, spleen size, anti-Leishmania antibody titer, T cell and anti-leishmanial macrophage function was carried out day 0, 10, 22 and 34 post treatments.

**Results:** The combination therapy was shown boosting significant proportion of T cells to express CD25 compared to SAG monotherapy. Although, the level of IFN-γ was not statistically different between combination vs monotherapy ($P$=0.298) but CD2 treatment even alone significantly influenced IFN-γ production than either SAG treatment ($P$=0.045) or with CD2 adjunct SAG treatment ($P$=0.005) in Ld-S strain as well as in Ld-R strain. The influence of CD2 adjunct treatment was also documented in anti-leishmanial functions in macrophages.

**Conclusions:** Drug resistance is the major impedance for disease control but the encouraging results obtained after infecting mice with resistant strain of the parasite strongly imply that this drug can be effective even in treating resistant cases of Kala-azar.

**Keywords:** CD2, Visceral Leishmaniasis




## PE-15

### Deciphering the Antipathogenic Actions of Epigallocatechin-3-Gallate against Coxiella Burnetii in Granulomatous Hepatitis: A Microbioinformatics Exploration

Astrid Ekklesia Saputri[1], Rian Ka Praja[2*], Reny Rosalina[3], Trilianty Lestarisa[4], Raiyan Fairozi[5], Qonita Sari Bustomi[6]

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**Aims:** *Coxiella burnetii*, the causative agent of Q fever, is a highly infectious intracellular bacterium responsible for granulomatous hepatitis, a severe and often chronic condition with limited treatment options. Epigallocatechin-3-gallate (EGCG), a polyphenolic compound found in green tea, has demonstrated potential in combating various infectious agents. This study aimed to uncover the mechanisms underlying EGCG's efficacy against *C. burnetii* in granulomatous hepatitis using a microbioinformatics approach.

**Methods:** We employed bioinformatics tools such as STITCH v.5.0 and VICMPred to identify protein targets and elucidate their functional roles. Furthermore, BepiPred v.2 software was utilized to predict peptide epitopes of *C. burnetii* proteins, while PSORTb v.3 was employed to examine the subcellular localization.

**Results:** Utilizing the STITCH v.5.0 program, a bioinformatics approach identified ten protein targets of *C. burnetii* affected by EGCG, including dihydrolipoyl dehydrogenase (lpdA), dihydrofolate reductase (folA), peptidyl-prolyl cis-trans isom-

erase surA (CBU_1980), DNA mismatch repair protein (mutL), (3R)-hydroxymyristoyl-ACP dehydratase (fabZ), aspartate aminotransferase (aspB), polyketide synthase (CBU_0788), methylated-DNA-[protein]-cysteine S-methyltransferase (ogt), hypothetical protein (CBU_1451), and ABC transporter permease (CBU_0933). These virulence factors are crucial for *C. burnetii* survival.

**Conclusions:** The antipathogenic mechanism of EGCG against *C. burnetii* in granulomatous hepatitis appears to involve blocking several virulence factors associated with bacterial cell survival and metabolism. However, further validation through *in vitro* and *in vivo* experiments is necessary to confirm the findings of this microbioinformatics study.

**Keywords:** Coxiella burnetii, Granulomatous hepatitis, Epigallocatechin-3-gallate

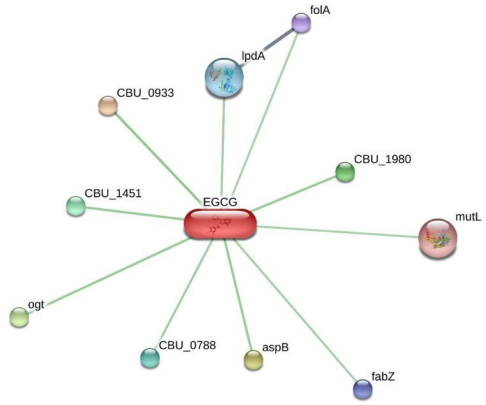


Figure 1. Molecular interactions between EGCG and several proteins of *C. burnetii*

## PE-16

### Burden of Viral Hepatitis and Syphilis Co-Infection among People Living with HIV in Nepal

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**Aims:** To investigate the coinfection of hepatitis infection and syphilis and its association with liver enzymes among HIV-infected individuals attending Sukra Raj Tropical and Infectious Disease Hospital in Kathmandu, Nepal.

**Methods:** A crossectional study was carried out on 241 HIV-infected individuals following ART at the Shukraraj Tropical Hospital, mean age of 41.24±10.635 were tested for HBsAg, anti-HCV IgG, and anti-HEV by immunochromatographic technique. Syphilis was tested by the flocculation method. Liver function was assessed by alanine and aspartate aminotransaminases.

**Results:** Overall male participants were 40.2 % with females 59.2%. Married were 92,5% with 96.3% being undergraduate. Overall, 10(4.1%) were infected with Hepatitis B, 21(8.7%) were infected with Hepatitis C, 3(1.2%) were infected with Hepatitis E and 31(12.9%) were syphilis positive. A significant association of Hepatitis C with sex was seen with a *P* value of 0.02. Similarly, a significant association was seen between syphilis and sex with a *P* value of 0.02. Significant association with Hepatitis C and ALP with 0.022, A Significant association was seen with Hepatitis C and SGOT with a *P*-value of 0.005.

**Conclusions:** High prevalence of HBV infection, HCV, and syphilis disease in HIV-infected patients visiting ART centers and there is a need for great attention to particular coinfections in HIV. Awareness and education should be promoted regarding coinfections and treatment.

**Keywords:** HIV, Coinfections, Burden, Hepatitis

# MASLD, Basic

## PE-01

### Lactobacillus Acidophilus Alleviates Metabolic Dysfunction–Associated Steatotic Liver Disease

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**Aims:** Metabolic dysfunction–associated steatotic liver disease (MASLD) is one of the most common chronic liver diseases globally. Gut-dysbacteriosis is related with MASLD development and progression. *Lactobacillus acidophilus* has been proven to maintain intestinal barrier function. This study aimed to demonstrate the role of gut microbiome in the High-fat diet induced MASLD and explore the effects of *L. acidophilus* in the prevention of MASLD by utilizing gut microbiota profiles.

**Methods:** From the Korean cohort study, a total of 127 stool sample selected and divided into three groups (Healthy control; n=39, MAFLD; n=45, MASH; n=43). For *in vivo* study, 5 weeks old C57BL/6J mice were fed the high fat diet with/without *L. acidophilus* ($3.91*10^9$ CFU/day) for 18 weeks. We analyzed and compared liver/body weight ratio (L/B ratio), NAFLD activity score (NAS), oral glucose tolerance test (OGTT), and liver function tests with serum. We also conducted the histopathological examination, fecal analysis, and markers for inflammation, lipogenesis, and $\beta$-oxidation in the liver.

**Results:** In human data, genus *Lactobacillus* was decreased according to the liver disease progression. *L. acidophilus* group showed significant improvement in liver enzymes (AST 86.1±21.1, $P<0.05$; ALT 66.4±37.2, $P<0.05$; TC 217.7±32.3, $P<0.01$;

LDL 61.3±13.2, *P*<0.05), L/B ratio (3.1±0.4, *P*<0.01), fasting glucose (173.3±31.9, *P*<0.05), and NAS (1.4±1.5, *P*<0.01) compared with the untreated group (AST 154.2±62.1; ALT 190.4±104.0; TC 293.8±25.1; LDL 84.7±13.3; L/B ratio 4.7±0.9; fasting glucose 231.7±48.6; NAS 5.6±1.6). Moreover, *L. acidophilus* supplementation downregulated the expression of hepatic steatosis and inflammation biomarkers (TNF-$\alpha$, *P*<0.05;) and upregulated the expression of oxidation (PPAR-$\alpha$ *P*<0.05) and tight junction gene (occludin, *P<0.05; claudin, P<0.05). L. acidophilus* ameliorates MASLD progression and dysbiosis through the modulation of gut microbiota resulting in reduced hepatic inflammation, steatosis, and fatty acid synthesis.

**Conclusions:** Our study highlighted role of the *L. acidophilus* in MASLD and the importance of the gut-liver axis. *L. acidophilus* can alleviate MASLD by regulating glucose metabolism as well as reducing lipid accumulation and inflammation in the liver. We confirmed the potential of *L. acidophilus* on the prevention of MASLD progression and provide new insight into seeking therapeutic strategies.

**Keywords:** MASLD, Gut-microbiome, Probiotics, Insulin resistance

## PE-02

### Streptococcus Salivarius Mitigates Metabolic Dysfunction-Associated Steatotic Liver Disease by Modulating the NLRP3 Inflammasome Pathway

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**Aims:** Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most prevalent liver diseases worldwide. However, definitive medical treatments have not been established apart from lifestyle modifications. This study aimed to demonstrate the role of gut microbiome in the Western diet-induced MASLD and explore the effects of *Streptococcus salivarius* in the prevention of MASLD by utilizing gut microbiota profiles.

**Methods:** A total of 76 patients' stools (healthy controls [HC, n=19], fatty liver (FL=16), hepatitis (n=24), and cirrhosis (n=17) were analyzed by 16s rRNA sequencing. For *in vivo* study, 6 weeks old C57BL/6N mice were fed the Western diet with/without *S. salivarius* for 9 weeks. *S. salivarius* were administered at a concentration of $10^9$ CFU/day. We compared liver/body weight ratio (L/B ratio), NAFLD activity score, liver function tests, histopathology, fecal analysis, and markers for inflammation, lipogenesis, and $\beta$-oxidation in the liver.

**Results:** In the human stool microbiota analysis, the species level of *S. salivarius* increased in cirrhosis group. In the animal study, Western diet group showed elevation in the proportion of *Proteobacteria* and *Firmicutes* and reduction in *Bacteroidetes. S. salivarius* groups revealed significant improvement in liver enzymes (AST 78.3±8.6, *P*=0.03), L/B ratio (5.0±0.5, *P*=0.03) and improved NAS (2.6±1.4, *P*<0.01) compared with the untreated group (AST 105.7±32.1; L/B ratio 5.6±0.5; NAS 5.8±1.5). Moreover, *S. salivarius* supplementation downregulated the expression of inflammation biomarkers (Il-1$\beta$, *P*=0.05; *Nlrp3*, *P*<0.01). *S. salivarius* supplementation ameliorates MASLD progression, and dysbiosis through the modulation of gut microbiota resulting in improving hepatic inflammation.

**Conclusions:** Our study highlighted the association between gut microbiota and MASLD through the gut-liver axis. We confirmed the potential of *S. salivarius* on the prevention of MASLD progression and the detailed mechanisms for the novel therapy.

**Keywords:** MASLD, NLRP3 Inflammasome

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N1 | N1 | N2 | N2 | N3 | N3 | N1 | N1 | N2 | N2 | N3 | N3 |
| N4 | N4 | N5 | N5 | W1 | W1 | N4 | N4 | N5 | N5 | W1 | W1 |
| W2 | W2 | W3 | W3 | W4 | W4 | W2 | W2 | W3 | W3 | W4 | W4 |
| W5 | W5 | W6 | W6 | W7 | W7 | W5 | W5 | W6 | W6 | W7 | W7 |
| S1 | S1 | S2 | S2 | S3 | S3 | S1 | S1 | S2 | S2 | S3 | S3 |
| S4 | S4 | S5 | S5 | S6 | S6 | S4 | S4 | S5 | S5 | S6 | S6 |
| S7 | S7 | S8 | S8 | | | S7 | S7 | S8 | S8 | | |

| Gene | rxn | Sybr Green | Primer | Water | Total Volumi |
|---|---|---|---|---|---|
| GAPDH | 45 | 225 | 22.5 | 90 | 360 |
| CTLA4 | 45 | 225 | 22.5 | 90 | 360 |
| | | 0 | 0 | 0 | 0 |

## PE-03

### The Combination of Pterocarpus Marsupium Extract and Glibenclamide Leads to Significant Ultrastructural and Biochemical Alterations in a Liver of Non-Alcoholic Fatty Liver Disease

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**Aims:** Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide, affecting up to more than half of these patients have type 2 diabetes mellitus (T2DM) through Insulin resistance. The prevalence of diabetes mellitus (DM) is rapidly increasing worldwide, making it a significant metabolic disorder. Glibenclamide (GLB) is commonly

prescribed for diabetes treatment, but it is associated with potential adverse effects. As a result, herbal treatments have gained popularity as alternative medicine for managing diabetes due to their lower risk of side effects. Hence, this research aimed to investigate the combined therapeutic effects of GLB and Pterocarpus marsupium (PM), to ensure a safe and effective treatment approach for NAFLD in DM.

**Methods:** Mice were rendered diabetic by injecting alloxan at a dose of 150 mg/kg body weight. PM and GLB were administered at the dose of 150 mg/kg body weight and 500 µg/kg bodyweight respectively to diabetic animals individually and in combination. Serum was isolated for the estimation of glucose, insulin, triglyceride, total cholesterol, and high-density lipoprotein cholesterol concentrations. Liver ultra-structure analyzed through transmission electron microscopy and the estimation of lipid peroxidation, lipid hydroperoxide, advanced oxidation protein products, superoxide dismutase, catalase. Histological analysis of liver tissue was carried out.

**Results:** Indicated that alloxan-induced adverse effects were normalized by GLB and PM co-treatment as evidenced by significantly marked to suppression in glucose, triglyceride, total-cholesterol, lipid-peroxidation, and lipid-hydroperoxides with increase in antioxidants status and liver glycogen content, more effectively than either of agents did alone. Liver ultra-structure analyzed through transmission electron microscopy and histology revealed the apparent repair of ALX-induced damaged hepatocytes. The presence of epicatechin as major phytoconstituent responsible for antidiabetic and antioxidative activity was confirmed by HPLC.

**Conclusions:** The combination of Pterocarpus marsupium with glibenclamide demonstrates synergistic effects in terms of both antidiabetic and antioxidative properties. These results strongly support the concurrent use of these drugs for the effective management of NAFLD in DM.

**Keywords:** Non-alcoholic fatty liver disease, Liver histology & transmission electron microscopy, Oxidative stress, Pterocarpus marsupium and glibenclamide

## PE-04

### Essential Adolescent Lifestyle: Coffee Drinking Habit Contributes to Liver Disease: Evidence from Asia

Vivi Usmayanti[1], Helena Kartika Utami[2]

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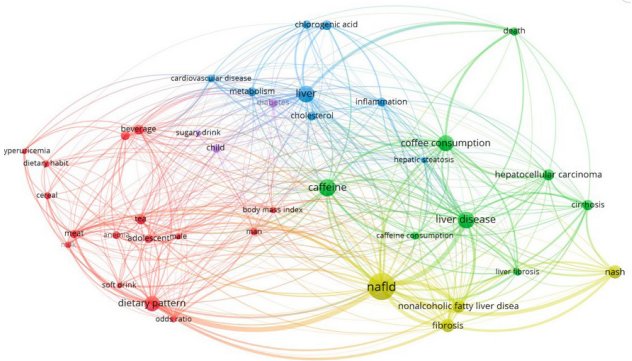
**Aims:** This study aims to evaluate papers that discuss the trend of coffee consumption for adolescents contributing to preventing liver disease and Non-alcoholic fatty liver disease (NAFLD) and other liver diseases by discovering research that may be beneficial for coping and developing preventive ways with similar situations in the future.

**Methods:** This study used the review procedures with modifications, including co-word analysis, to map themes. The articles to be reviewed were identified by entering the search keywords "liver disease" AND "Coffee Consumption" and "liver" AND "young" in the Scopus database. After applying a set of criteria, 75 articles were used in the subsequent analysis in Asia countries.

**Results:** Results of this study showed the sophistication of drinking coffee in a young adult's lifestyle, having low liver disease, and its impact is seen in many countries in Asia. Several types of research found that coffee consumption decreases the risk of dying from liver disease, including liver-associated digestive disease, cirrhosis, and liver cancer. These five clusters identified by VOSviewer are related to coffee/caffeine consumption. As can be seen from the picture, in the green and yellow clusters, coffee/caffeine consumption is highly related to liver disease, NAFLD (non-alcoholic fatty liver disease), NASH, hepatocellular carcinoma, and cirrhosis. Then, the red clusters explain the association of the habit of adolescents to coffee/caffeine drinking habits. These networks indicate that many types of research supported the association between coffee/caffeine consumption with liver disease, especially in Asia, where coffee is a part of daily activity for studying, learning, and leisure, with the increasing of adolescent consumers. However, the mixing results showed different associations, with the most significant for coffee/caffeine drinker habit lowering the risk of liver disease.

**Conclusions:** This study found a significant coffee/caffeine consumption among young adults related to decreased risk of liver disease among young coffee drinkers.

**Keywords:** NAFLD, Coffee consumption, Adolescent, Asia




## PE-05

### Psychosocial Problems and Coffee Consumption as Coping Strategy to Prevent Non-Alcoholic Fatty Liver Disease: An Observation

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[1]Economics Faculty, Universitas Sriwijaya, Indonesia; [2]Medical Doctor, Bhayangkara Hospital, Jambi, Indonesia

**Aims:** Stress and Depression are the most popular of psychosocial problems among students. To cope with these problems, coffee consumption is a popular habit for them. In the long run, consuming coffee can be the prevention of non-alcoholic fatty liver disease (NAFLD) as the most frequent chronic liver disease which has 25-30% worldwide with 37 cases per 1000 population. Specifically, NAFLD can be found in around 35% of Indonesian cases of Hepatitis B. This study investigated the relationship the stress, depression, psychosocial problems, and coffee consumption in college students as a lifestyle to prevent NALFD.

**Methods:** This study employs quantitative research by collecting online survey data from 89 college students in several areas of Indonesia. Then, this study adopts the partial least squares approach to structural equation modeling (PLS-SEM) to examine data.

**Results:** The results of this study show that stress and depression have a positive association with coffee intention. The regression analysis showed the path coefficient supported with t-statistics and *P*-values 3.707 (0.000), and 3.587 (0.001). Then, the next stage is to measure coffee intention to coffee consumption with a 3.107 (0.000), positive association. In college, as students have huge tasks and group projects, they consume coffee as their companionship. Therefore, their background that relates to their stress, and depression, has a huge contribution to coffee consumption as one of the best preventive paths to NAFLD.

**Conclusions:** Coffee consumption is the best treatment for students with psychosocial problems, and this consumption has an additional positive influence on preventing NAFLD.

**Keywords:** NAFLD, Coffee consumption, College students, Psychosocial problems

**Table** Path Coefficient

| | Hypothesis | Coefficient | Sample Mean (M) | Standard Deviation | T-Statistics | P-Values | Result |
|---|---|---|---|---|---|---|---|
| H1 | Stress -> Coffee Intention | 0.340 | 0.343 | 0.092 | 3.707 | 0.000 | Supported |
| H2 | Depression -> Coffee Intention | 0.308 | 0.315 | 0.086 | 3.587 | 0.000 | Supported |
| H3 | Coffee Intention -> Coffee Consumption | 0.322 | 0.323 | 0.089 | 3.107 | 0.005 | Not Supported |

Source: data processed (2024)

## PE-06

## Analyzing the Role of Advanced Biomarker Kallistatin in NAFLD

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**Aims:** Cirrhosis of liver is a pathological condition characterized by diffuse fibrosis, severe disruption of intrahepatic arterial and venous flow, portal hypertension and finally liver failure. Liver fibrosis/cirrhosis is generally the end result of majority of chronic liver insults; major global health concern associated with a significant morbidity and mortality. It is 14th common cause of death globally.

In the present study, Kallistatin is the newly discovered protein biomarker candidate; known as kallikrein inhibitory protein belongs to serine proteinase inhibitor family, documented to play a vital role in screening, diagnosis and prognosis of cirrhosis of liver. This molecule of research interest needs further research among the population. It is also known to have inhibitory action on tissue kallikrein and a role in inhibiting inflammation, oxidative stress, angiogenesis and apoptotic reactions.

**able 1**: Statistical analysis of biochemical parameters (n=25 cases and controls)

| Variables | Groups | Mean ± SD | p-Value |
|---|---|---|---|
| RBS (mg/dl) | I | 100.10 ± 10.08 | 0.49 |
| | II | 102.12 ± 10.86 | |
| Blood Urea (mg/dl) | I | 30.19 ± 5.90 | 0.23 |
| | II | 35.10 ± 6.24 | |
| Creatinine (mg/dl) | I | 1.06 ± 0.20 | 0.47 |
| | II | 1.08 ±0.18 | |
| Kallistatin (pg/ml) | I | 4000.66 ± 550.40 | 0. 01* |
| | II | 1680.54 ± 470.40 | |
| Uric acid (mg/dl) | I | 3.40 ± 0.30 | 0.01* |
| | II | 6.50±0.60 | |

:0.05: significant; **Group II**: Clinically& diagnostically proven NAFLD subjects; **Group I**: Healthy jects; **SD**: Standard Deviation

**able 2**: Statistical analysis of biochemical parameters (n=25 cases and controls)

| Variables | Groups | Mean ± SD | p-Value |
|---|---|---|---|
| AST (U/L) | I | 36.90 ± 12.40 | 0.01* |
| | II | 220.90 ± 50.20 | |
| ALT (U/L) | I | 32.50 ± 12.20 | 0.01* |
| | II | 280.78 ± 50.48 | |
| ALP (U/L) | I | 120.50 ± 20.30 | 0.01* |
| | II | 340.70 ± 45.40 | |
| γ-GT (U/L) | I | 36.50 ± 12.00 | 0.01* |
| | II | 280.00 ± 50.00 | |
| otal Protein (g/dl) | I | 6.00 ± 0.32 | 0.01* |
| | II | 4.50 ± 0.50 | |
| Albumin (g/dl) | I | 3.50 ± 0.30 | 0.01* |
| | II | 2.50 ± 0.40 | |
| Total Bilirubin (mg/dl) | I | 0.80 ± 0.20 | 0.01* |
| | II | 5.60 ± 1.48 | |

*p<0.05: significant; **Group II**: Clinically& diagnostically proven NAFLD subjects; **Group I**: Healthy subjects; **SD**: Standard Deviation; **AST**: Aspartate Transaminase; **ALT**: Alanine Transaminase; **ALP**: Alkaline Phosphatase; **γGT**: Gamma Glutamyl Transferase

**able 3**: Statistical analysis of biochemical parameters (n=25 cases and controls)

| Variables | Groups | Mean ± SD | p-Value |
|---|---|---|---|
| TAC (nmol/µL) | I | 32.34 ± 6.00 | 0.01* |
| | II | 22.70 ± 5.00 | |
| TOS(µmol $H_2O_2$ Equiv/L) | I | 12.12 ± 4.00 | 0.01* |
| | II | 34.18 ± 5.98 | |

<0.05: significant; **Group II**: Clinically& diagnostically proven NAFLD subjects; **Group I**: althy subjects; **SD**: Standard Deviation; **TAC**: Total Anti-oxidant Capacity; **OS**: Total Oxidative Status

**Methods:** Blood samples were collected from NAFLD (n=25) age and gender matched healthy subjects (n=25) from Department of Medicine and analysed in Department of Biochemistry, RDMC, Banda U.P, India. Serum was used to estimate Kallistatin, serum transaminases (Aspartatetransaminase

[AST] & AlanineTransaminase (ALT), γ -Glutamyl Transferase (γ -GT), Total protein, albumin, total bilirubin, uric acid, total antioxidant capacity and total oxidative stress

**Results:** Hyperuricemia with significant reducation of kallistatin levels in NAFLD patients compared to healthy subjects were observed. There was an increase in total oxidative stress with decreased antioxidant capacity in NAFLD compared to healthy subjects. Serum levels of Kallistatin was positively correlated with activities of ALT, AST and γ -GT with concentration of Total Bilirubin, total oxidative stress. Negative correlation was observed between serum levels of uric acid, Kallistatin to serum levels of total protein, albumin and total antioxidant capacity.

**Conclusions:** Kallistatin expression decreased during disease progression and can serve as direct biomarkers of NAFLD which needs to be validated in diverse population. Hyperuricemia with elevated liver enzymes activity lead to poor prognosis.

**Keywords:** Endothelial dysfunction, Hyperuricemia, Kallistatin, Antioxidant, Oxidative stress, Inflammatory cytokines

## PE-07

### CKD-01, a Novel Triple LOXL2/LOXL3/VAP-1 Inhibitor Effectively Mitigates Hepatic Fibrosis

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**Aims:** Metabolic dysfunction-associated steatohepatitis (MASH, formerly known as nonalcoholic steatohepatitis; NASH) is a type of chronic liver disease caused by accumulation of fat in the liver and is accompanied by inflammation with or without liver fibrosis. If fibrosis is left untreated, it progresses from cirrhosis to hepatocellular carcinoma. Recently, resmetirom, a thyroid hormone receptor beta-selective agonist, approved by the FDA for MASH-related fibrosis but its efficacy is moderate. Lysyl oxidase-like 2/3 (LOXL2/3), amine oxidases, contribute to fibrosis progression and promote collagen cross-linking, limiting the reversibility of liver fibrosis. Vascular adhesion protein-1 (VAP-1), also known as semicarbazide-sensitive amine oxidase (SSAO), is a transmembrane protein and copper containing amine oxidase enzyme. It plays a role in lymphocyte rolling, adhesion and transmigration in chronic inflammatory liver diseases. In this study, we conducted various models of fibrotic liver disease to test the effect of a novel LOXL2/3/VAP-1 triple inhibitor, CKD-01, developed by Chong Kun Dang (CKD Pharmaceutical Corp., Korea).

**Methods:** In characterizing CKD-01, the half-maximum inhibitory concentration (IC50) values for LOXL2, LOXL3, and VAP-1 were determined by measuring enzymatic activity using an Amplex-Red oxidation assay. The effects of LOXL2 and LOXL3 on collagen gel contraction and the levels of deoxypyridinoline (DPD), a crosslink product of collagen molecules, were measured in hepatic stellate cells. The anti-inflammatory effect of CKD-01 related to VAP-1 was confirmed using an *in vivo* model using a carrageenan-induced air pouch model. Finally, the therapeutic role of CKD-01, a LOXL2/3/VAP-1 inhibitor, was studied in *various animal models* of *fibrosis*.

**Results:** CKD-01 inhibited human LOXL2, LOXL3 and VAP-1 with IC50 values of 530nM, 990nM and 16nM. LOXL2/3 inhibition by CKD-01 reduced formation of collagen cross-links as measured by levels of mature cross-linked pyridinoline (PYD) and deoxypyridinoline (DPD). In addition, we found that CKD-01 attenuates contractile activity through collagen gel contraction assay, an indirect manner of collagen cross-linking. CKD-01 attenuated neutrophil infiltration in air-pouch model, which supporting inhibition of VAP1 activity *in vivo.* Moreover, we observed significant reductions in inflammation score, NALFD fibrosis score, ISHAK score and collagen staining area in CKD-01 treated in CCl4-induced model and TAA-induced model.

**Conclusions:** We have demonstrated that CKD-01 exhibited anti-inflammatory and anti-fibrosis effect in various liver fibrosis models, improving liver function and reducing inflammation and fibrosis scores. Taken together, these results demonstrate that inhibition of the enzymatic activity of LOXL2/3/VAP-1 represents a potential therapeutic approach for the treatment of MASH with fibrosis.

**Keywords:** LOXL2, LOXL3,VAP-1, Liver fibrosis

## PE-08

### Effect of Combined Treatment with Statins and Ezetimibe in NASH Model: Inhibition of Macrophage via NF-kB Translocation and Activation

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**Aims:** The beneficial effects of simvastatin in cirrhosis have been reported in various experimental studies. Statin-Ezetimibe combination therapy is widely used as a treatment of hyperlipidemia. There was limited treatment options for Non-alcoholic steatohepatitis (NASH) cirrhosis and many drugs are under clinical trials. In both vivo and vitro studies, we aimed to investigate the effects of statin and ezetimibe combination therapy and putative anti-inflammation capacity in NASH-related liver fibrosis in the mouse NASH-cirrhosis model.

**Methods:** A High-fat diet and Thioacetamide (300mg/kg, intraperitoneal injection twice a week for 8 weeks) was given to establish mice models with non-alcoholic steatohepatitis (NASH) related histological change. 36 male C57BL/6J mice were di-

vided into six groups as follows: (1) regular diet (RD), (2) high-fad fed (HFD) and not treated, (3) HFD and Thioacetamide (TAA) injected (HFD-TAA), (4) HFD-TAA, and ezetimibe treated (HFD-TAA-EZET), (5) HFD-TAA and statin treated group (HFD-TAA-Statin), and (6) HFD-TAA and ezetimibe and statin combination (HFD-TAA-Combination) treated group. All mice were sacrificed 10 weeks after the beginning of the experiment.

**Results:** After treatment of combination therapy, hepatic fibrosis is ameliorated in the statin and ezetimibe combination group than the control group. *In vivo*, statin and ezetimibe combination therapy inhibits the migration of macrophages via lowering expression of CCR5 and lowered inflammation markers such as IL-1b, IL-6 and TNF-a. Also, it reduces the transcription mRNA level of a-SMA, Collagen type 1, TGF-b, PDGF-d and GFAP. *In vitro*, statin and ezetimibe combination therapy inhibit macrophage activation resulting inhibition of NA-kB pathway resulting anti-fibrosis effect.

**Conclusions:** Combined administration of statin and ezetimibe synergistically ameliorated NASH change with anti-fibrotic, anti-steatotic, and anti-inflammatory effects through reducing the expression of CCR 5 expression and downregulation the NF-kB.

**Keywords:** Cirrhosis, Nonalcoholic fatty liver, Dyslipidemia, NASH

## PE-09

### Solid Lipid Nanoparticle Ganodric Acid Ameliorates the High Fat Induced Nonalcoholic Fatty Liver Disease via Alteration Gut Microbiota and PI3K/AKT/mTOR Signaling Pathway

D Chauhan[1], **V Kumar**[2]

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by the accumulation of fat in the liver. NAFLD is considered a spectrum of liver conditions, ranging from simple fatty liver (steatosis) to a more severe form called nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and, in some cases, hepatocellular carcinoma (HCC), the most common type of primary liver cancer. Ganodric acid already showed the antioxidant and anti-inflammatory effect against various diseases. In this study, we fabricated the solid lipid nanoparticle (SLN) of ganodric acid (GA) and scrutinized the chemoprotective effect against high fat diet (HFD) and Diethylnitrosamine (DEN) induced NAFLD in rats.

**Methods:** Double emulsion solvent displacement model was used for the preparation of SLN-GA. Intraperitoneal administration of DEN (100 mg/kg) was used for the induction of HCC in rats for 2 weeks. The rats were divided into 2 groups and received the HFD with or without treatment with SLN-GA for 20 weeks. Body weight, tumor incidence, tumor nodules, hepatic, non-hepatic, apoptosis, antioxidant, pro-inflammatory and inflammatory were estimated. For the determination of gut microbiota, we collected the stools of all rats.

**Results:** Surface methodology showed the particle size (174.3 nm) and polydispersity index (0.228) for SLN-GA. SLN-GA remarkably suppressed tumor nodules (87.4%), tumor incidence (76.5%) and average size nodules (54.4%).SLN-GA remarkably decreased the level of AFP (76.4%), ALT (65.5%), AST (58.7%), ALP (61.7%), GGT (54.6%); non-hepatic parameters viz., bilirubin (53.5%), total protein (57.6%), respectively. SLN-GA also suppressed the level of SOD (47.6%), GSH (48.7%), GPx (53.4%), CAT (45.3%) and boosted the level of LPO (58.7%). SLN-GA significantly ($P$<0.001) suppressed the level of inflammatory cytokines like TNF-$\alpha$ (43.2%), IL-1$\beta$ (49.1%), IL-6 (54.6%); inflammatory parameters such as COX-2 (54.3%), PGE2 (59.4%), VEGF (64.3%), iNOS (67.6%) and NF-$\kappa$B (48.7%), respectively. SLN-GA significantly ($P$<0.001) altered the expression of Erbb2 (23.4%), Pik3rl (27.7%), Plk3ca (31.4%), Akt1 (32.5%) and Map3k1 (34.3%), respectively. Moreover, SLN-GA enhanced gut microbial richness and diversity and altered the relative abundance of *firmicutes* and *bactericides*, respectively.

**Conclusions:** SLN-GA remarkably suppressed the HFD-induced NAFLD in rats via alteration of gut microbiota and PI3K/AKT/mTOR Signaling pathway.

**Keywords:** Solid lipid nanoparticle, Nonalcoholic fatty liver disease, Antioxidant, Inflammation

## PE-10

### Comprehensive of Non-Alcoholic Fatty Liver Disease: Study Based on Indian Railway Employee (NWR)

**Rahul Kumar Meena**, Tara Singh, Gokul Ram

Indian Railway, Goverment Of India

**Aims:** Non-alcoholic fatty liver disease (NAFLD) is a common source of chronic liver disease and liver transplantation in western countries. Increasing incidence of NAFLD has been well documented from Asian countries like Japan and China. Diabetes mellitus (DM), fatness, hyperinsulinemia are predisposing factors for NAFLD. There is increase in prevalence of DM, obesity and insulin resistance in India in last two decades. Hence it is logical to expect increase in incidence of NAFLD in India. There is limited data on the Comprehensive of NAFLD from India. Majority of data comes from hospital based studies including small number of patients. Therefore this study was planned to estimate the Comprehensive of NAFLD in Indian railway employee population.

**Methods:** Residents and working place of Railway employee colonies were evaluated on history, clinical examination, an-

thropometric measurements, biochemical tests and abdominal ultrasound

**Results:** 1,168 participants were predictable. Persons with any amount of alcohol consumption, HBs Ag positive, Anti HCV positive, persons with other known liver diseases and taking medications causing liver disease were excluded. Comprehensive of NAFLD on ultrasound was 16.6%. Out of 730 subjects above the age of 20 years (341 male 384 female 389) mean age 39.08±12.3 years, 4% had diabetes, 57% had central obesity. Comprehensive of NAFLD based on the ultrasound above 20 years of age was 18.9%. NAFLD was more prevalent in male than female (24.6% vs 13.6%, $P$<0.001). Risk factors associated with NAFLD were age more than 40 years, male gender, central obesity, high BMR > 25, elevated fasting blood sugar, raised AST and ALT.

**Conclusions:** Comprehensive of NAFLD in Indian railway employee population is comparable to the NWR.

**Keywords:** NAFLD, Indian railway employee, Comprehensive, NWR

## PE-11

### Prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) in Metabolic Syndrome and Contribution of Metabolic Risk Factors in Non-Diabetic North Indian Males

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**Aims:** Non-alcoholic fatty Liver Disease (NAFLD) is a growing concern worldwide, particularly in populations with a high prevalence of metabolic syndrome. This study aimed to investigate the prevalence of NAFLD in individuals with metabolic syndrome and to assess the contribution of metabolic risk factors in the causation of NAFLD among non-diabetic North Indian males.

**Methods:** A total of 495 non-diabetic, non-alcoholic male subjects aged 30–65 years were included in the study. Metabolic syndrome was assessed using ATP III and ADA (2005) criteria, while anthropometric factors, blood pressure, and various metabolic parameters were measured. Liver ultrasonographic scanning was used to assess fatty liver.

**Results:** The prevalence of metabolic syndrome and NAFLD was found to be 24% and 14.8%, respectively, in the non-alcoholic population. Notably, 27% of individuals with metabolic syndrome had NAFLD, associated with hyperinsulinemia, insulin resistance, insulin insensitivity, elevated waist circumference, blood pressure, triglyceride levels, free fatty acids, and decreased HDL cholesterol. Moreover, the prevalence of NAFLD increased with insulin resistance and clustering of metabolic risk factors.

**Conclusions:** The present study's findings underscore the significant association between metabolic syndrome and NAFLD in non-diabetic North Indian males and highlight the importance of addressing metabolic risk factors in the prevention and management of NAFLD.

**Keywords:** Non-alcoholic fatty liver disease (NAFLD), Metabolic syndrome, Insulin resistance, Hyperinsulinemia

## PE-12

### Assessment of Nonalcoholic Fatty Liver Disease Knowledge among Healthcare Workers in a Easter Province: A Cross-Sectional Pilot Study

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) remains underdiagnosed in primary healthcare centers, indicating potential gaps in healthcare professionals' awareness. Educational interventions have been shown to improve the identification and management of NAFLD patients. This study aimed to evaluate the knowledge of NAFLD among healthcare workers in a marginalized region to address their educational needs.

**Methods:** A cross-sectional survey was conducted among 261 healthcare professionals in Eastern Province Mongolia, between January 2022 and March 2019. A tailored questionnaire focusing on key aspects of NAFLD knowledge was administered.

**Results:** Data from 426 completed questionnaires revealed insights into healthcare workers' perspectives. A significant proportion of nurses (49.3%) and female participants (78.4%) participated in the survey. Most respondents recognized NAFLD as a prevalent (85%) and preventable (91%) condition. Commonly identified risk factors included hypertension (29%) and obesity (82%). While some associations between NAFLD and conditions such as cancer, cirrhosis, and cardiovascular disease were acknowledged by respondents, gaps were notable in areas like diagnostic procedures, treatment approaches, and available therapies.

**Conclusions:** This study highlights specific knowledge deficits regarding NAFLD among primary healthcare workers. Addressing these gaps through targeted educational interventions could lead to improved detection of NAFLD cases and better management strategies to prevent disease complications.

**Keywords:** Nonalcoholic fatty liver disease, Healthcare professionals

## PE-13

### Amelioration of HOMA-IR and Hepatoprotective Properties of Dipeptidyl Peptidase-IV Inhibitors against Metabolic Associated Fatty Liver Disease in Type 2 Diabetic Mellitus

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**Aims:** Metabolic associated fatty liver disease (MAFLD) is earlier knowing as Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide, affecting up to more than half of these patients have type 2 diabetes mellitus (T2DM) through Insulin resistance which is aggravated by oxidative stress and aberrant inflammatory signals. Novel approach for treatment of T2DM is based on incretin hormone, glucagon-like-peptide 1 (GLP-1). Dipeptidyl peptidase-IV (DPP-IV) inhibitors from sitagliptin (SG) and vildagliptin (VG) t have the pleiotropic effect because incretin hormones receptor present on various tissues, including liver and pancreas. We examined whether DPP-IV inhibitors with antioxidant capacity affects $\beta$-cell function, insulin resistance, and MAFLD in T2DM rat's model.

**Methods:** T2DM model was induced in Wistar rats with high sucrose diet along with dexamethasone. Biochemical, toxicology and histological variable were evaluated between all groups. Apart from serum DPP-IV inhibition, GLP-1, Glucose, Insulin, glycosylated hemoglobin, HOMA-IR, HOMA- $\beta$, hepatic lipid peroxidation, SGOT, SGPT and endogenous antioxidant in tissue were measured with serum lipid profiles to correlate with antiperoxidative effects of SG and VG.

**Results:** Diabetes induction by corticosteroid and high sucrose diet confirmed by HOMA-IR = 2.9 %, Consequently, *in-vivo* assay of SG & VG has showed DPP-IV inhibition has showed 93.1 $\pm$2.8% and 87.1$\pm$2.8% activity in serum. GLP-1 increased in both treated drugs. DPP-IV inhibitor reduced the level of aminotransferases i.e. SGOT & SGPT and alkaline phosphatase with increasing the level of insulin and decrease HbA1c. Triglyceride and cholesterol level were also significantly in the normal range as compared to control group. SG has shown a better antioxidant capacity to protect lipid peroxidation. Liver Histology also improved

**Conclusions:** DPP-IV inhibitors improve insulin sensitivity, $\beta$-Cell function, reduce oxidative stress and toxicity which lead to improve the liver dysfunction in T2DM.These findings also suggest that GLP-1 in the liver has beneficial effects on MAFLD

**Keywords:** Metabolic associated fatty liver disease, Dipeptidyl peptidase-IV, Glucagon-like-peptide 1, Sitagliptin & vildagliptin

## PE-14

### Histopathological Analysis of Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) in Swiss Albino Mice after Exposure to Refined Diet

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**Aims:** The aim of the present study is to assess relationship between high fructose diet and risk, progression of MASLD.

**Methods:** Forty eight female albino mice of 21 years old were divided into eight groups. Group A: normal control diet for 40 days (control 40), Group B: High fructose diet for 40 days (HFD 40 days), Group C: Palm jaggery diet for 40 days (PJD 40), Group D: refined oil diet (ROD 40), Group E: normal control diet for 100 days (Control 100), Group F: High fructose diet for 100 days (HFD 100), Group G: Palm jaggery diet for100 days (PJD 100). Group H: unrefined oil diet (UROD 100), The mice are fed control diet, refined high sugar diet, Palm jaggery diet, refined & unrefined oil diet, tap water ad libitum. The body weight was measured at regular intervals. At the end of the experimental period the animals were sacrificed and blood samples were collected by cardiac puncture for biochemical analysis and liver tissues were processed for histoarchitecture analysis.

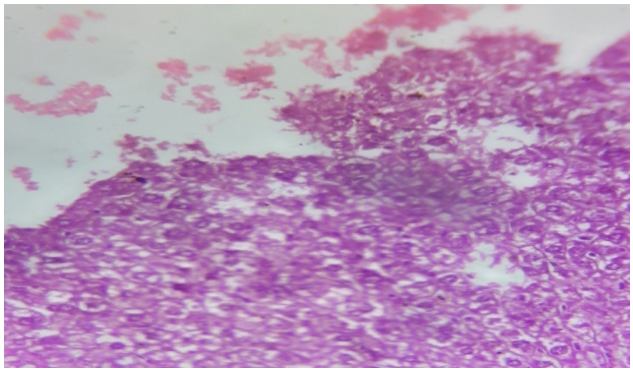

**Figure 1.** Light micrograph of liver section of mice fed HFD for 100 days showing liver parenchyma with partially effaced architecture with apoptotic changes and degenerative changes..

**Results:** HFD 100 mice shows liver parenchyma with partially effaced architecture. Many hepatocytes show cytoplasmic vaculations around central vein with apoptotic changes. The concentration of collagen fibres were increased apparently. Degenerative changes of hepatocyes were observed in some regions of liver with fat droplets. Apoptotic changes and less number of fat droplets were observed in some part of liver of PJD 100 group. Most of the perivenular and periportal hepatocytes appear normal. Control groups (control 40, 100) show normal liver parenchyma with intact liver architecture. No significant changes were observed in HFD40, PJD40 & ROD 40 liv-

er architecture. Serum insulin level was increased significantly in PJD 40, HFD 40 & HFD 100. Increased TBARS level in HFD 100 with other findings shows features of dyslipidemia ($P$<0.01).

**Conclusions:** This study concludes that chronic exposure to high fructose diet (HFD) in mice induces oxidative stress and this manifested as structural changes in liver similar to Metabolic dysfunction-associated steatotic liver disease (MASLD). Our study suggests that intake of palm jaggery will be a good alternative to fructose to maintain the normal liver morphology.

**Keywords:** MASLD, HFD, PJD

## PE-15

### Evaluation of Liver Function Test Results in Vegetarian and Non-Vegetarian Subjects

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**Aims:** The range of foods that can be eaten is restricted by a vegetarian diet, which forgoes all meat and animal products and instead favors plant-based meals, dairy products, and milk. Meat, poultry, fish, and other animal items, as well as any type of plant food, are all included in a non-vegetarian diet. According to certain research, vegetarians are less likely than non-vegetarians to develop fatty liver and fibrosis. In this study, the liver function test parameters of vegetarians and non-vegetarians were compared. Additionally, the likelihood of fatty liver and fibrosis in each research group was examined.

**Methods:** 174 vegetarians and 174 non-vegetarians from Frontline Hospital, Kathmandu, Nepal, participated in this hospital-based study. In addition to asking about each patient's medical history of fibrosis and fatty liver, LFTs were performed using the fully automated Mindray BS-360E analyzer.

**Results:** Among vegetarians, fibrosis affected 0.1% of individuals, while among non-vegetarians, it affected 2%. Furthermore, fatty liver was present in 52% of vegetarians and 59% of non-vegetarians. The mean ±SD of total bilirubin was found to be 0.42±0.18 for vegetarians and 0.83±0.32 for non-vegetarians, with both groups demonstrating statistical significance at $P$<0.05. Similarly, direct bilirubin was also significant at $P$<0.05, with a mean±SD of 0.27± 0.13 among vegetarians. Furthermore, SGPT, ALP, and albumin did not substantially differ between the groups, while SGOT and total protein were significantly higher in the non-vegetarian community at $P$<0.05.

**Conclusions:** This study clearly shows that meal patterns and liver function tests are significantly correlated and indicated a positive correlation between liver enzymes and a vegetarian diet, suggesting that the former is preferable to the latter. Additionally, compared to non-vegetarians, vegetarians were found to have a decreased risk of fibrosis and fatty liver.

**Keywords:** Fatty liver disease, Vegetarian and non vegeterian diet, Liver function test, Fibrosis

# MASLD, Clinical

## PE-01

### Non-Invasive Diagnostic Tools for NAFLD: Meta-Analysis in Clinical Practice

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**Aims:** This meta-analysis aims to evaluate the diagnostic accuracy and utility of non-invasive methods, including imaging modalities and serum biomarkers, for diagnosing and staging non-alcoholic fatty liver disease (NAFLD) in clinical settings.

**Methods:** A systematic literature search was conducted across major databases such as PubMed, Scopus, and Web of Science, up to January 2024. Studies evaluating non-invasive diagnostic tools for NAFLD in clinical practice were included. Diagnostic accuracy measures, such as sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC), were extracted and analyzed.

**Results:** A total of 56 articles met the inclusion criteria, comprising both prospective and retrospective studies. The meta-analysis revealed that several non-invasive tools demonstrated high diagnostic accuracy for NAFLD, with AUROC values ranging from 0.80 to 0.95. Imaging modalities, including transient elastography (TE) and magnetic resonance imaging (MRI), showed excellent performance in detecting hepatic steatosis and fibrosis. Additionally, serum biomarkers, such as cytokeratin-18 (CK-18) and enhanced liver fibrosis (ELF) score, exhibited promising diagnostic utility for NAFLD staging.

**Conclusions:** Non-invasive diagnostic tools, including imaging modalities and serum biomarkers, offer high diagnostic accuracy and utility for diagnosing and staging NAFLD in clinical practice. These findings underscore the importance of integrating non-invasive approaches into routine clinical practice to improve the diagnosis and management of NAFLD, ultimately enhancing patient outcomes and reducing the need for invasive procedures.

**Keywords:** NAFLD, Non-invasive diagnostic tools, Meta-analysis, Clinical practice

## PE-02

### Association between Sarcopenia and Coronary Atherosclerosis in Metabolic Dysfunction-Associated Steatotic Liver Disease

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**Aims:** This study aimed to assess the association between sarcopenia and incident coronary atherosclerosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

**Methods:** Among individuals who underwent abdominal ultrasound during a health check-up between 2012 and 2016, those with MASLD were selected. Appendicular skeletal muscle mass (ASM), adjusted for body mass index (BMI), was used to define sarcopenia. Coronary atherosclerosis was defined as > 100 calcium score or 50% diameter stenosis on coronary computed tomography. Associations were estimated using a multivariable Cox model and confirmed using propensity score matching for covariates, including baseline fibrosis and cardiovascular risk burden. Sensitivity analyses were conducted.

**Results:** Among the 1,872 patients with MASLD, 149 (8.0%) and 1,723 (92.0%) were sarcopenic and non-sarcopenic, respectively. At baseline, sarcopenic MASLD patients were significantly older (57 vs. 47 years) and had a higher atherosclerotic cardiovascular disease (ASCVD) risk score (9.19 vs. 3.75) than those in the non-sarcopenic group (*P*s<0.05). During the median follow-up of 5.6 years, 373 patients (19.9%) developed coronary atherosclerosis. Sarcopenia was significantly associated with the risk of coronary atherosclerosis (hazard ratio [HR], 1.73, 95% confidence interval [CI], 1.28–2.34; *P*<0.001), together with age, hypertension, and cigarette use. The results from the sensitivity analysis (HR, 1.96; 95% CI, 1.23–3.11; *P*=0.004) and propensity score matching (HR, 2.00; 95% CI, 1.10–3.65; *P*=0.008) confirmed the significant association.

**Conclusions:** Sarcopenia was associated with the incidence of coronary atherosclerosis in patients with MASLD, independent of baseline fibrosis or the ASCVD risk burden.

**Keywords:** Metabolic dysfunction, Hepatic steatosis, Skeletal muscle mass, Sarcopenia

## PE-03

### Association of Metabolic Syndrome and Other Related Factors with Nonalcoholic Fatty Liver Disease (NAFLD) Severity

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**Aims:** Previous studies have demonstrated that nonalcoholic fatty liver disease (NAFLD) is an emerging health challenge in the world as lifestyle changes. Studies had investigated underlying risk factors for NAFLD so far but yet the exact pathogenesis is not fully described. metabolic syndrome, hyperlipidemia, oxidative stress, insulin resistance (IR), obesity and diabetes are among the known risk factors. This study aims to investigate the association factors for NAFLD in community dwelling individuals.

**Methods:** During 2003 to 2018, all community dwelling individuals (n=897) who referred to Shahid Beheshti hospital for annual health check up were enrolled in the study. Age, BMI, Fasting Blood Sugar (FBS), Cholesterol (Chol), Triglyceride (TGL), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were measured. NAFLD diagnosis was based on transabdominal ultrasonography and categorized to normal, focal fatty infiltration, and grade I to III.

**Results:** Alongside age and BMI, serum levels of TGL, Chol, TGL, LDL, AST and ALT were significantly different between the categories of NAFLD. Logistic regression analysis showed that age (OR=1.1), BMI (OR=1.3), FBS (OR=1.04), ALT (OR=1.2) has significant independent effect of NAFLD classification.

**Conclusions:** Interventions targeting FBS and liver function tests and obesity control can be helpful in reducing the risk of NAFLD in community dwelling individuals.

**Keywords:** NAFLD, Metabolic syndrome, Hyperlipidemia, Insulin resistance

## PE-04

### Effectiveness of the ALT/AST Ratio for Predicting Insulin Resistance in a Korean Population: A Large-Scale, Cross-Sectional Cohort Study

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**Aims:** Insulin resistance is a common pathophysiology in patients with type 2 diabetes mellitus, cardiovascular disease, and non-alcoholic fatty liver disease. Thus, screening for the risk of insulin resistance is important to prevent disease progression. We evaluated the alanine aminotransferase/aspartate aminotransferase (ALT/AST) ratio to predict insulin resistance in the general population, regardless of comorbidities.

**Methods:** Datasets from the 2015, 2019, and 2020 Korea National Health and Nutrition Examination Surveys were used, and the following four indices were implemented to indicate insulin resistance: fasting serum glucose, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), and $\beta$-cell function. We analyzed the degree of association between the liver enzyme profile and insulin resistance indices using Pearson's correlation coefficient and determined the associations using linear or logistic regression analysis.

**Results:** Accordingly, ALT levels in both sexes were positively and consistently correlated with the four aforementioned insulin resistance indices in stratification analyses based on diabetes, dyslipidemia, alcohol consumption, and obesity status. In multivariate linear regression, when comparing with ALT levels, the ALT/AST ratio exhibited superior predictive performance for fasting serum glucose and HOMA-$\beta$ in Korean men and improved outcomes for all insulin resistance indices in Korean women.

**Conclusions:** In this analysis that included a large community-based population, the ALT/AST ratio was a more useful predictive marker than the HOMA-IR. Regarding the predicted presence or absence of insulin resistance, the ALT/AST ratio could better predict HOMA-IR than the ALT level alone in Koreans. A simple, precise marker that represents the ALT/AST ratio could be a practical method to screen for insulin resistance in the general population, regardless of diabetes mellitus, alcohol intake, and sex.

**Keywords:** Insulin resistance, Fatty liver, Metabolic syndrome, Liver function test

## PE-05

### Association between Nonalcoholic Fatty Liver Disease and Breast Density in Premenopausal Women in Primary Institution

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**Aims:** Metabolic dysfunction-asscociated steatotic liver disease (MASLD) and breast density are significant factors in metabolic disorders and breast cancer risk among premenopausal women. However, their relationship remains poorly understood in this population.

**Methods:** In our cross-sectional study involving 50 screening participants, 20 individuals were diagnosed with MASLD, while 30 had normal liver status. Within the MASLD group, approximately 10 participants exhibited increased breast density, compared to 20 out of 30 individuals with normal liver status showing the same.

**Results:** Our analysis revealed a notable association between MASLD and elevated breast density in premenopausal women. The observed odds ratio (OR) indicated a significant link between MASLD and increased breast density ($P$<0.05). Subgroup analyses consistently supported this observation.

**Conclusions:** Our study highlights a significant association between MASLD and increased breast density among premenopausal women, as observed in a cross-sectional analysis. These findings suggest potential interplay between metabolic disorders and breast health in this demographic. Further prospective investigations are needed to elucidate underlying mechanisms and clinical implications.

**Keywords:** Metabolic dysfunction-asscociated steatotic liver disease (MASLD), Breast density, Premenopausal women

## PE-06

### Modifiable Risk Factors for Hepatocellular Carcinoma in Patients with Non-Alcoholic Fatty Liver Disease

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**Aims:** The increasing incidence of non-alcoholic fatty liver disease (NAFLD) has led to the gradual increase of NAFLD-related hepatocellular carcinoma (HCC). In this context, we aim to investigate the association of modifiable factors with incident HCC risk among people with NAFLD.

**Methods:** Two authors independently searched the electronic databases (PubMed, Embase, and the Cochrane Library) through 01 April 2023. Observational studies reporting the association between modifiable risk factors and NAFLD-related HCC were eligible. The effect size on study outcomes was calculated using random-effect model and presented as risk ratio (RR) with 95% confidence interval (CI).

**Results:** A total of 31 studies covering 1.02 million individuals were included in the study. Regarding lifestyles factors, ever smoking and alcohol consumption were associated with 30% [1.30 (1.08-1.57)] and 140% [2.41 (1.03-5.65)] risk increase of HCC in NAFLD populations, respectively. In terms of metabolic risk factors, NAFLD patients with overweight or obesity [1.31 (1.13-1.52)], diabetes [2.08 (1.71-2.53)] and hypertensiton[1.42 (1.12-1.80)] had a higher risk of incident HCC, while the diag-

nosis of dyslipidemia was protective against NAFLD-HCC [0.78 (0.65-0.93)]. Use of metformin, statin and aspirin were associated with 18% [0.82 (0.68-0.98)], 55% [0.45 (0.36-0.56)] and 36% [0.64 (0.44-0.92)] risk reduction in incident HCC. No significant associations were observed regarding increasing body mass index and sulphonylurea or inlusin use.

**Conclusions:** This comprehensive systematic review and meta-analysis showed statistically significant increases in the risk of developing HCC in NAFLD patients with smoking, alcohol use, obesity, diabetes and hypertension, while metformin, statin and aspirin therapy might modify disease progression.

**Keywords:** Modifiable risk factors, Nonalcoholic liver disease (NAFLD), Hepatocellular carcinoma (HCC)

## PE-07

### Quantifying Microvascular Changes in Early-Stage Nonalcoholic Steatohepatitis (NASH) through Multiscale Mathematical Modeling

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**Aims:** Nonalcoholic Steatohepatitis (NASH) progresses silently and often becomes irreversible before clinical symptoms manifest. Key to this progression are the microvascular changes in the liver, which are poorly understood and rarely quantified in early stages. This research aims to develop and validate a multiscale mathematical model that specifically quantifies these changes in early-stage NASH, thereby offering a predictive tool for early diagnosis and intervention.

**Methods:** We constructed a mathematical model using a combination of fluid dynamics and network analysis to simulate blood flow and shear stress in liver microvasculature. The model parameters were derived from high-resolution hepatic ultrasound images and blood flow measurements from a cohort of 500 patients diagnosed with early-stage NASH. Each patient's vascular network was digitally reconstructed to analyze flow patterns and shear stress distributions. The model employed advanced computational techniques, including finite element analysis and machine learning algorithms, to predict areas of potential endothelial dysfunction and fibrosis.

**Results:** The model successfully identified microvascular regions susceptible to increased shear stress, correlating these areas with sites of subsequent fibrotic development. Early-stage NASH patients showed a 25% increase in regions of low shear stress (95% CI: 22.3%-27.7%), compared to controls. These areas had a significant association with the early deposition of collagen fibers, marking the onset of fibrosis. The model's predictions were consistent with actual progression observed in a 5-year longitudinal follow-up, achieving a sensitivity of 94.5% and specificity of 91.2%.

**Conclusions:** This study presents a new approach to understanding microvascular dynamics in early-stage NASH. By focusing on microvascular changes, which occur before visible clinical symptoms, our model offers a novel diagnostic tool that can significantly help in the early detection and potentially stop the progression of NASH. This research not only adds a valuable layer of understanding to the pathophysiology of NASH but also opens avenues for targeted therapeutic strategies at microvascular health in liver disease.

**Keywords:** Nonalcoholic steatohepatitis (NASH), Multiscale mathematical modeling, Microvascular changes, Early diagnosis

## PE-08

### Effects of Obeticholic Acid (OCA) in the Management of Nonalcoholic Steatohepatitis (NASH)

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**Aims:** Nonalcoholic steatohepatitis (NASH) is the commonest chronic liver disease in Western countries, which can progress to cirrhosis and is associated with increased risk of cardiovascular disease. Current pharmacological treatment of NASH has limited efficacy and therefore, there is a pressing need to develop more effective and safe agents. The aim of the study was to assess the efficacy of Obeticholic acid (OCA) in the management of NASH.

**Methods:** Patients with liver biopsy-proven NASH diagnose were randomly assigned to receive OCA 10 mg/day (group A) or placebo (group B) for 12 months. The primary study end points were improvement in aminotransferases levels and liver histology secondary end points was changes of body weight.165 patients were included 95 in the group A, 70 in the group B 7 patients dropped out, non because of side effects. Baseline characteristics were not significantly different between groups. Pre- and posttreatment liver biopsies were available in 85 patients for review at the end of the study

**Results:** After 12 months treatment with OCA as compared with placebo, was associated with a significant reduction of mean in ALT, AST and GGT levels, whereas in case of liver histology, significant improvement in steatosis, hepatocellular ballooning, lobular inflammation and fibrosis was observed. The NASH activity score (NAS) improved more in the OCA- (—

2.7 *P*<0.001) and placebo-treated patients (−0.9, *P*=0.03). ALT levels also improved in OCA- (−43 *P*=0.12) and placebo-treated patients (−9 U/L, *P*=0.02). Weight loss occurred in 46% of OCA and 30% of placebo-treated patients (*P*=0.08).

**Conclusions:** OCA was superior to placebo in improving serum ALT, AST, GGT levels and liver histology OCA therapy also reduced weight. OCA is an effective and safe treatment option in patients with NASH.

**Keywords:** Nonalcoholic steatohepatitis, Obeticholic acid, Aminotransferases

## PE-09

### Gut Microflora Composition in Patients with Non-Alcoholic Fatty Liver Disease

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in developed countries and affects about 25-30% of the population. An increasing number of studies have indicated a close relationship between dysbiosis and NAFLD. Hence, there is an interest in exploring the fatty infiltration as the result of the dysbiosis, that includes bacterial composition disturbance, with profound analysis of preventive and aggressive factors that impact on liver disease occurrence and progress. The aim of this study was to analyze the gut microbiota composition in patients with NAFLD with possible examination of aggressive and protective factors, including small intestinal bacterial overgrowth existence and biochemical markers

**Methods:** This study recruited 93 subjects with median age of 58 (22–78) diagnosed with NASH/NAFLD based on a fibro scan of the liver, ultrasound and biochemical tests. The criteria for fatty infiltration existence was a diffuse increase in the echogenicity of the liver parenchyma, decreased attenuation on the liver and ratio between the brightness level of the liver and the right kidney that was calculated for the hepato-renal index (HRI) determination. Biochemical evaluation included liver functional tests lipid profile. Stool sample examination was performed using Real time-PCR. glucose hydrogen breath test was performed to all patients

**Results:** The study's findings were as follows: A 55.1% correlation was found between NAFLD and SIBO in the gut microbiome.

The following bacteria were present in the microbiota in the following proportions: Firmicutes (46.3±1.99), Actinobacteria (26.1±18), and Firmicutes/Bacteroidetes ratio (F/B)-5.99± 1.85). Bacteroidetes and Firmicutes had a markedly negative connection (r = -0.89), as did the Bacteroidetes and Firmicutes/Bacteroidetes index (r = -0.74) and Bacteroidetes and Actinobacteria (r = -0.90). Additionally, there was a significant positive association between the F/B index and ALT (r = 0.5) and triglycerides (r = 0.52). Also, there was a middle-strong connection (r = 0.43) between the presence of SIBO and the growth of Firmicutes in NAFLD patients.

**Conclusions:** According to the study, increased Firmicutes and Actinobacteria are caused by decreased levels of Bacteroidetes, which raises triglycerides and ALT levels in patients with NAFLD and is associated with SIBO. The F/B index may be a marker for the presence of NAFLD, while Bacteroidetes may act as potential inhibitors of NAFLD progression. Patients with NAFLD should be tested for SIBO, and vice versa.

**Keywords:** NAFLD, NASH, SIBO, GUT Microflora

## PE-10

### The Predominant Impact of the Number of Risk Factors on Coronary Atherosclerosis Progression in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease

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**Aims:** Individuals with metabolic dysfunction-associated steatotic liver disease (MASLD) who are at an increased risk of cardiovascular disease (CVD) are critical to identify and manage. We aimed to assess whether the risk of CVD in patients with MASLD differed according to the type or number of cardiometabolic risk factors.

**Methods:** This longitudinal cohort study involved 5,674 adults who underwent at least two health checkups between 2004 and 2020. Steatotic liver disease (SLD) was assessed using ultrasonography and participants with SLD were classified as having either cryptogenic SLD or MASLD. CVD risk was evaluated using coronary artery calcium (CAC) progression as measured using multidetector computed tomography scans.

**Results:** Over an average 5.8-years follow-up period, patients with MASLD exhibited faster CAC progression than those with cryptogenic SLD (18% vs. 11%, *P*<0.01). MASLD with any cardiometabolic risk factor exacerbated CAC progression; however, the degree of CAC progression was similar among the different risk components. The adjusted ratios (95% CI) of CAC progression rates comparing cryptogenic SLD with MASLD

with one, two, three, four, and five cardiometabolic risk factors were 1.02 (0.99, 1.06), 1.04 (1.01, 1.08), 1.07 (1.03, 1.10), 1.08 (1.05, 1.11), and 1.11 (1.07, 1.15), respectively.

**Conclusions:** In individuals with MASLD, all cardiometabolic risk factors contributed to the deterioration of coronary atherosclerosis, with no specific factor exerting a dominant influence. Coronary atherosclerosis progression is directly associated with the cumulative number of cardiometabolic risk factors. Therefore, identifying and managing an increasing number of these factors is imperative in clinical practice, even when MASLD is diagnosed based on only one risk factor.

**Keywords:** Metabolic dysfunction-associated steatotic liver disease (MASLD), Coronary artery calcium progression, Cardiometabolic risk factors

## PE-11

### Effects of Lifestyle Modification on Liver Fat, Liver Function Test, and Fecal Microbiota in Pediatric Metabolic Dysfunction-Associated Steatotic Liver Disease

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**Aims:** Metabolic dysfunction-associated fatty liver disease (MASLD) has been steadily increasing worldwide, with a diagnosis made when there is an accumulation of liver fat by 5% or more along with meeting at least one cardiometabolic criterion. Dietary adjustments and exercise interventions are key components in managing MASLD, and studies have shown that these interventions can lead to changes in the composition of gut microbiota among MASLD patients. This study aims to evaluate the impact of lifestyle changes on liver fat, liver function, and gut microbiota in pediatric MASLD.

**Methods:** This study investigated changes in liver fat, liver function, and gut microbiota following 12 weeks of lifestyle modifications, including diet and exercise, among pediatric MASLD patients aged 10 years and older but under 18 years, who visited Seoul National University Children's Hospital from October 2022 to June 2023. Anthropometric measurements, blood tests, fecal microbiota analysis, and liver MRI were evaluated at the beginning and end of the study.

**Results:** During the study period, a total of 31 patients were enrolled, and significant reductions were observed in body weight, body mass index (BMI), waist circumference, liver enzymes, and triglyceride levels after three months of exercise and dietary adjustments. The degree of hepatic steatosis decreased from 27.1% to 20.8% on liver MRI. Subgroup analysis based on improvement in hepatic steatosis on MRI revealed that body weight, BMI, and waist circumference significantly improved in the group with improved hepatic steatosis. Patients engaging in exercise exceeding 3000 MET showed significant improvements in body weight, BMI, and HDL cholesterol. Microbiota analysis revealed significant increases in certain genera, such as *Streptococcus* and *Sellimonas*, in the group with improved ALT levels, and *Eggerthella* in the group with improved triglyceride levels.

**Conclusions:** The lifestyle modifications over three months were effective in improving anthropometric measurements, biochemical parameters, and hepatic steatosis in MASLD patients, with observed changes in fecal microbiota composition. Furthermore, improvements in body weight, BMI, and waist circumference were associated with the amelioration of hepatic steatosis, particularly notable in the group with higher levels of physical activity.

**Keywords:** Metabolic dysfunction-associated steatotic liver disease, Lifestyle intervention, Pediatric, Gut microbiota

## PE-12

### Appendicular Skeletal Muscle Mass Is Associated with Metabolic Dysfunction-Associated Steatotic Liver Disease Severity in Young Men: A Cross-sectional and Longitudinal Study

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**Aims:** While appendicular skeletal muscle mass (ASM) has been linked to the severity of hepatic steatosis, investigations into its correlation among younger age groups are lacking. This study aims to elucidate the role of ASMM in the severity of metabolic dysfunction-associated steatotic liver disease (MASLD) among a younger demographic.

**Methods:** Retrospective data were collected from patients under the age of 35 who visited the 'Liver Health Clinic' at Armed

Forces Goyang Hospital between June 2022 and February 2024. Steatosis presence was determined by a CAP score ≥ 250 dB/m, and significant fibrosis was identified with LSM > 8.0 kPa. ASM was measured using multi-frequency bioelectrical impedance analysis (Inbody 620).

**Results:** Among 910 study participants, 630 were diagnosed with MASLD. Patients with MASLD exhibited higher ASM/BMI (1.04 vs. 0.91/m$^2$, $P$<0.001) and ASM/body weight (ASM/W) (33.8 vs. 29.5%, $P$<0.001) compared to non-MASLD patients. Additionally, ASM/BMI and ASM/W demonstrated significant decreases with worsening steatosis severity and were notably lower in patients with significant fibrosis. Among 107 MASLD patients who underwent examinations twice with a median interval of 6.0 months, those with increased ASM/BMI and ASM/W showed a higher proportion of steatosis regression compared to those with decreased ASM (ASM/BMI: 44.4% vs. 20.0%, $P$=0.016; ASM/W: 45.1% vs. 19.4%, $P$=0.005). Both ASM/BMI (OR 1.13, $P$=0.024) and ASM/W (OR 1.81, $P$=0.023) were significant factors for steatosis regression during the study period.

**Conclusions:** ASM is associated with the severity of steatosis and significant fibrosis in MASLD among young adults under the age of 35.

**Keywords:** Appendicular skeletal muscle mass, Young adults, Metabolic dysfunction-associated steatotic liver disease, Significant fibrosis

## PE-13

### Performance of Non-Invasive Steatosis Indices for Discrimination of Metabolic Dysfunction-Associated Steatotic Liver Disease in Young Adults

Jaejun Lee[1,2], Chang In Han[3], Dong Yeup Lee[4], Pil Soo Sung[1,2], Si Hyun Bae[1,5], Hyun Yang[1,5]

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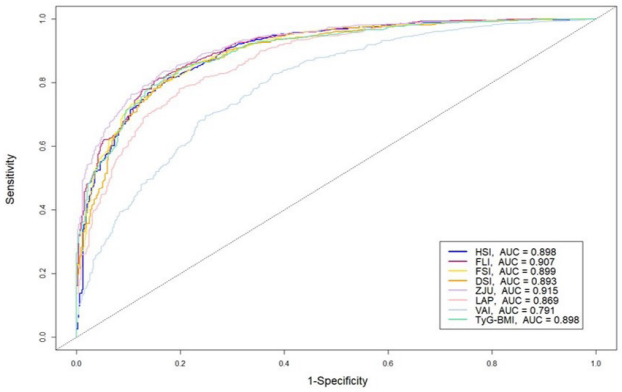
**Aims:** Although numerous non-invasive steatosis indices have been developed to assess hepatic steatosis, none have yet been validated in young adults for evaluating metabolic dysfunction-associated steatotic liver disease (MASLD). This study aims to validate these indices in younger populations.

**Methods:** Data from patients under the age of 35 who visited the 'Liver Health Clinic' at Armed Forces Goyang Hospital between July 2022 and January 2024 were retrospectively collected. The presence of steatosis was determined using a CAP score ≥ 250dB/m. MASLD was defined as the presence of steatosis in patients with at least one cardiometabolic risk factor.

**Results:** Among the 1382 study participants, 901 were diagnosed with MASLD. All eight steatosis indices showed significant differences between the MASLD and non-MASLD groups ($P$<0.001 for all). Regarding predictive performance, HSI exhibited an area under the curve (AUC) of 0.898, FLI of 0.907, FSI of 0.899, DSI of 0.893, ZJU of 0.915, LAP of 0.869, VAI of 0.791, and TyG-BMI of 0.898. The cut-off values for FLI and HSI were re-examined, indicating a need for alternative cut-off values for HSI, with a rule-in value of 42 and a rule-out value of 36 in this young population.

**Conclusions:** This study presents novel findings regarding the predictive performance of established steatosis markers in young adults. Additionally, alternative cut-off values for HSI in this population have been proposed that warrants further validation.

**Keywords:** Non-Invasive biomarker, Metabolic dysfunction-associated steatotic liver disease, Young adults, Hepatic steatosis index




## PE-14

### Impact of Korean Military Service on Steatotic Liver Disease: A Longitudinal Study of Pre-Enlistment and In-Service Health Check-Ups

Jaejun Lee[1,2], Jae Hyeop Jung[3], Sung Jun Choi[4], Beomman Ha[3], Hyun Yang[1], Pil Soo Sung[1], Jeong-A Yu[3], Si Hyun Bae[1]

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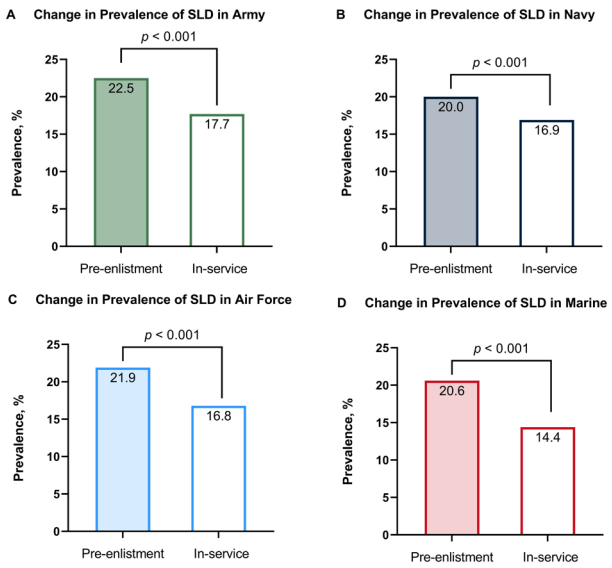
**Aims:** Young Korean men are obligated to serve in the military for 18–21 months. We investigated the effects of military service on steatotic liver disease (SLD) and other metabolic parameters.

**Methods:** Pre-enlistment health check-up performed from 2019 to 2022 and in-service health check-up performed from 2020 to 2022 were merged as paired data. SLD was defined as hepatic steatosis index of 36 or higher. Patients with hypertension or hypertriglyceridemia were included in the analysis.

**Results:** A total of 503,136 paired cases were included in the analysis. Comparing pre-enlistment and in-service health check-ups, the prevalence of SLD (22.2% vs. 17.6%, *P*<0.001), hypertension (7.6% vs. 4.3%, *P*<0.001), and hypertriglyceridemia (8.1% vs. 2.9%, *P*<0.001) decreased during military service. In terms of body mass index, the proportion of underweight (8.2% vs. 1.4%, *P*<0.001) and severe obesity (6.1% vs. 4.9%, *P*<0.001) individuals decreased over time. Regarding factors associated with SLD development and resolution, age was positively associated with SLD development (odds ratio [OR] 1.107, *P*<0.001). A health checkup interval of < 450 days was associated with SLD development (OR 0.811, *P*<0.001) and positively correlated with SLD resolution (OR 1.041, *P*<0.019). Those serving the marine and air forces were less likely to develop SLD, whereas those serving the navy were more likely to develop SLD. Serving in the army was against SLD resolution, whereas serving in the air force was an inducible factor for SLD resolution.

**Conclusions:** The prevalence of SLD, HTN, and hypertriglyceridemia decreased substantially during Korean military service.

**Keywords:** Nonalcoholic fatty liver disease, Metabolic dysfunction-associated steatotic liver disease, Young men, Korea military




## PE-15

### Limited Performance of the Steatosis-Associated Fibrosis Estimator Score in Young Asian Subjects with Steatotic Liver Disease

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**Aims:** The steatosis-associated fibrosis estimator (SAFE) score has developed in distinguishing clinically significant fibrosis in patients with steatotic liver disease (SLD). However, validation of its performance in Asian subjects are limited. To evaluate the performance of the SAFE score in Asian subjects with biopsy proven SLD and in different subgroups according to age, sex, and body mass index.

**Methods:** We retrospectively analysed 6,383 living liver donors who underwent liver biopsy between 2005 and 2023. Of these, 1,551 subjects with biopsy-proven SLD were included. Performance of the SAFE score was evaluated using area under the curves (AUCs) and compared to those of NAFLD fibrosis scores (NFS) and fibrosis-4 index (FIB-4).

**Results:** The prevalence of clinically significant fibrosis in the cohort was 2.2%. The proportion of subjects with a 'low-risk' SAFE score was the highest (91.0%), followed by those with 'intermediate' (7.8%) and 'high-risk' (1.2%) scores. The prevalence of fibrosis in subjects with low-, intermediate-, and high-risk scores was 1.6, 6.6, and 21.1%, respectively. The SAFE outperformed FIB-4 and NFS (AUC: 0.70 vs. 0.64 for both NFS and FIB-4). However, it showed low diagnostic accuracy and sensitivity (27%) at the low cutoff (SAFE < 0) in subjects aged 30–39 years (fibrosis: 1.2%), despite having a high negative predictive value (0.99). In subgroup analysis, male subjects and subjects with high BMI (≥ 25 kg/m$^2$) showed better performance than their counterparts.

**Conclusions:** The SAFE performs better than other noninvasive tests in Asian subjects. However, its performance in young Asian subjects with SLD is limited.

**Keywords:** Steatotic liver disease, The steatosis associated fibrosis estimator score, Liver fibrosis, Noninvasive test

## PE-16

### Association of Weight-Adjusted-Waist Index with Liver Steatosis and Fibrosis in Biopsy Proved NAFLD

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**Aims:** Many obesity indices, including the commonly used waist circumference (WC) and BMI, have been shown to be associated with NAFLD. However, it is important to note that BMI cannot differentiate fat distribution. Association of weight-adjusted-waist index(WWI) is a recently proposed new anthropometric index, which exhibits a weaker correlation with BMI and reduces the risk of the "obesity paradox" associated with BMI. The purpose of this study was to explore the association of WWI with liver steatosis and fibrosis in biopsy proved NAFLD

**Methods:** A cross-sectional study including 249 participants was conducted in biopsy proved NAFLD. Multiple linear regression was used to validate the association of WWI with NAFLD and liver fibrosis, Subgroup analyses were used to verify the stability of the relationship between the independent and dependent variables in different populations.

**Results:** There was a positive association of WWI with NAFLD and liver fibrosis. In the model adjusted for all covariates, the effect values of WWI with NAFLD and liver fibrosis were (OR=2.44, 95% CI: 2.09–3.82) and (OR=1.40, 95% CI: 1.05–1.79), respectively. This positive correlation became more significant as WWI increased when WWI was presented in quartiles. However, there was a linear correlation between WWI and liver fibrosis (LLR=0.291). When subgroup analyses were performed by indicators such as age and gender, we found that the positive association between WWI and the dependent variables (NAFLD and liver fibrosis) was more pronounced in white male participants with older age.

**Conclusions:** WWI was positively associated with the prevalence of NAFLD and liver fibrosis. Participants with a WWI less than 11 should be cautious about the possibility of an increased risk of NAFLD development due to a higher WWI. Meanwhile, white males older than 50 years of age should be more cautious about the higher risk of NAFLD and liver fibrosis that might be associated with an increased WWI.

**Keywords:** NAFLD, Biopsy,Waist, BMI, Steoatosis, Fibrosis

## PE-17

### Exploring Autophagy-Related microRNAs in NAFLD Progression: A Machine Learning Approach to Epigenetic Mechanisms

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**Aims:** Exploring the relationship between autophagy and the evolution from Non-Alcoholic Fatty Liver Disease (NAFLD) to Non-Alcoholic Steatohepatitis (NASH) is at the forefront of liver disease research. This investigation focuses on microRNAs (miRNAs) that regulate autophagy pathways, offering a perspective on the progression of NAFLD. Our study leverages advanced machine learning (ML) techniques to dissect the interactions between autophagy-related miRNAs and NAFLD progression, aiming to identify novel epigenetic markers and therapeutic targets.

**Methods:** We constructed a comprehensive dataset from 1,500 simulated subjects across various NAFLD stages, incorporating detailed miRNA expression profiles, autophagy marker levels, and clinical indicators of disease progression. An ML pipeline was developed, employing Elastic Net regularization for feature selection to isolate relevant miRNAs and autophagy markers. This was followed by the deployment of a Convolutional Neural Network (CNN) for the predictive assessment of progression risk. The dataset was segmented into an 80% training subset and a 20% validation subset, with model performance evaluated through metrics such as accuracy, sensitivity, specificity, and predictive value.

**Results:** Our approach identified a key subset of autophagy-related miRNAs, including miR-33a, miR-34a, and miR-101, as pivotal in NAFLD progression. Utilizing these miRNAs and autophagy markers, the CNN model achieved exceptional predictive accuracy (94.6%), sensitivity (95.2%), specificity (93.8%), and an impressive AUC of 0.98 (95% CI, 0.96-0.99). The model also revealed a new interaction between miR-33a and the autophagy gene ATG7, suggesting a previously unknown epigenetic mechanism in NAFLD pathogenesis.

**Conclusions:** This study shows the critical role of autophagy-related miRNAs in NAFLD progression, supported by machine learning. The identified miRNAs and their interactions with autophagy pathways open new paths for understanding NAFLD's molecular mechanisms, offering promising directions for targeted treatment and diagnostic advancements. Our findings underscore the potential of integrating machine learning with epigenetic research to advance precision medicine in treating complex diseases like NAFLD.

**Keywords:** NAFLD progression, Autophagy-related micrornas, Machine learning, Epigenetic mechanisms

## PE-18

### Short-Chain Fatty Acids as Predictive Markers and Modulators of Metabolic Associated Fatty Liver Disease Progression through Machine Learning Analysis

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**Aims:** Short-chain fatty acids (SCFAs), primarily produced by the gut microbiota through the fermentation of dietary fibers, have been implicated in the regulation of host energy metabolism and immune response, suggesting a potential link to Metabolic Associated Fatty Liver Disease (MAFLD) progression. This study aims to investigate the specific role of SCFAs in MAFLD, employing machine learning algorithms to analyze SCFA profiles and their predictive value for disease progression, thereby offering a novel approach to early diagnosis and intervention in MAFLD patients.

**Methods:** A cohort of 2,500 individuals at varying stages of MAFLD (confirmed via liver biopsy and comprehensive metabolic profiling) and 2,500 control subjects were enrolled in this prospective study. Fecal samples were collected biannually to analyze SCFA concentrations using gas chromatography-mass spectrometry (GC-MS). We leveraged a specialized machine learning framework combining feature selection techniques and gradient boosting machines (GBMs) to discern patterns in SCFA profiles correlating with MAFLD progression or remission. The model's predictive accuracy was rigorously validated against a reserved test set, using metrics such as sensitivity, specificity, and the Matthews correlation coefficient (MCC).

**Results:** The predictive model distinguished MAFLD progression with a sensitivity of 88%, specificity of 90%, and an MCC of 0.78. Specific SCFA profiles, characterized by elevated acetate and reduced butyrate and propionate levels, were identified as significant predictors of MAFLD progression, with a 95% confidence interval (CI). Individuals with this SCFA signature were found to have a 4.5-fold increased risk of MAFLD progression (CI: 4.2-4.9) compared to those with balanced SCFA levels. Additionally, machine learning analysis indicated that interventions aimed at modulating SCFA profiles (e.g., dietary adjustments) could potentially reduce MAFLD progression risk by up to 60% in susceptible individuals.

**Conclusions:** This study investigates the predictive role of SCFA profiles in MAFLD progression using advanced machine learning techniques. Our findings emphasize the importance of gut microbiota-derived metabolites in metabolic liver disease and open new avenues for non-invasive diagnostics and targeted dietary interventions to mitigate MAFLD progression. By focusing on metabolic biomarkers such as SCFAs, this research facilitates personalized medicine approaches in managing MAFLD, offering hope for improved patient outcomes through early detection and preventive strategies.

**Keywords:** Short-chain fatty acids (SCFAs), Metabolic associated fatty liver disease (MAFLD), Machine learning, Dietary intervention

## PE-19

## Differential Exercise Requirements for Nonalcoholic Fatty Liver Disease Resolution Across Age Groups: A Longitudinal Study of Korean Military Officers

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**Aims:** Nonalcoholic fatty liver disease (NAFLD) is a global health concern, and despite its high prevalence, lifestyle modifications such as exercise remain the only practical option for resolving this condition. This study aims to identify factors associated with NAFLD resolution, with a focus on the role of exercise, in different age groups.

**Methods:** Longitudinal data from Korean military officers, during the period 2019–2021, were obtained from the National Health Information Database. NAFLD was defined as a hepatic steatosis index (HSI) ≥ 36, and NAFLD resolution was defined as individuals achieving HSI < 36 in the subsequent year of diagnosis. Information on alcohol consumption, exercise frequency, and family history of diabetes was collected through self-reported questionnaires.

**Results:** The analysis included a total of 163,728 individuals, with a mean age of 36.87, predominantly male (91.62%). The prevalence of NAFLD was 27.04%, 28.11%, and 28.54% in 2019, 2020, and 2021, respectively. Favorable factors for NAFLD resolution encompassed moderate-intensity exercise for more than 180 minutes/week, vigorous-intensity exercise for more than 90 minutes/week, female sex, age, and resistance exercise for more than 3 d/week. Hypertension, family history of diabetes, and smoking were identified as factors against NAFLD resolution. The exercise requirements for NAFLD resolution varied among age groups, with those < 30 years old requiring more than 180 minutes/week of moderate or vigorous-intensity exercise and those > 50 needing only 90 minutes/week of such exercise.

**Conclusions:** The exercise requirements for NAFLD resolution exhibit age-related differences. Individualized guidance for NAFLD management should consider these variations and be tailored to specific age groups.

**Keywords:** NAFLD, Age, Exercise, Military

## PE-20

### Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Burden among People Living with HIV (PLHIV): A Cross-Sectional Study

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**Aims:** This study aims to provide the prevalence of liver steatosis and characteristics of MASLD in PLHIV in a tertiary hospital in the Philippines. Our data will establish the need to include multiple liver and metabolic risk factors screening for primary healthcare in the Philippines.

**Methods:** This is a cross-sectional study involving a total of 51 Filipino male patients with HIV were screened which included 35 patients divided into two groups: 21 with NAFLD and 14 without, resulting in a 60% NAFLD prevalence.

**Results:** The average age of patients was 40 years, with an HIV duration of 7 years and a mean CD4 count of approximately 630 cells/mm3. Antiretroviral regimens included Lamivudine + Tenofovir with Dolutegravir (54%), Efavirenz (43%), and one patient on Lamivudine + Zidovudine + Efavirenz (3%).

Both groups have dyslipidemia, with 86% of MASLD patients and 64% of those without MASLD affected. Among MASLD patients, 62% were overweight to obese, often associated with Type 2 Diabetes and Hypertension (20%). In contrast, 93% of those without MASLD had a normal BMI and a higher rate of opportunistic co-infections (30%).

Liver-related measurements, including mean transaminase levels (AST: 68, ALT: 126), liver stiffness (7.41 kPa), and CAP scores (323 dB/m), were higher in the MASLD group compared to those without MASLD. Although mean FIB4 scores indicated mild fibrosis (0.82) in all patients, mean APRI scores revealed evidence of fibrosis (0.67) in the MASLD group, while those without MASLD showed an absence of fibrosis (0.46). Those with elevated AST (OR: 1.05, 95%CI: 1.002 – 1.09) and those who were given LTE (OR: 6.53, 95% CI: 1.10 – 38.98) were significantly associated with MASLD.

**Conclusions:** The prevalence of MASLD among PLHIV is high, with the majority having classic MASLD. Nevertheless, a considerable number of lean MASLD cases were also identified. The choice of ARV regimen emerges as a potentially significant risk factor in the development of MASLD. This emphasizes the need for thorough screening for MASLD in PLHIV and investigation of the factors associated with this increased risk to prevent cardiovascular and liver-related morbidity and mortality.

**Keywords:** NAFLD, MASLD, HIV, PLHIV

## PE-21

### Repurposing SGLT2 Inhibitor to Attenuate Oxidative Stress Mediated Hepatic Injury in Wistar Rats

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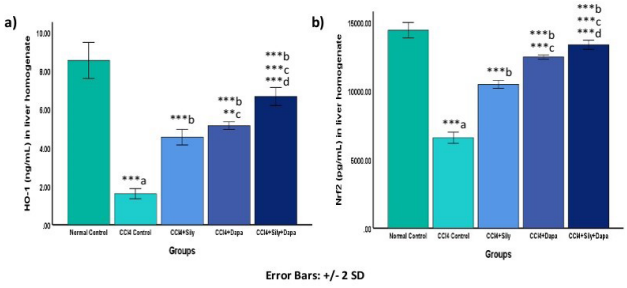
**Aims:** This study aimed to investigate the *in vivo* antioxidant potential of dapagliflozin and silymarin alone and in combination against carbon tetrachloride-induced oxidative stress-mediated hepatic injury in Wistar rats.

**Methods:** 30 adult Wistar rats (body weight 140-200 g) were randomly divided into five groups (n=6/group): Group I- Normal control, Group II- Disease control, Group- III- Silymarin, Group IV- Dapagliflozin and Group V- Dapagliflozin + Silymarin. Oxidative stress-mediated hepatic injury was induced to group II-V by administering CCl 4 every 48 hours for 14 days. AST/ALT ratio, Total bilirubin, and heme oxygenase- 1 were estimated, and qualitative histopathological examinations of the liver were performed.

**Results:** Oxidative stress-mediated hepatic injury was significantly (p<0.05) observed in the disease control rats compared to the normal control group. Both dapagliflozin and silymarin alone and in combination significantly (p<0.05) decreased the serum AST/ALT ratio, Total bilirubin, and increased the levels of heme oxygenase-1 compared to the disease control rats.

**Conclusions:** The present study demonstrated *in vivo* antioxidant potential of dapagliflozin and silymarin alone and in combination against CCl 4 -induced oxidative stress-mediated hepatic injury in Wistar rats.

**Keywords:** Hepatotoxicity, Antioxidant, SGLT-2 inhibitor




## PE-22

### AI-Driven Analysis of Phytonutrient Impact on Non-Alcoholic Fatty Liver Disease Progression: A Machine Learning Approach

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**Aims:** Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as a significant global health issue, directly associated with dietary habits. The influence of specific dietary elements, particularly phytonutrients, on the development of NAFLD is not well understood. This study focuses on analyzing the effect of phytonutrient intake on the advancement of NAFLD by employing machine learning methods. This approach provides a new perspective on managing liver health via diet, emphasizing the potential of phytonutrients to change the progression of this disease.

**Methods:** We employed a dataset combining high-resolution dietary intake logs, focusing on phytonutrient consumption (flavonoids, carotenoids, and polyphenols), with liver health metrics derived from advanced imaging techniques over a period of five years. Dietary data were meticulously quantified using a validated food nutrient database. We designed a custom machine learning model incorporating feature extraction methods to identify relevant phytonutrient patterns and a gradient boosting framework to predict NAFLD progression stages. The model's predictive capacity was assessed via precision, recall, F1-score, and the Matthews correlation coefficient (MCC).

**Results:** Our model achieved a precision of 89.7%, recall of 87.5%, F1-score of 88.6%, and MCC of 0.85, showcasing high predictive accuracy and reliability. It identified a significant inverse relationship between total flavonoid intake and NAFLD progression, with an odds ratio (OR) of 0.62 (95% CI: 0.59-0.65) for each standard deviation increase in daily flavonoid consumption. Specifically, diets high in epicatechin (found in dark chocolate and green tea) and quercetin (found in onions and apples) were associated with a 40% decreased risk of advancing from mild to moderate NAFLD (95% CI: 37%-43%).

**Conclusions:** This study reveals the protective role of specific phytonutrients against NAFLD progression, using machine learning analysis. It shows the potential for targeted dietary interventions in managing and preventing NAFLD. By identifying the beneficial effects of select phytonutrients, we prepare for personalized nutrition strategies, emphasizing the importance of diet in liver health. This research advances the field of nutritional science and the ability of machine learning to explore the complex relationships between diet and health.

**Keywords:** NAFLD (Non-alcoholic fatty liver disease), Phytonutrients, Machine learning techniques, Diet-related liver health management

## PE-23

### Clinico-Demographic Profile of Individuals with Incidental Ultrasound Finding of Fatty Liver

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**Aims:** Fatty liver is one of the most common incidental finding of ultrasound abdomen. This study aims to assess the clinico-demographic profile of apparently healthy individuals with incidental ultrasound finding of fatty liver.

**Methods:** It is a prospective single center study conducted from 1st July, 2023 to 31st December, 2023 where apparently healthy individuals with incidental ultrasound finding of fatty liver were included. Their clinico-demographic profile was then recorded and analysed.

**Results:** A total of 483 apparently healthy individuals were included among which majority (66%) were from 40-50 years age-group. 59% of the population with fatty liver were male. Most (48%) of them were literate. Majority (70%) of them were overweight.

**Conclusions:** Ultrasound finding of fatty liver was more commonly found among apparently healthy male who were overweight, which predicts being overweight as risk factor for fatty liver.

**Keywords:** Clinicodemographic profile, Incidental, Ultrasound, Fatty liver

## PE-24

### Prevalence and Risk Factors of Metabolic-Associated Fatty Liver Disease among Hospital Staff, Single Center Study

**Nyam Biziya**[1], Saranchimeg Udirsad[2], Uugantuya Tumenjargal[3], Bayaraa Sanga[4]

Dornod Medical Center, Choibalsan, Mongolia

**Aims:** Metabolism-related fatty liver disease (MAFLD) prevalence among hospital staff remains poorly reported. The goal of this study was to estimate the prevalence and risk factors of MAFLD among hospital staff aged ≥18 years.

**Methods:** Using type B ultrasonics, hospital staff undergoing medical examinations at the Second Affiliated Hospital of Dornod Medical Center from January 2022 to September 2023 were categorized into a health control group (312 subjects) and an MAFLD group (98 subjects). Demographic, biochemical, and blood examination data were compared between the two groups. Logistic regression was used to identify independent risk factors for MAFLD, and receiver operating characteristic (ROC) curves were employed to evaluate the predictive

values of MAFLD risk factors.

**Results:** The prevalence of MAFLD was 38.2%. Older age (OR=1.08, *P*<0.001), triglyceride-glucose (TyG) index (OR=7.003, *P*<0.001), low-density lipoprotein cholesterol (LDL-C) (OR=2.086, *P*=0.029), red blood cell count (RBC) (OR=2.486, *P*=0.001), eating out (OR=0.05, *P*=0.001), regular exercise (OR=24.018, *P*<0.001), and overweight (OR=3.917, *P*=0.003) were independently associated with MAFLD. The area under the curve (AUC) of the MAFLD prediction model was 0.920 [95% CI (0.887, 0.935)], with a sensitivity of 0.892 and specificity of 0.910. The diagnostic value of the model was higher in the female MAFLD group after stratified analysis by gender. TyG index contributed more significantly to MAFLD in the model, with a higher diagnostic value observed in the female MAFLD group compared to the male MAFLD group.

**Conclusions:** The prevalence of MAFLD among hospital staff was 38.2%. The TyG index can effectively predict MAFLD, particularly among female hospital staff.

**Keywords:** Metabolism-related fatty liver disease, Health-care workers

## PE-25

### Association between Fatty Liver and Colonic Polyp

**Khishgee**[1], Amarjargal[2], Enkhjargal[2]

Intermed Hospital

**Aims:** Metabolic syndrome components such as obesity and hyperlipidemia are considered the most common etiological factors for colon polyps as well contributing to the pathogenesis of fatty liver disease. We aimed to assess the relationship between fatty liver and colon polyps.

**Methods:** To determine the possible association between ultrasound fatty liver stage and colonic polyps.

This retrospective cohort observational study conducted at the Intermed Hospital in Ulaanbaatar, Mongolia, included subjects who underwent screening colonoscopy over a 3 months period. Data were extracted from the patient charts and included demographics, anthropometric measurements, vital signs, underlying diseases, medical therapy, laboratory data, and results of the abdomen ultrasound. The colonoscopy report extracted polyp were also evaluated.

**Results:** A total of 105 patients were enrolled in study; 52.3% of patients were males. Their mean age was 48.48±11.56 years. Fatty liver stages that are determined by abdominal ultrasonography: Mild fatty liver accounts for 25.7%, moderate fatty liver 26.7%, severe fatty liver 4.8%. Polyps are determined by colonoscopy. 42.8% of patients were evaluated polyps. Fatty liver stages were determined colon polyps. 9(20%) polyps were in mild fatty liver stage, 17 (37.7%) polyps were in moderate fatty liver stage, 2(4%) polyps were in severe fatty liver stage. Colon polyps and fatty liver abdominal ultrasonography is a statistically significant difference (OR-2.52, *P*<0.01 95%CI 1.36-1.98. The multivariate analysis, after adjusting for, age, BMI, glucose, HBA1c, triglycerides, HDL, LDL, total cholesterol, showed that the presence of was associated with increased risk for colon polyps (*P*<0.01). Colon polyps were more common in overweight men (*P*<0.01).

**Conclusions:** Colon polyps and fatty liver abdominal ultrasonography is a statistically significant difference. Fatty liver is specifically associated with an increased risk of colorectal adenomatous and hyperplastic polyps in men.

**Keywords:** Fatty liver, NAFLD, Colon polyp

## PE-26

### Relationship between the Hepatic Steatosis Index and Microalbuminuria : Using Large Sized Cohort Real World Data

**Seul Ki Han**[1,3,4], Myung Jae Seo[2], Taesic Lee[2,4],Soon Koo Baik[1,3,4], Moon Young Kim[1,3,4]

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**Aims:** Several studies have attempted to demonstrate the relationship between fatty liver and microalbuminuria. Due to the limitation of radiologic finding and biopsy, non-invasive parameter such as the hepatic steatosis index (HSI) was developed to predict steatosis. The current study aims to demonstrate the association between HSI and microalbuminuria.

**Methods:** Korea National Health and Nutrition Examination Surveys from 2011 to 2014, 2019, and 2020 were used to confirm our hypothesis. Univariate and multivariate linear regressions were used to reveal the relationship between NAFLD and microalbuminuria.

**Results:** In both Korean men and women, the positive relationship between HSI and urine albumin creatinine ratio (UACR) was exhibited. The positive correlation was replicated after grouping HSI into deciles. In all three Korean men and women models, HSI showed an independently positive association with UACR. In Korean women, not men, independent positive relationships between HSI deciles and UACR were observed after medical and laboratory variables adjustment.

**Conclusions:** Fatty liver disease could be a significant and potent risk factor for microalbuminuria.

**Keywords :** Fatty liver, Albuminuria, Hepatic steatosis index

## Liver Cancer, Basic

### PE-01

### Cholangiocarcinoma Cancer Modelling by CRISPR-Cas9 and Hepatic Progenitor Organoid Recapitulates Cholangiocarcinoma Carcinogenesis and Pathophysiology

Michael Adisasmita[1], Hyomin Lee[2], Myounghoi Kim[1], Michael Girma Mamo[1], Ji Hyun Shin[1], Woochang Hwang[3], Junho Hur[2], Dongho Choi[1]

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**Aims:** Cholangiocarcinoma (CC) is a fatal malignancy of the biliary epithelial cells in the liver, consisting of intrahepatic and extrahepatic biliary system. A vital discovery that significantly advances cancer research is the development of disease modelling technology like the cancer organoid technique. These organoids can be generated from CC patients' tissue specimens but with limited efficiency. In addition, cancer organoids can be derived from normal adult stem cells subjected to CRISPR gene editing to simulate the gene mutation that occurred during early carcinogenesis.

**Methods:** To generate the iCC cancer organoid model, we co-transfected normal human chemically-derived hepatic progenitor cells (hCdHs) with CRISPR-Cas9 plasmid and gRNA plasmids for TP53 and BAP1. Following the transfection, we generated cancer organoids from these mutant cells and performed multiomics analysis (sanger sequencing, qPCR, and RNA-Seq) of this cancer disease organoid model.

**Results:** We successfully generated cancer organoid from hCdHs that can be massively expanded from a relatively small clinical sample by the knock-out of TP53 and BAP1, a well-established iCC cancer driver gene. These CRISPR-engineered cancer organoids showed comparable pathophysiological properties with the CC features. We observed cribriform feature on these organoid derived from intrahepatic biliary cell-derived adenocarcinoma (CK19+, ALB-), as well as mucin (MUC1+) overexpression in the organoid lumen by immunofluorescent staining. Transcriptomic profile by bulk RNA-Seq of this cancer organoid, as well as cell line, suggested malignant transformation (CEACAM5/S100P/CA9/TSPAN1+) that is significantly altered from the wildtype organoid.

**Conclusions:** These results demonstrated the capability of our CRISPR-engineered hCdHs-derived cancer organoid as a powerful cancer disease modelling platform.

**Keywords:** Cholangiocarcinoma, Crispr, Liver organoid

### PE-02

### Hesperidin Attenuates DEN Induced Liver Cancer in Rats via Inhibition of Activation of AMPK and Blocking of MTOR-Dependent Signaling Pathway

Deepika Singh

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**Aims:** The excessive buildup of the extracellular matrix that characterizes liver fibrosis is a wound-healing response to chronic liver diseases/ inflammatory diseases and also lead to liver cancer When liver cancer and mammalian target of rapamycin (mTOR) activity are present, inhibition of AMPK activity may be a key mechanism. In the current work, we examined the impacts of hesperidin against DEN-induced liver cancer in rats and its underlying mechanism.

**Methods:** The excessive buildup of the extracellular matrix that characterizes liver fibrosis is a wound-healing response to chronic liver diseases/ inflammatory diseases and also lead to liver cancer When liver cancer and mammalian target of rapamycin (mTOR) activity are present, inhibition of AMPK activity may be a key mechanism. In the current work, we examined the impacts of hesperidin against DEN-induced liver cancer in rats and its underlying mechanism.

**Results:** Hesperidin significantly elevated the level of aspartate transaminase, alkaline phosphatase acid phosphatase, blood urea nitrogen, creatinine, and total protein. It also significantly ($P$<0.05) suppressed the antioxidant profile malondialdehyde (MDA,) glutathione-S-transferase (GST), catalase, and superoxide dismutase. It also significantly ($P$<0.05) reduced the s $\alpha$-SMA, TIMP-1, and collagen I protein expressions It also inhibited the phosphorylation of PI3 K and Akt, enhanced the p-AMPK expression, and reduced p-mTOR.

**Conclusions:** The result of the present study indicates that hesperidin induced the HSC activation apoptosis and attenuated liver cancer via inhibition of mTOR and AMPK activation signaling pathways.

**Keywords:** Hesperidin, Liver cancer, Rats

### PE-03

### Disparities in Hepatic Microbial Composition between Tumor and Adjacent Normal Liver Tissue: A Pivotal Role in Hepatocellular Carcinoma Development

Hee Eun Jo[1,2], Sophallika Khom[3], Sumi Lee[3], Su Hyeon Cho[3], Shin Young Park[3], Ga Ram You[4], Hyosin Kim[5], Nah Ihm Kim[6], Hak-Jong Choi[1], Jae-Ho Jeong[2], Misun Yun[1], Jae Hyun Yoon[3]

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Gwangju, Korea; [2]Department of Biomedical Sciences and Department of Microbiology, Chonnam National University Medical School, Gwangju, Korea; [3]Department of Gastroenterology and Hepatology, Chonnam National University Hospital and Medical School, Gwangju, Korea; [4]Department of Gastroenterology and Hepatology, Hwasun Chonnam National University Hospital and Medical School, Hwasun, Korea; [5]Department of Surgery, Chonnam National University Hospital and Medical School, Gwangju, Korea; [6]Deparment of Pathology, Chonnam National University Hospital and Medical School, Gwangju, Korea

**Aims:** Via gut-liver axis, the interactive pathway, alteration of microbiome has been suggested as principal contributor in not only various liver disease but also in development of HCC (hepatocellular carcinoma). Thus, our inquiry sought to delineate disparities in microbial composition within HCC cohorts, concurrently conducting a comparative analysis with the microbial composition observed in adjacent non-tumor tissue.

**Methods:** This study enrolled a total of 9 samples from 6 patients who underwent surgical resection for HCC at Chonnam national university hospital from April 2023 to September 2023 [Non-tumor (n = 5) and Tumor (n = 4)]. Liver tissues were immediately stored at –80 ℃ until analysis. The Illumina MiSeq sequencing system was used to conduct 16s rRNA amplicon sequencing from bacterial genomic DNA extracted from liver tissues. The 16s rRNA sequence data were analyzed using QIIME2 (version 2023.2).

**Results:** We analyzed the disparities in hepatic microbiome linked to HCC progression, there were no significantly differences in microbial richness and community composition with HCC progression. Nevertheless, the results of phylogenetic profiles revealed significantly altered microbial taxa between the groups at the phylum (Figure 1A) and genus levels (Figure 1B). After normalizing relative abundance in the genus level, distinct taxonomic patterns correlation with HCC progression were discernible in the heatmap (Figure 2A). At the species level, unclassified Tepidisphaerales ($P$=0.035) and unclassified *Aquabacterium* ($P$=0.046) exhibited significantly abundant in the Non-tumor group compared to the Tumor group. Conversely, the abundance of unclassified Frankiales ($P$=0.044), unclassified *Conexibacter* ($P$=0.020), unclassified Acidimicrobiia ($P$=0.022), and unclassified Ktedonobacteria ($P$=0.031) increased in the Tumor group (Figure 2B).

**Conclusions:** Our findings underscore that the disparities in hepatic microbial composition between tumor and adjacent normal liver tissue may potentially playing a pivotal role in HCC development.

**Keywords:** Hepatocellular carcinoma, Microbiome, Tumor stage, Prognosis

Figure 1.

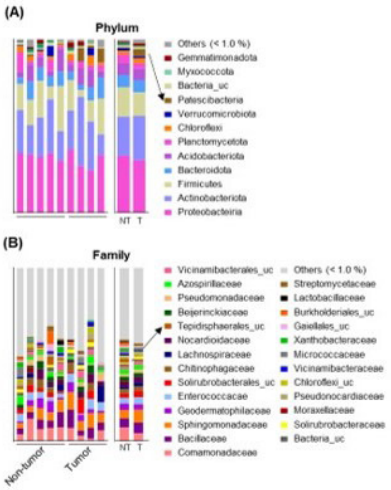


**Figure 1. Phylogenetic profiles of microbes in patients with HC**

Taxonomic composition of hepatic microbiota of HCC patients at the phylum (A) and family (B) levels. Statistical analysis was conducted using one-tailed Student's *t*-test (*; $p < 0.05$). uc; unclassified taxa, others; sum of the taxa with an average of less than 1 % of relative abundance, NT; Non-tumor group, T; Tumor group.

Figure 2.

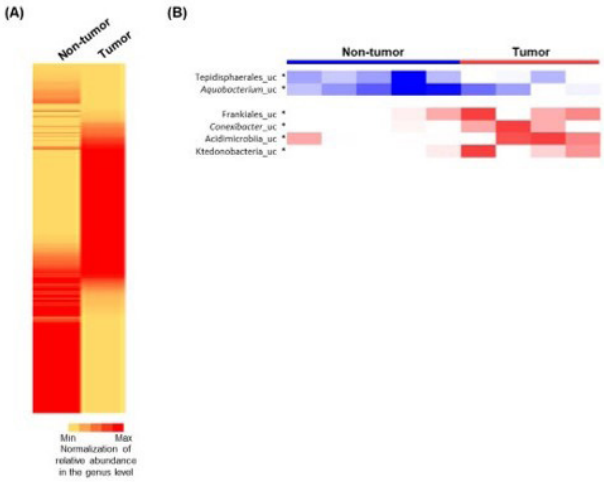


**Figure 2. Differential composition in the hepatic microbiome in patients with HCC.**

(A) Normalized heatmap of the bacterial abundance at the genus level in the Non-tumor and Tumor groups. (B) The heatmap represents the relative abundance at the species level. Statistical analysis was performed using one-tailed Student's *t*-test (*; $p < 0.05$). Uc; unclassified taxa.

## PE-04

### Younger Male Predominance of TERT Genetic Alterations and HBV Integration: Implications for Sex Disparity in HBV-Related HCC

HS Kim[2], JS Kim[2], KY Tak[3], JE Jang[2], JM Han[2], JW Han[1,2], PS Sung[1,2], SH Bae[1,2], JY Choi[1,2], SK Yoon[1,2], JW Jang[1,2]

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**Aims:** Hepatocellular carcinoma (HCC) exhibits sex disparity, yet its molecular mechanisms remain unclear. We aimed to investigate the role of telomerase reverse transcriptase (TERT) alterations and hepatitis B virus (HBV) integration, both known contributors to HCC, in sex-specific risk for HBV-related HCC.

**Methods:** We comprehensively analyzed 310 tissue samples (210 tumor and 100 non-tumor) from chronic HBV carriers with HCC. Utilizing next-generation sequencing, we explored sex-specific HBV integration profiles. Additionally, we compared TERT promoter (TERT-pro) mutations and expression between sexes, stratifying by age, and validated the data using single-cell RNA sequencing (scRNA-seq) derived from public databases.

**Results:** Tumors predominantly displayed TERT-pro mutations and HBV-TERT integration, with no instances of TERT-pro mutations observed in non-tumors. Additionally, tumors exhibited a higher propensity for HBV integration into promoters and CpG islands. TERT-pro mutations increased with age for both sexes, while HBV integration decreased with age, especially in males. In tumors, younger males (≤ 60 years) harbored significantly greater enrichment of HBV integration in promoters and PreS/S regions, along with a trend for increased CpG island integration, compared to younger females. Moreover, younger males exhibited a marked predominance of TERT-pro mutations (25.7% vs. 3.2%) and HBV-TERT integration (44.7% vs. 16.6%) compared to younger females, with no such differences observed in older individuals. TERT genetic alterations were associated with increased TERT expression. The skewed TERT abnormalities in younger males were further corroborated by scRNA-seq data from an independent dataset.

**Conclusions:** Our findings highlight the critical role of TERT genetic alterations and HBV integration in HCC sex disparity, providing insights into the molecular basis behind sex differences in younger HBV-related HCC. These results lay the groundwork for future research aimed at improving patient care and surveillance strategies tailored to these differences.

**Keywords:** Hepatocellular carcinoma, Telomere, Mutation, Virus integration

## PE-05

### Inhibition of SFK and Its Effect on Cancer Stem Cell Markers Expression in HBV-Related HCC

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**Aims:** Chronic infection of hepatitis B virus (HBV) remains the main etiological factor for hepatocellular carcinoma (HCC). HBV-related HCC pathogenesis has been associated with the expression of HBV X protein (HBx), which can interact directly with key regulatory protein including Src family kinase (SFK). HBx interaction with Src are important for regulation of stem-like properties and liver cancer formation. Here, we determined the effect of treatment with Src inhibitors on cancer stem cell (CSC) markers expression in HBV-related HCC.

**Methods:** Hep3B, a HCC cell line with integrated HBV genome, was treated with two Src inhibitors, saracatinib (SAR) and dasatinib (DAS) with increasing doses of 1.25, 2.5, and 5.0 μM for 48 hours based on each of their $LC_{50}$ concentrations. mRNA and protein expressions of different CSC markers and other liver-related markers were assessed by qRT-PCR and flow cytometry.

**Results:** Hep3B cells highly expressed CSC markers EpCAM, CD13, CD133, and CD24, but only lowly expressed PD-L1, CD95 and its ligand CD95L. Treatment with SFKs inhibitors, SAR and DAS, reduced both Src gene and protein expressions. SAR treatment increased *CD133* ($P<0.01$) but reduced *CD90* expressions, while DAS treatment caused no changes in other CSC markers. In addition, SFK inhibitors also reduced fibrosis markers, *TGFB1, ACTA2, HGF, CTGF*, and *FSP1* and have no significant effects on liver marker AFP and albumin expressions, mostly noted for SAR.

**Conclusions:** Src inhibitors treatment may have anticancer effect by reducing the expression of CSC markers, as well as a possible antifibrotic effect in HBV-related HCC.

**Keywords:** HBV-related hcc, Cancer stem cell markers, SRC kinases, SRC inhibitors

## PE-06

### Liver-Specific Long Non-Coding RNA Suppresses Hepatocellular Carcinoma (HCC) Migration and Invasion, and Its Correlation with HCC Patient Survival in Hepatocellular Carcinoma Progression

Se Ha Jang[1,2], Geum Ok Baek[1], Moon Gyeong Yoon[1], Ji Hyang Weon[1,2], Su Jin Kim[1,2], Min Ji Kang[1,2], Ji Yi Choi[1,2], Ji Eun Han[1], Hyo Jung Cho[1], Soon Sun Kim[1], Jung Woo Eun[1], Jae Youn Cheong[1]

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**Aims:** The regulatory role of Liver-specific long non-coding RNA #01 (LIncR#01) remains unexplored. This study aims to elucidate the roles of LIncR#01 in hepatocellular carcinoma (HCC) migration and invasion.

**Methods:** The function of HTLR#01 was investigated through qRT-PCR analyses in HCC cell lines and one hundred pairs of HCC tissues along with corresponding non-tumor liver tissues. Subsequently, HCC cell lines were transfected with either an empty vector or an LIncR#01 overexpression vector. Wound healing and transwell assays were conducted to assess the impact of LIncR#01 on HCC cell behavior. Additionally, orthotopic models were employed to validate the *in vitro* findings *in vivo*.

**Results:** LIncR#01 expression was found to be suppressed in HCC tissues and positively correlated with overall survival. qRT-PCR analysis revealed downregulation ofLIncR#01expression in HCC tissues compared to non-tumor liver tissues. Overexpression of LIncR#01 inhibited migration and invasion in HCC cell lines both *in vitro* and in orthotopic models *in vivo*, confirming the consistency of the results across experimental settings.

**Conclusions:** These findings highlight the significance of LIncR#01 as a potential biomarker and therapeutic target in HCC.

**Keywords:** Hepatocellular carcinoma, Long non-coding rna, Therapeutic targets, Tumor suppressor

## PE-07

### Therapeutic Potential of Methanol Extract from Peronema Canescens Targeting VEGFR-BRAF Signaling in Hepatocellular Carcinoma: Docking and ADMET Study

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[1]Department of Chemistry, Universitas Palangka Raya, Indonesia, [2]Department of Pharmacy, Universitas Palangka Raya, Indonesia

**Aims:** Hepatocellular carcinoma (HCC) remains a significant global health burden with a tendency to increase every year, leading to a large investigation on the development of HCC drugs and effective treatment options. The Vascular Endothelial Growth Factor Receptor (VEGFR) and B-rapidly accelerated fibrosarcoma (BRAF) signaling pathway plays a crucial role in tumor angiogenesis and progression, making it an attractive target for therapeutic intervention. This study aims to investigate the potential of methanol extract from *Peronema canescens* as a novel therapeutic agent against HCC by targeting VEGFR-BRAF signaling, comparing its efficacy and safety profile with sorafenib, a common drug used in HCC treatment VEGFR-BRAF.

**Methods:** This study investigated the therapeutic potential of five natural compounds and one reference compound (sorafenib) against two important HCC player proteins: VEGFR (4ASD) and BRAF (1UWH) by using Autodock Vina 4. Furthermore, the SwissADME and pkCSM servers were used to predict absorption, distribution, metabolism, excretion, and toxicity (ADMET).

**Results:** Pregnan-20-one,3-(acetyloxy)-5,6:16,17-diepoxy-,(3α,5α,6α,16α)-, resibufogenin, and butyl-4,7,10,13,16,19 docosahexaenoate showed strong binding affinity toward VEGFR-BRAF, according to docking results. The binding affinities of the natural compounds against VEGFR were -9.3, -8.5, and -8.2 kcal/mol, respectively. Then, the binding affinities against BRAF were -8.9, -8.1, and -8.0 kcal/mol, respectively. These findings are comparable to sorafenib in terms of natural ligand/common drug, with binding affinities of -11.7 and 12.0 kcal/mol toward VEGFR-BRAF, respectively. The drug-target interaction patterns of these compounds bound to VEGFR-BRAF at 40–83% toward sorafenib. These substances also showed beneficial downstream signaling effects on BRAF. Interestingly, those compounds showed better ADMET characteristics.

**Conclusions:** The methanol extract from *Peronema canescens* demonstrates promising therapeutic potential in targeting VEGFR-BRAF signaling in Hepatocellular carcinoma, as evidenced by favorable binding affinity and favorable ADMET properties. Further *in vitro* and *in vivo* studies are warranted to validate its efficacy and safety as a potential therapeutic agent for HCC treatment.

**Keywords:** Hepatocellular carcinoma, VEGFR-BRAF signalling, *Peronema Canescens*, Docking

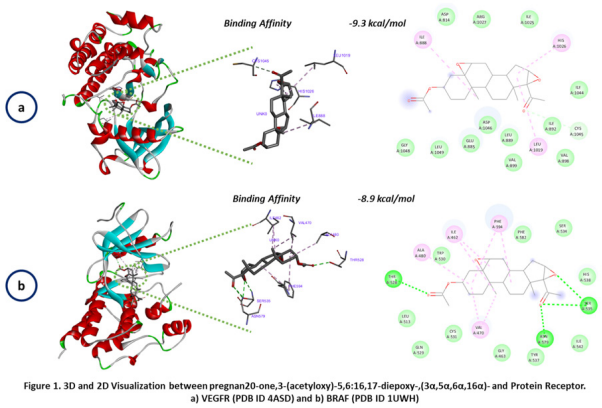


Figure 1. 3D and 2D Visualization between pregnan20-one,3-(acetyloxy)-5,6:16,17-diepoxy-,(3α,5α,6α,16α)- and Protein Receptor. a) VEGFR (PDB ID 4ASD) and b) BRAF (PDB ID 1UWH)

**Figure 1.** 3D and 2D Visualization.

## PE-08

### Clinicopathologic and Molecular Characteristics of Hepatic Angiomyolipoma: TP53 Mutation Can Be Associated with Malignant Behavior

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of Medicine, Seoul, Republic of Korea; [2]Department of pathology, Ewha Womans University College of Medicine, Seoul, Republic of Korea

**Aims:** Hepatic angiomyolipomas are mostly benign, but malignant cases have been rarely reported. To more accurately predict their clinical behavior, we evaluated the malignancy score based on histological variables and investigated the correlation between the score and prognosis.

**Methods:** A total of 135 patients with histologically confirmed hepatic angiomyolipoma, both benign and malignant, were retrospectively collected and reviewed. We measured the malignancy score based on tumor size, infiltrative border, high-grade nuclear atypia, increased mitotic activity, necrosis, and vascular invasion. P53 and Ki-67 immunohistochemical stains were performed in all cases. Targeted next-generation sequencing was performed in three cases with the highest malignancy scores.

**Results:** The male-to-female ratio was 1:3.2 with a median age of 46 years (range, 23—79). The median size of the tumor on imaging was 2.8 cm (range, 1—20). The preoperative diagnoses on imaging studies were mostly hepatocellular carcinoma (63/135, 47%) or angiomyolipoma (50/135, 37%). After biopsy, 59 patients (44%) were observed without treatment and 6 (4%) received local ablation, with none showing recurrence or metastasis. Among 70 patients (52%) who received surgical resection, one patient developed local recurrence six years after surgery, and another patient developed multiple peritoneal metastases within a month. When the resected tumors were histologically reviewed, high-grade nuclear atypia with marked pleomorphism and increased cellularity were observed in 12.9% (9/70) and increased mitotic activity (> 1/50 HPFs) was identified in 8.6% (6/70). The aforementioned patient with malignant angiomyolipoma not only showed the highest malignancy score of 6 but also exhibited abnormal p53 immunostaining, a high Ki-67 labeling index (49%), and a pathogenic *TP53* mutation (E286K).

**Conclusions:** Hepatic angiomyolipoma can rarely be malignant. We suggest our malignancy score to predict the malignant behavior of hepatic angiomyolipoma. Immunohistochemistry for p53 and Ki-67 and *TP53* mutation testing can also be helpful in diagnosing malignant hepatic angiomyolipoma.

**Keywords:** Angiomyolipoma, Immunohistochemistry, Mutation, Prognosis

## PE-09

## Diagnostic and Prognostic Significance of the PTEN Gene in Periampullary Carcinoma

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**Aims:** Periampullary Adeno Carcinoma (PAC) is a heterogeneous and rapidly growing carcinoma that arises near the duodenal papilla and is identified in its advanced stages. In periampullary tumours, the influence of a PTEN (phosphatase and tensin homolog) gene mutation on prognosis is unknown. The effect of PTEN downregulation and hypermethylation of the promoter region on survival in periampullary cancer has yet to be investigated. As a result, the goal of this work was to look into the expressional value of PTEN gene methylation as a potential biomarker.

**Methods:** One hundred and one tumour tissues and their non-adjacent tissues from patients were investigated for the mutational, expressional, and apoptotic state of the PTEN gene. Sanger sequencing was used for molecular profiling, immunohistochemistry for protein expression, methylation specific PCR for methylation status, and a terminaldeoxynucleotidyltransferase biotin–dUTP nick end labelling test for programmed cell death (apoptosis). The changes were linked to clinicopathological features, overall survival (OS), and recurrence-free survival (RFS).

**Table 3: Different factors affecting survival of periampullary cancer patients**

| Survival analysis (n=101) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| S. No. | Parameters | Deaths | Median survival | 3 Year survival | 5 Year survival | 95%CI Lower bound | 95% CI Upper bound | *p*- Value |
| 1 | Age | | | | | | | |
| | ≥60 | 37 | 46 | 64.4 | 0.00 | 33.2 | 58.7 | 0.476 |
| | <60 | 64 | 40 | 51.7 | 33.9 | 31.5 | 48.4 | |
| 2 | Sex | | | | | | | |
| | Male | 74 | 45 | 59.5 | 27.6 | 35.9 | 54.0 | 0.271 |
| | Female | 27 | 36 | 46.0 | 0.00 | 25.8 | 46.1 | |
| 3 | T Stage | | | | | | | |
| | T1 | 5 | - | 0.00 | 0.00 | - | - | |
| | T2 | 34 | - | 72.2 | 0.00 | - | - | 0.000 |
| | T3 | 59 | - | 56.0 | 0.00 | - | - | |
| | T4 | 3 | - | 0.00 | 0.00 | - | - | |
| 4 | LN Positivity | | | | | | | |
| | Yes | 59 | 36 | 45.4 | 0.00 | 25.7 | 46.2 | 0.004 |
| | No | 42 | - | 0.00 | 59.4 | 32.2 | 47.7 | |
| 5 | Adjuvant CTRT | | | | | | | |
| | Yes | 64 | 36 | 51.7 | 28.6 | 26.4 | 45.5 | 0.010 |
| | No | 37 | - | 0.00 | 62.2 | - | - | |
| 6 | Tumor Site | | | | | | | |
| | 1 | 68 | 45 | 68.0 | 42.7 | 38.1 | 51.8 | |
| | 2 | 20 | 43 | 53.6 | 0.00 | 23.6 | 62.3 | 0.000 |
| | 3 | 05 | 16 | 0.00 | 0.00 | 9.3 | 33.6 | |
| | 4 | 08 | 11 | 0.00 | 0.00 | 0.7 | 21.2 | |
| 7 | Differentiation | | | | | | | |
| | Well | 40 | 38 | 51.6 | 27.9 | 27.8 | 48.1 | |
| | Moderate | 52 | 45 | 60.5 | 0.00 | 21.2 | 68.7 | 0.811 |
| | Poor | 09 | 46 | 71.4 | 0.00 | 30.6 | 61.3 | |
| 8 | Perineural Invasion | | | | | | | |
| | Yes | 25 | 20 | 16.5 | 0.00 | 8.9 | 31.0 | 0.000 |
| | No | 76 | 45 | 69.7 | 56.5 | 36.4 | 53.5 | |
| 9 | Recurrence | | | | | | | |
| | Yes | 31 | 26 | 21.7 | 0.00 | 21.8 | 30.1 | 0.000 |
| | No | 70 | - | 90.4 | 78.0 | - | - | |
| 10 | Expression | | | | | | | |
| | Yes | 48 | 40 | 61.8 | 42.2 | 33.3 | 46.6 | 0.430 |
| | No | 53 | 40 | 68.2 | 0.00 | 27.4 | 52.5 | |
| 11 | Methylation | | | | | | | |
| | Positive | 55 | 36 | 66.6 | 0.00 | 22.7 | 49.2 | 0.761 |
| | Negative | 46 | 40 | 64.2 | 0.00 | 37.4 | 42.6 | |
| 12 | Apoptosis | | | | | | | |
| | Yes | 48 | 40 | 57.5 | 0.00 | 30.3 | 49.6 | 0.481 |
| | No | 53 | 43 | 64.5 | 0.00 | 30.8 | 55.1 | |

**Results:** In ampullary tumours, the clinicopathological relationship was significantly downregulated (*P*=0.06), although hypermethylation (*P*=0.08) and apoptosis loss (*P*=0.06) were dramatically elevated in patients under 50 years of age. The ampullary tumour had a higher survival rate than the bile duct, duodenum, and pancreatic head cancers (*P*=0.00). Furthermore, early stage T1 patients have a better prognosis than later stage T1 patients (*P*=0.017). Patients who got adjuvant CTRT had a greater survival rate than those who did not (*P*=0.010).

**Conclusions:** The absence of PTEN gene expression is detected in the ampullary subgroup of periampullary tumours. Those who have positive hypermethytion but modest expression has a poor overall survival. PTEN apoptosis-negative patients, on the other hand, had a higher survival rate.

**Keywords:** Periampullary adeno carcinoma (PAC), Pten gene, Methylation, Biomarkers

## PE-10

### Association of Obesity with Risk of Liver Cancer: A Systematic Review and Meta-Analysis

Muh Syaiful Akbar

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**Aims:** Liver cancer, also known as hepatocellular carcinoma (HCC), is a type of cancer that originates in the liver cells. This study aimed to conduct a systematic review and meta-analysis to evaluate the association of obesity with risk liver cancer.

**Methods:** A systematic search was conducted in several electronic databases such as PubMed, MEDLINE, EMBASE, the Cochrane Library, and ProQuest published from 2018 to 2023. Research examining the correlation between BMI and the occurrence or fatality rates of primary liver cancer in prospective studies, as well as those providing hazard ratios (HRs) or data suitable for HR estimation, were incorporated.

**Results:** Four studies were included in this meta-analysis consisting of 964 people with liver cancer spread across different countries. The findings indicated that in the meta-analysis, there was a link between higher BMI and the incidence of primary liver cancer (HR, 1.65; 95% confidence interval, 1.10–2.45, I2=75%). A rise in BMI was correlated with an elevated risk of primary liver cancer occurrence. A random-effects model was used because the heterogeneity was high (I2 = 99%).

**Conclusions:** A high BMI contributes to the escalation of liver cancer. Obesity represents a distinct risk factor for the onset of liver cancer. One of the key mechanisms linking obesity to liver cancer is the accumulation of fat in the liver, leading to nonalcoholic fatty liver disease (NAFLD).

**Keywords:** Liver cancer, Hepatocellular carcinoma, Obesity

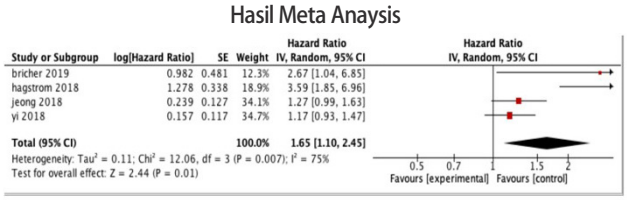


**Figure 1.** Forestplot.

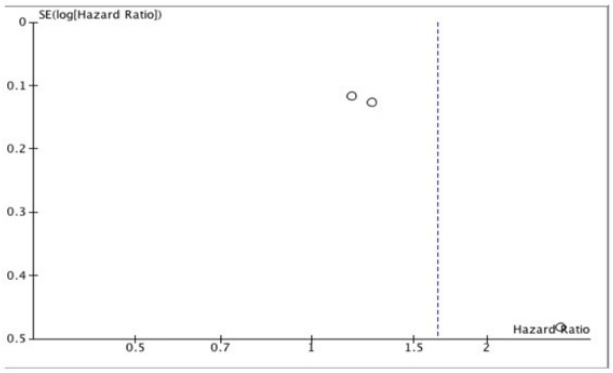


**Figure 2.** Funnel plot of publications bias.

## PE-11

### Synergistic Anticancer Effects of MicroRNA-21 Inhibitor Combined with Sorafenib in Hepatocellular Carcinoma

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**Aims:** Hepatocellular carcinoma (HCC) remains one of the most common cancers worldwide. Sorafenib is an oral multi-kinase inhibitor used to treat advanced HCC but it often develops resistance as well variety of side effects. MicroRNAs (miRNAs) bind to the 3′ UTR of target genes mRNA and repress translation. It has reported that aberrant expression of microRNA is involved in the development of pathophysiologic processes including cancer. Hence, our study aims to provide an enhanced treatment strategy for HCC by modulating miRNA regulation.

**Methods:** We measured miRNA and target mRNA expression in HCC patients' samples and cell lines using qRT-PCR analysis. Western blot was performed to detect protein level in miRNA inhibitor or mimic treated HCC cell lines as well tissue samples from HCC patients' or xenograft animal model. The orthotopic xenograft mouse model was established with NRG mice transplanted human HCC cells into liver. Then the effects of miRNA inhibitor and sorafenib combined treatment was evaluated using the model.

**Results:** The expression of miR-21 was upregulated in tumor tissues from HCC patients and HCC cells under hypoxic condition where the cancer microenvironment was mimicked. Besides, the expression of SASH1, the target gene of miR-21, was downregulated in that. The miR-21 inhibitor induced decrease of cell viability and colony formation in HCC cells, increasing SASH1 expression. Interestingly, the inhibitor and sorafenib shown synergistic anticancer effects in xenograft model not only in HCC cells.

**Conclusions:** Our findings suggest that miR-21 plays an important role in promoting HCC tumorigenesis by inhibiting SASH1 expression and that inhibition of miR-21 combined with sorafenib could be beneficial for the treatment of liver cancer.

**Keywords:** HCC, miRNA, Combined treatment

## PE-12

### Polymeric Nanoparticles Loaded Gallic Acid Mitigates Diethylnitrosamine Induced Hepatic Cancer via Targeting Endoplasmic Reticulum (ER) Stress Markers, Apoptotic Markers and Autophagy Markers and PI3K/pAKT/mTOR/NF-κB/FOXO3a Pathway

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**Aims:** Liver cancer is a major health concern globally with various treatment options but they have various side effects. Gallic acid has traditionally been used in the management of liver problem such as liver cirrhosis and inflammation. We fabricated and characterized the polymeric nanoparticles of gallic acid and scrutinized against the diethylnitrosamine (DEN) induced HCC via underlying mechanism

**Methods:** Ionic gelation method was used to fabricate the polymeric nanoparticles of gallic acid (GA-CNPs) using chitosan and characterised by FTIR, UV, FESEM, AFM and Zeta potential. *In vitro* anti-tumor activity of GA-NPs was evaluated using MTT assay on HepG2, CT-26, Hepa1-6, 4T1, A549, L929, and MC3T3-E1 cells line. DEN (carcinogen) at a dose level of 200 mg/kg was used for hepatic cancer induction in rats. Serum and tissue homogenate were used for biochemical analysis. We also measured endoplasmic reticulum (ER) stress markers, tumor markers (HGFR, p-AKT, PI3K, mTOR, NF-κB, FOXO3a), apoptotic markers (Bax (apoptotic marker) and Bcl2 (anti-apoptotic protein) and autophagy markers (Beclin-1 and LC3), and performed morphological and histopathological study.

**Results:** The finding of present study shows that fabricated GA-CNPs were spherical in shape with 167.33 in particle size. The MTT assay suggested that GA-CNPs exhibited maximum towards HepG2 and Hepa1-6 cells, with $IC_{50}$ values were 42.5 and 78.2 μg/mL after a 24-hour exposure, and 10.0 and 15.0 μg/mL after 48 h, respectively. GA-CNPs significantly ($P$>005) alleviates liver (AFP, CEA, ALT, ALP, AST, GGT and non-liver parameter (BUN, total protein, albumin, direct bilirubin, bilirubin. It also significantly alters the antioxidant parameter LPO, SOD, CAT, GPx, GST, GSH, respectively. It also inhibited the PI3K/AKT/mTOR/NF-κB signalling pathway as well as enhanced gene expression of FOXO3a levels and apoptotic parameters, apoptotic markers (Bax (apoptotic marker) and Bcl2 (anti-apoptotic protein) and autophagy markers (Beclin-1 and LC3) and also improved ER stress markers that was induced by DEN administration . Additionally, GA-CNPs improved the hisptopathological changes which were deteriorated by DEN treatment.

**Conclusions:** We can say that the study explored the underlying mechanism by which GA-CNPs may offer a unique therapeutic option for hepatocellular carcinoma (HCC) obtained from a plant derived source, via mitigating signalling pathway and ER stress markers.

**Keywords:** Hepatic cancer, Gallic ACID, Endoplasmic reticulum stress marker, Apoptosis

## PE-13

### O-GlcNAcylation of PRDX1 Enhances Its Stability and Promotes Hepatocellular Carcinoma Progression via Enhancing LRP6-Metiated Wnt Signaling

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**Aims:** It is well known that O-linked β-N-acetylglucosaminylation (O-GlcNAcylation) is closely related to tumor progression and is a potential target for cancer therapy, peroxiredoxin 1 (PRDX1) plays a crucial role in combating reactive oxygen species (ROS) and antioxidant processes. However, the role and molecular mechanism of PRDX1 in Hepatocellular Carcinoma (HCC) still needs further investigation.

**Methods:** Western blotting was performed to determine the levels of PRDX1 and O-GlcNAcylation in HCC tissues. Colony formation, scratch test, transwell assay and nude mouse tumor model assays were used to determine the roles of PRDX1 and O-GlcNAcyclion in HCC progression. Immunoprecipitation-Mass Spectrometry (IP-MS) was used to expore the O-GlcNAcylation of PRDX1, and screen the interacting protein LRP6 of PRDX1, Cycloheximide (CHX) chase assay, ubiquitination test were used to determine the stability, proximity ligation assay (PLA), immunofluorescent staining (IF) were perfomed to

confirm the O-GlcNAcylation of PRDX1.

**Results:** Here, we demonstrate that PRDX1 promotes HCC progression both *in vitro* and *in vivo*, and importantly, we found that PRDX1 was highly modified by O-GlcNAcylation and that O-GlcNAcylation inhibited the ubiquitination degradation of PRDX1, in addition, PRDX1 interacts with LRP6 and stabilizes its expression, then leading to Wnt/$\beta$-catenin signaling pathway activation.

**Conclusions:** We conclude that O-GlcNAcylation of PRDX1 enhances its stability and promotes hepatocellular carcinoma progression via enhancing LRP6-metiated Wnt signaling. O-GlcNAcylation of PRDX1 is an important way to coordinate glucose metabolism and HCC progression, it provides a new idea for the clinical treatment of HCC.

**Keywords:** O-glcnacylation, PRDX1, Hepatocellular carcinoma, Ubiquitination

## PE-14

### Combined Hepatocellular-Cholangiocarcinoma: A Case Report and Literature Review

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HPB Surgical Department, National Cancer Center of Mongolia, Mongolia

**Aims:** Combined hepatocellular and cholangiocarcinoma (cHCC-CC) is a vary rare primary liver cancer. It is more rare in young women with no risk factors for HCC or CC. The risk of recurrence higher than with other primary liver cancers such as hepatocellular carcinoma. We report a case of cHCC-CC in a 33-year-old woman with large combined cancer in right liver intrahepatic metastasis in SII and solid left lung metastasis treated with combined therapy.

**Methods:** Before surgery: no flag CBC and biochemistry. AFP-1712U/ml, CA19-9:-1000U/ml, CEA-2.59 ng/ml Tumor compressed to stomach and located whole right abdominal cavity although she couldn't eat anything. Consequently she received right hepatectomy, tumorectomy from SII, cholecystectomy, and periportal lymph node dissection. Surgical pathology demonstrated multiple cHCC-CC of the liver. Immunohistochemistry (IHC) staining was strong positive for CK 7, CK 19, AFP, while negative for Hepar-1, and CK20. The patient was progressed using RECIST criteria after receiving first-line treatment with gemcitabine + cisplatin in four cycles every 21 days. 6 months later CA19-9:-88.57U/ml, CEA-2.17 ng/ml. We recommended FOLFOX as a second-line chemotherapy regimen for her, and she received six cycles of FOLFOX chemotherapy every 21 days. Unfortunately, her cancer progressed after second-line chemotherapy, therefore after surgery 14 months later we planned a targeted therapy TAFINLAR + MEKINIST based on positive BRAFV600E molecular biology tests.

**Results:** We used combined therapy but tumor is progressing so we chose target therapy.

**Conclusions:** cHCC-CC was first described in 1949. Unfortunately survival rate is vary poor, therefore we are waiting result for target therapy.

**Keywords:** Combined HCC-CC, Chemotherapy for combined HCC-CC, Mixed hepatocellular carcinoma-cholangiocellular carcinoma

## PE-15

### Therapeutic Potential of Avicularin in the Medicine for the Treatment of Various Forms of Cancerous Disorders: A Phytotherapeutic Approach for the Treatment of Hepatocellular Carcinoma

Dinesh Kumar Patel

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**Aims:** Natural products have numerous applications in the medicine and other allied health sectors due to their pharmacological activities and effectiveness against numerous disorders. Medicinal products have been used in the different system of medicine for the treatment of human health complication. Plants contain both primary and secondary metabolite useful for Human being to treat diseases. Flavonoids are secondary metabolites of plants which have been used in the medicine due to their anti-oxidant, anti-cancer, anti-inflammatory, anti-bacterial and hepatoprotective activities.

**Methods:** Numerous literature databases have been searched and analyzed to know the biological importance and health beneficial properties of avicularin in the medicine. Literature databases have been searched and analyzed to know the biological importance of avicularin for their health beneficial aspects in the medicine. Molecular study literature data has been also collected in the present work to analyze their therapeutic benefit in the medicine. All the collected pharmacological information of avicularin has been further correlated with other biological properties of avicularin to know their health beneficial aspect in the modern medicine.

**Results:** Literature data analysis of various scientific research work revealed that avicularin have huge biological potential to treat numerous human health complication including their anti-inflammatory, hepatoprotective, anti-allergic, anti-oxidant and anti-tumor properties. Literature data analysis of various scientific research works revealed the biological importance of avicularin for the treatment of hepatocellular carcinoma. Molecular study literature data analysis revealed the biological importance of avicularin in the medicine for the treatment of hepatocellular carcinoma as it showed binding power on the novel site of tubulin.

**Conclusions:** Literature data analysis revealed the biological importance of avicularin in the medicine for the treatment of various types of hepatic complications including hepatocellular carcinoma.

**Keywords:** Avicularin, Tubulin, Anticancer compounds, Hepatocellular carcinoma

## PE-16

### Biological Potential of Hernandezine for Their Antitumor Effects in Hepatocellular Carcinoma (HCC) in HepG2 and Hep3B Cells with Their Molecular Mechanisms

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Faculty of Health Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, India

**Aims:** Plant derived phytochemicals have been used as lead molecules in the healthcare system for the development of better drugs against human disorders. Hernandezine is a biologically active bisbenzylisoquinoline alkaloid found to be present in *Thalictrum hernandezii,* and *Thalictrum fendleri.*

**Methods:** Biological potential of hernandezine from *Thalictrum simplex* for their antitumor effects has been investigated in hepatocellular carcinoma (HCC) in the present work through scientific data analysis. Therapeutic potential of hernandezine in HepG2 and Hep3B cells have been investigated with their molecular mechanisms of action in the present work. However, biological role of hernandezine in the proliferation and cell apoptosis of HepG2 and Hep3B cell have also been investigated in the present work. Further, other pharmacological activities of hernandezine were also correlated with the present work in order to know the therapeutic potential of hernandezine in medicine.

**Results:** Scientific data analysis of the present investigation revealed that hernandezine significantly induced G0/G1 phase arrest, inhibited the proliferation and promoted cell apoptosis in liver cancer cell. The antitumor effects of hernandezine on liver cancer cells were also mediated by reactive oxygen species (ROS). Hernandezine treatment caused ROS accumulation in liver cancer cells and caused mitochondria injury which further influenced the expression of apoptosis-related proteins and resulted to HepG2 and Hep3B cell apoptosis. Present work scientific data analysis signified that hernandezine is a promising antitumor drug for hepatocellular carcinoma treatment.

**Conclusions:** Present work scientific data signified the therapeutic potential of hernandezine for their antitumor effects in hepatocellular carcinoma.

**Keywords:** Hernandezine, Antitumor, Hepatocellular carcinoma, Molecular mechanisms

## PE-17

### Biological Potential and Therapeutic Effectiveness of Magnolin for the Treatment of Hepatocellular Carcinoma through Its Effect on Proliferation, Cell Cycle Arrest and Apoptosis

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**Aims:** Lignans are important class of phytocompounds mainly responsible for the defense mechanism of the plants. Magnolin also called 1-(3,4-dimethoxy-phenyl)—4-(3,4,5-trimethoxy-phenyl)-tetrahydro-furo[3,4-c]furan, was found to be present in the volatile oil components of the *Magnolia fargesii*. Magnolin have anti-inflammatory, anti-oxidative, and vasodilatory effects and can protect against contrast-induced nephropathy.

**Methods:** Biological potential of magnolin to treat hepatocellular carcinoma has been investigated in the present work with their molecular mechanism through scientific data analysis of different scientific research work. In order to know the therapeutic potential of magnolin against liver carcinoma, detail scientific data of pharmacological activity of magnolin have been analyzed in the present work.

**Results:** Present work signified the biological potential and therapeutic effectiveness of magnolin for the treatment of hepatocellular carcinoma in medicine. Scientific data analysis signified that magnolin suppressed the proliferation and promoted cell cycle arrest and apoptosis in hepatocellular carcinoma cells Bel-7402 and SK-Hep1. Furthermore, combination of magnolin and with BRAF led to increased impaired proliferation through the inhibition of the ERK MAPK pathway which signified its therapeutic potential for the improvement of hepatocellular carcinoma.

**Conclusions:** Present work signified the therapeutic effectiveness of magnolin for the treatment of hepatocellular carcinoma.

**Keywords:** Magnolin, Hepatocellular carcinoma, Proliferation, Cell cycle Arrest

## PE-18

### Molecular Docking and Structure-Based Drug Design Strategies for Liver Cancer

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**Aims:** The biggest cause of cancer-related death worldwide is liver cancer. Low-dose computed tomography liver cancer screening increases mortality. For diagnosis and staging, nu-

merous techniques are available. The type and stage of cancer will influence the course of treatment; there are now a number of tailored medicines that were not available only a few years ago. Environmental factors, aging, food, infectious diseases, hormone imbalance, and chronic inflammation are major cancer-causing variables. Although there are many synthetic medications on the market, plant derivatives are known to cure various cancers with greater effectiveness and fewer side effects. The anticancer activity of the phytochemicals has been assessed using a number of molecular docking experiments, which are helpful in illuminating molecular identification. When looking for possible hits during the drug discovery process, molecular docking research is a crucial tool. This lesson focuses on the results of a molecular docking study conducted on numerous phytochemicals and cancer-causing proteins, as well as the possibility for new drugs to be developed using these findings.

**Methods:** The phytochemicals that are known to have therapeutic activities are used as ligands in the current study. Any structural method, such as LCMS, GCMS, NMR, etc., was used to first determine the structures of the ligands. The chemical composition of the selected phytochemicals was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and represented in Advanced Chemistry Development's Chemsketch before being converted into a three-dimensional (3D) structure with the help of the Open Babel or Lig prep 2.2 applications. These ligands are currently used in additional molecular docking analyses. A computer simulation approach called molecular docking is used to forecast how a receptor-ligand combination would interact, with the receptor typically being a protein or a nucleic acid molecule and the ligand being either a tiny molecule or another protein.

**Results:** Through autocrine or paracrine secretion, the EGF pathway can be inappropriately activated in liver cancer, promoting cell migration and proliferation. EGF binds to the EGF receptors, and then through a series of subsequent signal transduction events, activates the PI3K/Akt, MAPK/ERK, P38/MAPK, or NF-kB proteins. As a result, the use of targeted anti-EGF therapy for the treatment of liver cancer may be beneficial. While EGFR is a protein found on the cell surface, it promotes tyrosine kinase phosphorylation, which is a critical step in the process that leads to cell proliferation. Therefore, we can directly stop malignant cell proliferation by blocking EGFR. Chemotherapy is combined with the EGFR inhibitor to treat liver cancer. With EGFR and VEGFR 2, several phytochemicals were docked. These three flavonoids were found to have the lowest binding scores in this study (-12.2 kcal/mol–9.8 kcal/mol).

**Conclusions:** Computed drug-likeness of phytochemicals, in addition to docking studies, also showed that the majority of compounds were in the range of promising candidates for high bioavailability according to Lipinski's rule of five. We were able to comprehend the mechanism underlying cancer-causing enzymes and their potential inhibitors thanks to the compilation of docking analysis data from a variety of phytochemicals. It is possible to further examine the anti-cancer behavior of the phytochemical components of medicinal plants using *in vitro* and *in vivo* models.

**Keywords:** Molecular docking, Phytochemicals, Liver cancer

## PE-19

### Detection of Liver Associated Noncoding RNAs in Liver Cancer Patients Tissue Based by Bioinformatics Analysis

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**Aims:** A cancer that originates in the liver is called liver cancer, sometimes referred to as hepatic cancer, primary hepatic cancer, or primary hepatic malignancy. Liver cancer is one of the most common life-threatening illnesses and one of the fastest-growing cancer types globally. Early diagnosis can help in cancer treatment and management. Many ncRNAs can control the onset and spread of cancer by acting as oncogenes or tumor suppressor genes. Because healthy people and cancer patients express NcRNAs differently, they can be employed as biomarkers for diagnosis and prognosis.

**Methods:** Through the use of bioinformatics and RNA-seq data from both malignant and healthy liver tissue samples from GEO and TCGA, we were able to identify potential liver cancer genes and conduct pathway enrichment analysis (PEI) and protein-protein interaction analysis.

**Results:** The findings demonstrate significant interindividual variation in the quantity of v2 and v3 transcripts as well as tumor- and tissue-specific expression patterns. These results imply that the variations affect glucuronidation differently in different tissues and that their significance may be greater in malignancies than in normal tissues.

**Conclusions:** Our findings add to the body of evidence supporting the role of genes linked to liver cancer in the onset and spread of the disease, and a number of these genes show promise as future research subjects. Future directions include employing immunohistochemistry to look into the localized expression of the tested genes in order to directly confirm these genes as potential biomarkers for liver cancer in liver cancer development, as well as additional validation on a larger number of samples for additional confirmation of the results.

**Keywords:** Liver cancer, NCRNA, Bioinformatics

## PE-20

### The Impact of Self-Fficacy as Self Management on Hepatocellular Carcinoma (HCC) Patient in Indonesia

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**Aims:** Of all primary liver tumours, hepatocellular carcinoma (HCC) accounts for about 90% of cases (Kwabena et al., 2023). The total 18,468 cases of liver cancer in Indonesia in 2018, as many as 18,148 (98, 26%) patients died. Hepatocellular carcinoma (HCC) is a primary malignant neoplasm derived from hepatocytes, accounting for about 80% of all liver cancers. To build patient confidence in dealing with this cancer, it is necessary to have the confidence that must be possessed by the patients. The purpose of this study was to perform a meta-analysis self-efficacy as a support for self-management for patients with HCC cancer in Indonesia.

**Methods:** This research uses the PRISMA method. PRISMA method means Preferred Reporting Items for Systematic Reviews and Meta-analyses. We collected articles from 2011-2023 from an electronic database lens.org, pubmed, ect for focus of discussion.

**Results:** The study's findings define self-efficacy as the belief in one's capacity to carry out self-management tasks, such as managing side effects, preventing fatigue, adhering to a diet, and communicating with healthcare professionals when dealing with chronic viral hepatitis as a cause of hepatocellular carcinoma (HCC). Self-efficacy is the conviction that one can handle particular stressors. It implies that one's belief in one's ability to succeed substantially influences that person's ability to succeed (Bandura 1977).

**Conclusions:** It can be concluded that building self-efficacy has the potential to maintain patient self-management in the face of HCC.

**Keywords:** Hepatocellular carcinoma, Self management, Indonesia

## PE-21

### Solid Lipid Nanoparticles Loaded Hesperidin Modulates High Fat Diet and Diethylnitosamine Induced Obesity and Hepatocarcinogenesis in a Rats via Targeting Protein Kinase C(PKC)α/Rac1 Signaling Pathway

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**Aims:** Adults with obesity who have nonalcoholic fatty liver disease (NAFLD) are at a significant risk of developing chronic liver disease due to its association with metabolic disorders. Tumor necrosis factor (TNF)-$\alpha$ and interleukin (IL)-6 are proinflammatory cytokines that are important in the development of steatohepatitis linked to obesity and the subsequent hepatocarcinogenesis. Hesperidin, a flavonoid are believed to have anticancer,antiobesity, hepatoprotective, antioxidant, anti-inflammatory, antidiabetic, and hypotensive qualities. In this work, we investigated the mechanisms that Solid lipid nanoparticles loaded hesperidin antitumorigenesis impact; in particular, ability to prevent hepatic inflammation and tumorigenesis that are generated by HFD + DEN in rats.

**Methods:** The rats were given a high fed diet for 12 weeks (the HD group) in which 0.01% diethylnitrosamine (DEN) was added to their drinking water to cause obesity and spontaneous hepatomas. They were also given SLN-HP orally, at daily doses of 10mg, 20 and 30 mg. After the 12-week trial, the liver tumors were examined for indicators of oxidative stress and antioxidant enzyme activity, and the liver function and nutritional health of the subjects were assessed by testing their serum. We also measure the lipid profile, complete blood profile and proflammatory mediators and cytokines. We conducted the morphological and histopathological studies of liver to measure the changes.

**Results:** Histopathological and morphological analysis shown that administration of SLN-HP significantly reduced the hepatic tumours incidence and severity that was induced by HFD+DEN. There was significant reduction in the liver tumours and liver to body weight and survival rate. SLN-HP significantly modulated the hepatic (AST, ALT, ALP, CEA, $\gamma$ GT, AFP,) and non-hepatic parameters (BUN, BUN, total protein, albumin, direct bilirubin, bilirubin) in a dose dependent manner. It also mitigates the total cholesterol, total triglyceride, liver cholesterol, liver triglyceride and adipokines (leptin and adiponectin). Antioxidant parameters ((GSH, GPx, SOD, catalase, GST-$\alpha$, and total GST assay), Proinflammatory cytokines (TNF-$\alpha$, and IL-6) and oxidative stress (TBARS and 8-OHdG) were also mitigates by SLN-HP significantly in a dose dependent manner. It also lowered the expression of protein kinase C (PKC)-$\alpha$ and Rac family small GTPase 1 (Rac1) in DEN+HFD groups.

**Conclusions:** According to these results, SLN-HP may inhibit the development of hepatocellular carcinoma caused by carcinogens and obesity by blocking the protein kinase C (PKC)$\alpha$ /Rac1 signaling pathway. For hepatocarcinogenesis associated with nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD), SLN-HP may be a useful chemoprevention strategy.

**Keywords:** Solid lipid nanoparticles of hesperidin, Hepatic cancer, Obesity, Inflammation

# Liver Cancer, Clinical

## PE-01

### Initial Experience and Feasibility of Laparoscopic Liver Resection and Regional Lymph Node Dissection of Intrahepatic Cholangiocarcinoma

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**Aims:** Intrahepatic cholangiocarcinoma (IHCCC) is originated from intrahepatic biliary system proximal to the second-order branches. IHCCC accounts for 10-15% of primary liver cancer and is second only in incidence to hepatocellular carcinoma. The incidence and mortality rate have been increasing over the past decades. Liver resection is the gold standard of treatment, which is effective and radical treatment of IHCCC. Open liver resection is the conventional surgical treatment of IHCCC. However, advancement of laparoscopic liver resection technique, laparoscopic approach in IHCCC is increasing. 3 cases of laparoscopic liver resection and regional lymph node dissection of IHCCC will be presented and discussed about surgical feasibility and oncologic safety.

**Methods:** 4 cases of laparoscopic liver resection and regional lymph node dissection was performed in IHCCC patients. 1 patient had preoperative chemotherapy and radiotherapy because of peritoneal seeding. 4 patients had laparoscopic left hepatectomy and regional lymph node dissection.

**Results:** The patients discharged at postoperative day 8-10 without any events. Oncologic safety was definite including surgical margin status and regional lymph node.

**Conclusions:** Laparoscopic liver resection and regional lymph node dissection in IHCCC have advantages in minimally invasive approach and proper oncologic safety. The implementation of laparoscopic approach in IHCCC should be encouraged as a standard surgical treatment, but in carefully selected patients by surgeon with surgical expertise in minimally invasive liver surgery.

## PE-02

### The Relationship between Operative Approach and Pulmonary Complications after Hepatectomy for HCC: A Multicenter Overlap Propensity Score-Weighted Analysis of Laparoscopic vs. Open Hepatectomy

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**Aims:** Postoperative pulmonary complications (PPCs) significantly affect patient recovery and long-term outcomes in hepatocellular carcinoma (HCC) post-hepatectomy. This study examines the potential benefits of laparoscopic hepatectomy (LH) over traditional open hepatectomy (OH) in reducing PPCs.

**Methods:** A multicenter retrospective cohort study across 12 Chinese centers (2010-2021) involved 4,694 HCC patients undergoing LH or OH. Primary endpoint: PPCs incidence, including pleural effusion, respiratory insufficiency, acute respiratory distress syndrome, pulmonary infection, and pulmonary embolism. Propensity score analysis, inverse probability of treatment weighting (IPTW), multivariable logistic regression, and subgroup analyses adjusted for confounders.

**Results:** Of 4,694 patients, 766 (16.3%) had LH, and 3,928 (83.7%) had OH. Overall PPCs incidence was 10.9%, significantly lower in LH (7.3%) than OH (11.6%, $P$=0.001). IPTW analysis supported these results (7.4% vs. 11.6%, $P$=0.011). Multivariable analysis revealed LH independently associated with lower PPCs risk (adjusted odds ratio 0.63, 95% CI: 0.42-0.92, $P$=0.018). Subgroup analyses across demographics and clinical parameters consistently validated this association.

**Conclusions:** Laparoscopic hepatectomy in HCC patients is linked to a significantly lower incidence of PPCs compared to the open approach. These findings suggest LH as a more favorable surgical option for HCC, emphasizing its potential benefits in improving postoperative pulmonary outcomes. The study contributes to the growing evidence favoring minimally invasive surgery in oncological procedures and underscores the need for wider adoption in clinical practice.

**Keywords:** Pulmonary complications, Hepatectomy, Hepatocellular carcinoma

## PE-03

### The Paradox of Bodyweight: Lean, but Not Obese, as a Predictor of Poor Prognosis after Surgical Resection for NAFLD-Associated Hepatocellular Carcinoma

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**Aims:** Non-alcoholic fatty liver disease (NAFLD) poses a rising risk for hepatocellular carcinoma (HCC), intensified by the global obesity epidemic. Despite obesity being a primary NAFLD and HCC factor, "lean NAFLD" incidence is not uncommon. This study evaluates preoperative body mass index (BMI) influence on long-term prognosis in NAFLD-HCC patients post-surgical resection.

**Methods:** Data from early-stage NAFLD-HCC patients (BCLC stage 0/A) undergoing curative resection were extracted from an Asian multicenter database. Patients were categorized by preoperative BMI into lean (< 23.0 kg/m$^2$), overweight (23.0-27.4 kg/m2), and obese (≥ 27.5 kg/m$^2$) groups. Long-term overall survival (OS) and recurrence-free survival (RFS) rates were compared.

**Results:** The study included 309 NAFLD-HCC patients (21.3% lean, 57.0% overweight, 21.7% obese). Liver, tumor, and surgery-related characteristics were similar. Lean patients exhibited poorer 5-year OS (55.4%) and RFS (35.1%) rates than overweight (71.3% OS, 55.6% RFS, *P*=0.017, 0.002) and obese patients (48.5% OS, 38.2% RFS, *P*=0.939, 0.442). Multivariable analysis identified lean bodyweight, not obese, as an independent predictor of reduced OS (HR: 1.69; 95% CI: 1.06-2.71; *P*=0.029) and RFS (HR: 1.72; 95% CI: 1.17-2.52; *P*=0.006).

**Conclusions:** Contrary to obese bodyweight, lean bodyweight is linked to inferior oncological prognosis post-surgical resection in NAFLD-HCC. This underscores the need for in-depth investigation into unique carcinogenic pathways in lean NAFLD-HCC and its implications for HCC recurrence, contributing to BMI-prognosis nuances in surgical interventions for NAFLD-HCC patients.

**Keywords:** NAFLD-associated hepatocellular carcinoma, Surgical resection, Bodyweight

## PE-04

### Quantifying Intraoperative Decision Support: Real-Time Deep Learning Augmentation for Hepatic Vascular Assessment in Hepatobiliary Resections

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**Aims:** Hepatic resections for hepatobiliary malignancies demand meticulous vascular assessments. This study evaluates the impact of real-time deep learning augmentation on surgical outcomes, specifically focusing on vascular precision, blood loss reduction, and complication rates.

**Methods:** In this prospective cohort study, 150 patients undergoing hepatic resections for hepatobiliary malignancies were included. Real-time deep learning algorithms, trained on dynamic contrast-enhanced CT scans and intraoperative ultrasound, continuously provided vascular assessments. Patients were categorized into surgeries with deep learning augmentation (DL group) and those without (control group). Propensity score matching ensured balanced baseline characteristics. Intraoperative outcomes, including vascular injuries, blood loss, and the need for vascular reconstruction, were recorded and compared between the groups.

**Results:** In the DL group (n=75), real-time deep learning demonstrated a 25% reduction in inadvertent vascular injuries (CI: 18-32%) compared to the control group (n=75). Blood loss significantly decreased by 20% (CI: 15-25%), and the need for vascular reconstruction was 18% lower (CI: 12-24%). The deep learning model achieved an AUC of 0.92 (95% CI: 0.88-0.95%) for identifying hepatic vascular structures during surgery.

**Conclusions:** This study emphasizes the significant impact of real-time deep learning on intraoperative decision-making during hepatobiliary resections. The observed reductions in vascular injuries, blood loss, and the necessity for reconstruction underscore the potential of deep learning to enhance surgical precision and patient safety. The integration of deep learning into the intraoperative workflow shows promise for enhancing outcomes in intricate hepatic surgeries, necessitating further validation across diverse surgical settings.

**Keywords:** Intraoperative decision support, Deep learning augmentation, Hepatic vascular assessment

## PE-05

### Comparative Analysis of Local Ablative Treatment Efficacy in Very Elderly vs. Elderly Patients with Hepatocellular Carcinoma

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**Aims:** Age-related factors significantly influence the selection and outcomes of treatments for hepatocellular carcinoma (HCC). This study aims to compare the efficacy of local ablative

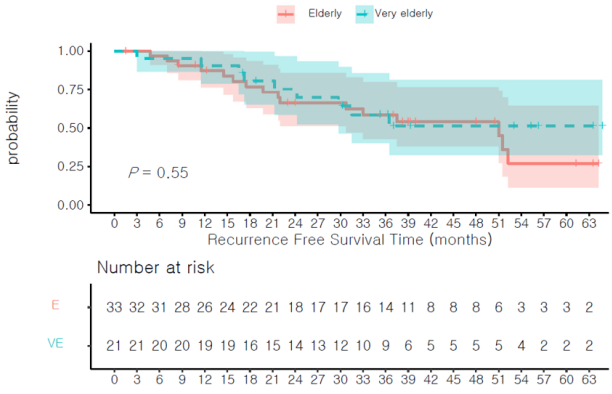
treatments in terms of recurrence-free survival (RFS) and overall survival (OS) between very elderly patients (aged over 75 years) and elderly patients (aged 65-74 years).

**Methods:** This retrospective cohort study analyzed 54 consecutive patients with HCC who received local ablative treatment as their first-line therapy between January 2019 and December 2021. Patients were divided into two age groups: very elderly (over 75 years) and elderly (65-74 years). The primary outcome was RFS and the secondary outcome was OS. Cox proportional hazards regression and the Kaplan-Meier method were used to evaluate differences in treatment outcomes between the groups.

**Results:** The study included 21 very elderly patients and 33 elderly patients. The median follow-up duration was 38.4 months (interquartile range, 26.0-51.5). Of the total 54 patients, recurrence occurred in 25 patients (46.3%) [9 in the very elderly group (42.9%) and 16 in the elderly group (48.5%); log-rank *P*=0.54]. No statistically significant difference in RFS was observed between the very elderly and elderly patients (aHR, 1.27; 95% CI 0.51-3.16; *P*=0.61). Similarly, OS did not differ significantly between the groups (aHR, 2.08; 95% CI 0.38-11.51; *P*=0.39).

**Conclusions:** The findings indicate that local ablative treatment for HCC is equally effective in very elderly patients as in elderly patients. The absence of significant differences in RFS and OS suggests that age alone should not preclude active treatment of HCC in very elderly patients. These results support continuing therapeutic interventions in this age group, highlighting the potential for favorable outcomes irrespective of advanced age.

**Keywords:** Hepatocellular carcinoma, Ablative treament, Very Elderly, Elderly




## PE-06

### Biomarkers for Early Detection and Prognostication of Liver Cancer: A Meta-analysis

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**Aims:** This meta-analysis aims to evaluate the diagnostic and prognostic value of biomarkers, including circulating tumor markers and genetic signatures, for early detection and risk stratification of liver cancer. The study seeks to provide insights into personalized treatment approaches based on biomarker profiles.

**Methods:** A systematic literature search was conducted in major databases such as PubMed, Scopus, and Web of Science, up to January 2024. Studies investigating the diagnostic and prognostic utility of biomarkers for liver cancer were included. Diagnostic accuracy measures, such as sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC), were analyzed. Additionally, prognostic parameters, including overall survival and recurrence-free survival, were assessed.

**Results:** A total of 65 articles met the inclusion criteria, comprising both prospective and retrospective studies. Circulating tumor markers, such as alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), exhibited moderate sensitivity and specificity for the early detection of liver cancer. Genetic signatures, including mutations in TP53 and CTNNB1, showed potential for prognostication and risk stratification.

**Conclusions:** Biomarkers play a crucial role in the early detection and prognostication of liver cancer. Integrating circulating tumor markers and genetic signatures into clinical practice can facilitate early diagnosis, risk stratification, and personalized treatment selection, ultimately improving patient outcomes and guiding therapeutic decisions.

**Keywords:** Liver cancer, Biomarkers, Meta-analysis, Personalized treatment

## PE-07

### Combination of Radiation Therapy Improve Efficacy of Atezolizumab plus Bevacizumab (ATE+BEVA) therapy IN Advanced Hepatocellular Carcinoma with High Risk Factor (Huge Tumor, Biliary and Main Portal Vein Invasion)

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**Aims:** Atezolizumab plus bevacizumab (Ate+Beva) proved better efficacy compared to sorafenib as a first line systemic therapy for advanced hepatocellular carcinoma (HCC). However, there is unmet need in the so called "high risk population"

(huge tumor, bile duct invasion, main portal vein invasion) because efficacy of Ate+Beva is worse in those group. Radiation therapy (RT) with immunotherapy could be expected synergic effect by immune stimulation. Therefore we describe the efficacy and safety of RT with immunotherapy in high risk population of advanced HCC.

**Methods:** The clinical course of patients with advanced HCC who received Ate+Beva therapy in single cancer center from September 2020 to December 2021 was assessed until May 2022. Overall response rate (ORR) and disease control rate (DCR) per RECIST v1.1 and mRECIST, median overall survival (OS), and safety were analyzed. Especially we divided two groups (RT vs non-RT) in high risk population and analyzed OS of two groups.

**Results:** 163 patients were treated with Ate+Beva therapy. Child A:B:C patients were 147:16:1, BCLC stage B:C patients were 23:140. Median OS of total patients was 10.2 months. ORR & DCR of total patients were 20.8%, 72.4%. Severe adverse event (SAE) beyond grade 3 was 12.9%. AE of grade 5 (hemoptysis, pneumonitis, variceal bleeding, duodenal ulcer perforation, autoimmune hepatitis) was 3.1%. Median OS of RT group and non-RT group in total patients were 10.7 vs 11.7 months ($P$=0.597), however those of two groups in high risk population were 11 vs 5 months ($P$<0.001). SAE of two groups wea not different significantly.

**Conclusions:** This study demonstrates that RT combined with Ate+Beva could improve efficacy about 2 times ompared to Ate+Beva without RT in high risk population of HCC without difference of AE. Further validation with large cohort in prospective study are needed to prove efficacy of Ate+Beva combined with RT in high risk population.

**Keywords:** Hepatocellular carcinoma, Atezolizumab plus bevacizumab, High risk patient, Radiation therapy

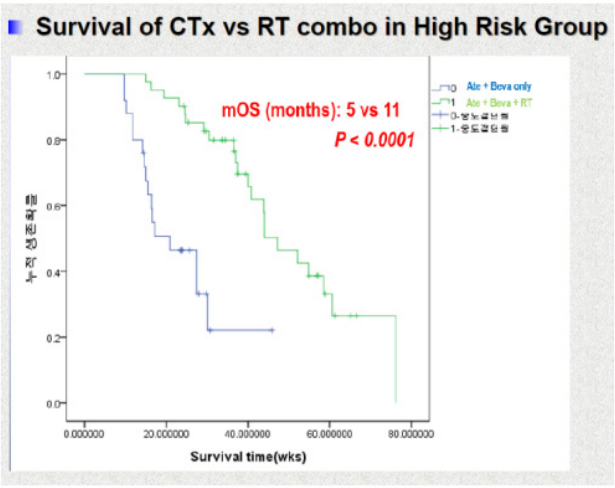


**Figure 1.** ATEBEVA in High risk patients.

## PE-08

## Clinical Biomarker to Predict Efficacy of Nivolumab Plus Ipilimumab in Advanced Heptocellular Carcinoma after Failure of Prior Atezolizumab plus Bevacizumab Therapy

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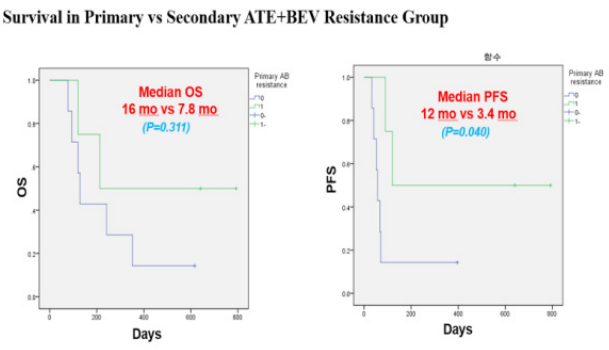
**Aims:** Atezolizumab plus bevacizumab (Ate+Beva) became a mainstream of first line systemic therapy for advanced hepatocellular carcinoma (HCC). However, studies about retrial of immune check point inhibitors after failure of AteBeva therapy are extremely rare. We describe the efficacy and safety of ipilimumab and nivolumab (Nivo+Ipi) in patients after the failure of prior Ate+Beva therapy and predictive factor.

**Methods:** The clinical course of patients with advanced HCC who received combined Nivo+Ipi after prior Ate+Beva therapy in single cancer center from October 2020 to November 2023 was assessed. Overall response rate (ORR) and disease control rate (DCR) per RECIST v1.1 and mRECIST, median progression free survival (PFS), overall survival (OS), and safety were analyzed between two groups (Primary Resistance Group : PD within 4 cycles of Ate+Beva, Secondary Resistance Group : PD beyond 4 cycles of Ate+Beva).

**Results:** Eleven patients (PRG;4 patients, SRG;7patients) received subsequent therapy with Nivo+Ipi. There were no significant difference between two groups. ORR, DCR, median OS and PFS of all patients were 27%, 36%, 11.3 months, 8.8 months. Tumor response and survival of PRG were significantly superior than those of SRG (ORR 75% vs 0%, $P$=0.001; DCR 75% vs 14%, $P$=0.032; median PFS 12 months vs 3 months, $P$=0.040). Grade 5 hepatitis happened in 1 patient, Grade 2 pneumonitis and adrenal insufficiency happened in each 1 patient, Grade 3 gastric ulcer happened in 1 patient.




**Conclusions:** Nivo+Ipi can be effective and tolerable after prior Ate+Beva therapy. Moreover patients that showed primary resistance of prior Ate+Beva therapy may have better efficacy

when they received subsequent Nivo+Ipi therapy. Further validation with large cohort in prospective study are needed to prove efficacy of this treatment sequencing and discover clinical biomarker.

**Keywords:** Atezolizumab, Bevacizumab, Primary resistance, Hepatocellular carcinoma, Ipilimumab, Nivolumab, Biomarker

## PE-09

### Improving Diagnostic Performance of Mucinous Cystic Neoplasm of the Liver: Validation and Modification of 2022 EASL Criteria

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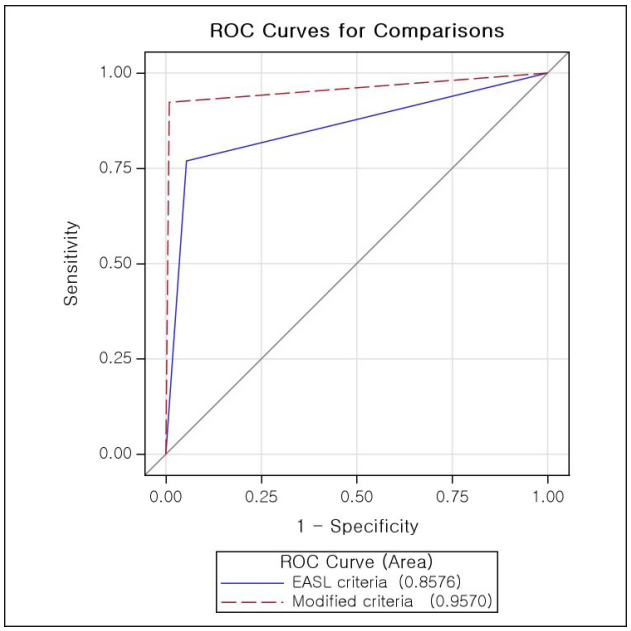
**Aims:** The 2022 EASL clinical practice guideline proposed imaging criteria to differentiate between mucinous cystic neoplasm (MCN) of the liver from hepatic cysts. The primary goal of our study is to validate the EASL criteria and propose a modified set with simplified diagnostic criteria and improved diagnostic performance.

**Methods:** Preoperative CT and MRI obtained from 124 patients with surgically resected MCN (n = 13) or hepatic cyst (n = 111) during 2016 and 2023 were retrospectively evaluated. The two major worrisome features (thick septation, nodularity) and five minor worrisome features (upstream biliary dilatation, thin septations, internal hemorrhage, perfusional change, < 3 coexistent hepatic cysts) of the EASL criteria were evaluated. Additionally, we analyzed whether septations arise without indentation. Logistic regression analysis was conducted using the image features and independent factors associated with MCN were identified. Based on the result of multivariable analysis we proposed modified criteria. The sensitivity, specificity, and accuracy of the modified criteria were compared to that of the EASL criteria using McNemar's test.

**Results:** Multivariable analysis revealed septa arising without indentation (odds ratio [OR]: 100.4; 95% confidence interval [CI]: 4.9–2076.0) and < 3 coexistent hepatic cysts (OR: 47.8; 95% CI: 1.5–1489.1) as independent factors for diagnosing MCN. We proposed a modified criteria, with a combination of septa arising without indentation and < 3 coexistent hepatic cysts. The modified criteria exhibited higher accuracy than the EASL criteria (98.4% vs. 92.7%; *P*=0.035), although there was no significant difference in sensitivity (92.3% vs. 76.9%; *P*=0.317) and specificity (99.1% vs. 94.6%; *P*=0.059).

**Conclusions:** The 2022 EASL criteria using seven imaging features for diagnosing MCN exhibited insufficient diagnostic performance. Our proposed modified criteria using only two imaging features may offer a promising alternative to improve diagnostic accuracy in diagnosing MCN.

**Keywords:** Liver, Mucinous cystic neoplasm of the liver, Easl guideline




## PE-10

### A Real-Life Experience of Atezolizumab and Bevacizumab Therapy in Patient with Advanced Hepatocellular Carcinoma in Gwangju-Jeonnam Province

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**Aims:** Atezolizumab plus bevacizumab therapy has been approved as a novel first-line chemotherapy in patients with advanced hepatocellular carcinoma. The aim of this study was to analyze real-life clinical results compared to tumoral response and survival rate in the IMbrave 150 study.

**Methods:** We enrolled 135 patients who underwent atezolizumab plus bevacizumab therapy in Gwangju-Jeonnam province from January 2021 to December 2023. Patients' clinical data and outcomes were investigated retrospectively according to medical records. Patients with response for atezolizumab plus bevacizumab therapy are classified according to modified RECIST criteria. $\chi$ 2 tests and Fisher exact tests were used to compare categorical variables and Kaplan-Meier survival analysis was used to compare outcomes between patients with risk factors.

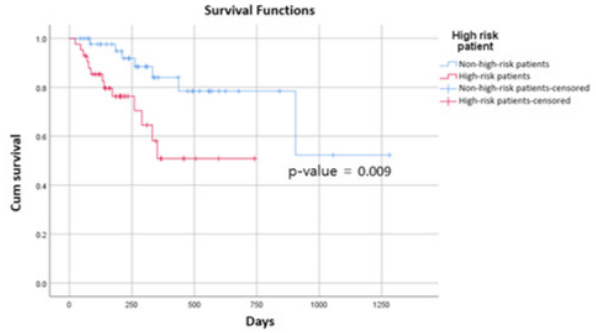
Table 1. Patent characteristics in real-life data in Gwangju-Jeonnam province compared to data of IMbrave 150 study.

| | CNUH | IMbrave 150 |
|---|---|---|
| | N= 135, (%) | N=336, (%) |
| Median age (year) | 67 (60-75) | 64 (56-71) |
| 39~50 | 6 (4.4) | - |
| 51~60 | 29 (21.5) | - |
| 61~70 | 47 (34.8) | - |
| 71~80 | 45 (33.3) | - |
| 81~87 | 8 (5.9) | - |
| Male sex | 119 (88.1) | 277 (82) |
| Cause of HCC | | |
| Viral (HBV/HCV/ HBV+HCV) | 74 (54.8) /9 (6.7)/3 (2.2) | 164 (49)/72 (21)/0 (0) |
| Non-viral (Alcohol/others) | 40 (29.6)/9 (6.7) | 100 (30) |
| Child-Pugh A | 124 (91.9) | 333 |
| Child-Pugh B | 11 (8.1) | |
| BCLC stage | | |
| A | 4 (2.9) | 8 (2) |
| B | 14 (10.4) | 52 (15) |
| C | 117 (86.7) | 276 (82) |
| AFP >400 | 56 (41.5) | 126 (38) |
| Macrovascular invasion | 66 (48.9) | 129 (38) |
| Extrahepatic spread | 51 (37.8) | 212 (63) |
| Prior local therapy | 45 (33.3) | 161 (48) |
| Tumor extent (>50%) | 43 (31.9) | - |

Table 2. Best tumoral response in real-life data in Gwangju-Jeonnam province compared to data of IMbrave 150 study.

| | CR | PR | SD | PD |
|---|---|---|---|---|
| Patient (N=123) | 4 (3.3) | 20 (16.3) | 63 (51.2) | 36 (29.3) |
| IMbrave 150 (N=325) | 33 (10.2) | 75 (23.1) | 127 (39.1) | 66 (20.3) |
| Tumor < 50% (N=83) | 2 (2.4) | 16 (19.3) | 44 (53.0) | 21 (25.3) |
| Tumor >50% (N=40) | 2 (5) | 4 (10) | 19 (47.5) | 15 (37.5) |

Figure 1. Survival outcomes according to high-risk factors (liver infiltration >50% of total liver volume, Vp4 thrombosis, alpha-fetoprotein over 400ng/dL) in patients treated with atezolizumab plus bevacizumab in advanced hepatocellular carcinoma.




**Results:** The radiologic best tumoral responses were showed to complete response (3.3%), partial response (16.3%), stable disease (51.2%), progressive disease (29.3%). Large number of patients had high risk factors such as macrovascular invasion (48.9%), extrahepatic metastasis (37.8%), massive tumor volume over 50% of total liver volume (31.9%). 33.3% of patients received local treatment before chemotherapy, and 43% of patients received chemotherapy combined radiotherapy. Overall survival was significantly related to various clinical risk factors with massive tumor volume (infiltration over 50% of liver), Vp4 thrombosis, alpha-fetoprotein level (over 400 ng/dL) (*P*-value < 0.05). 13.3% of patients had adverse events over grade 3. Bleeding events were occurred in 6 patients (2 variceal bleeding, 1 gastric ulcer bleeding, 1 intracranial hemorrhage, 1 hemoperitoneum, and 1 hemoptysis) and thrombotic events were occurred in 2 patients (1 subclavian thrombosis, and 1 anginal pectoris). One patient with duodenal ulcer perforation was died. Second-line therapy was done in 41% of patients with progressive disease after atezolizumab plus bevacizumab (71% on sorafenib, 15% on lenvatinib, and 14% on others).

**Conclusions:** Atezolizumab plus bevacizumab therapy showed safe and effective treatment for advanced hepatocellular carcinoma. In real-life, therapeutic efficacy tended to lowered by various clinical risk factors compared to pivotal study.

**Keywords:** Hepatocellular carcinoma, Systemic chemotherapy, Atezolizumab, Bevacizumab

## PE-11

### Clinical Characteristics and Risk Factors of Extrahepatic Recurrence after Hepatectomy of Hepatocellular Carcinoma without Intrahepatic Hepatocellular Carcinoma: A Multi-Institutional Observational Study

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**Aims:** Extrahepatic recurrence (EHR) is a well-known poor prognostic factor regarding hepatocellular carcinoma (HCC). Although EHR after hepatectomy of HCC may occur in high risk group of patients, little is known about EHR when there are no intrahepatic HCC. We investigated the clinical features and risk factors regarding EHR without remnant intrahepatic HCC at the time of EHR diagnosis.

**Methods:** Among 1,069 treatment-naive patients who underwent curative hepatectomy for HCC at four tertiary academic hospitals from January 2004 to December 2019, after exclusion of patients with intrahepatic recurrence (IHR) or EHR with IHR, and patients with insufficient clinical records, finally 569 pa-

tients were enrolled. The median follow-up duration was 3.91 years and multivariate analysis via Cox-regression was performed to identify the variables associated with EHR.

**Results:** Thirty-eight patients developed EHR after hepatectomy without remnant intrahepatic HCC during median follow-up duration of 1.04 years. Patients with EHR demonstrated significant early initial HCC recurrence than the patients without EHR; 1.73 vs. 4.43 years, respectively. On multivariate analysis, compared to patients without EHR, patients with EHR (without IHR) showed higher portion of venous/lymphatic involvement (HR 2.418, *P*=0.020), tumor necrosis (HR 2.592, *P*=0.009) and initial tumor stage beyond Milan criteria (HR=3.008, *P*=0.001). Also on analysis of factors related to survival after surgical resection of HCC, EHR was strongly associated with poor survival on multivariate analysis via Cox-regression (HR=14.044, *P*<0.001). Not only the cumulative rates of EHR correlated with the numbers of risk factors (Figure 1) but also the survival rates also exhibited step-wise relationship (Figure 2).

**Conclusions:** EHR without remnant viable HCC may occur in considerable number of patients after hepatectomy for HCC. Close monitoring for EHR is warranted in high risk group of patients despite of no HCC in liver.

**Keywords:** Hepatocellular carcinoma, Surgical resection, Prognosis, Extrahepatic metastasis

Figure 1.

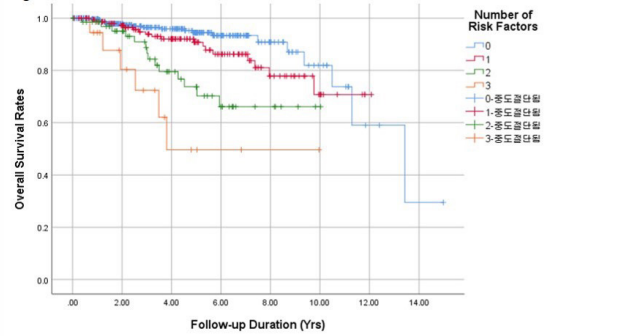
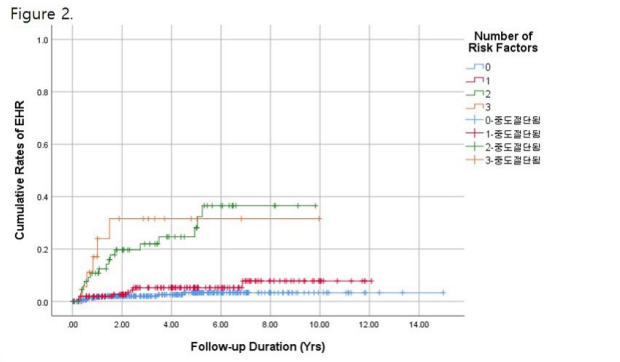



Figure 2.




## PE-12

### Metformin's Anti-Cancer Potential Short-Term Recurrence Following Hepatectomy for Hepatocellular Carcinoma

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**Aims:** Hepatocellular carcinoma (HCC) arising from chronic liver disease remains a significant cause of mortality. The aging population and the increasing prevalence of obesity have resulted in a rise in comorbidities such as hypertension and diabetes among patients with chronic liver disease. Vigilant surveillance for HCC has increased opportunities for early diagnosis, and there have been advancements in surgical techniques. Nonetheless, the recurrence rate of HCC post-surgery remains high, with over 10% within one year and approximately 70-80% within five years. Therefore, this study aims to investigate the association between the increasing prevalence of metabolic disorders and post-surgical HCC recurrence.

**Methods:** This retrospective cohort study was conducted on patients who underwent surgery for HCC diagnosis at two university hospitals in South Korea. A total of 187 patients' HCC tissues and blood test results were examined. Using the presence or absence of diabetes as a criterion, 1:1 matching based on gender and age allocated 64 patients each into the diabetes group and non-diabetes group. Cox regression tests were conducted on 128 patients after 1:1 matching to identify factors influencing HCC recurrence. Additionally, subgroup analysis using Kaplan-Meier tests aimed to identify factors influencing HCC recurrence in specific patient groups. T-tests were performed for continuous variables, while chi-square tests and Fisher's exact tests were conducted for categorical variables.

**Results:** When dividing the total cohort of 187 patients into diabetes and non-diabetes groups, the proportion of males was higher in the diabetes group (95.3% vs. 78.0%, p 0.002), and the mean age was higher in the diabetes group (65.0 ±11.04 vs. 58.4±11.69, *P*<0.001). Additionally, the diabetes group had a higher average weight (70.20±12.192 vs. 66.43± 11.604, *P* 0.04), and a greater number of patients with accompanying hypertension (71.9% vs. 28.5%, *P*<0.001). The MELD score was higher in the diabetes group (9.032±3.5074 vs. 7.710±1.4903, p 0.005), with creatinine, a component of the MELD score formula, also higher in the diabetes group (1.137 ±1.0562 vs. 0.853±0.1797, p 0.036). Even after 1:1 matching of diabetes and non-diabetes groups based on age and gender in a cohort of 128 patients, hypertension (71.9% vs. 39.1%, *P*<0.001), glycated hemoglobin (7.23±1.374 vs. 5.42±0.463, *P*<0.001), and metformin use (51.6% vs. 0%, *P*<0.001) were

higher in the diabetes group. Analysis of risk factors for HCC recurrence within 6 months in the cohort of 128 patients after 1:1 matching revealed that a higher MELD score was associated with approximately 1.2 times higher risk, and patients who received local treatment for HCC before HCC surgery had approximately 9.7 times higher risk compared to those who did not. Furthermore, the risk factor for HCC recurrence within 1 year was approximately 4.6 times higher in patients who received local treatment for HCC before HCC surgery compared to those who did not. While the use of the diabetes drug metformin did not have a statistically significant impact on HCC recurrence, subgroup analysis based on metformin use revealed no HCC recurrence within 6 months among patients who took metformin and did not undergo additional treatment before hepatectomy (p 0.045), had AFP levels < 400 (p 0.032), and had no vascular invasion (p 0.043).

**Conclusions:** This study revealed that in a specific subgroup, the use of metformin was associated with the absence of short-term recurrence following HCC surgery. Therefore, within limited subsets, the potential anti-cancer effects of metformin can be anticipated. Furthermore, in the selection of diabetes medication for HCC patient cohorts with diabetes, metformin might be considered as a primary option.

**Keywords:** Hepatocellular carcinoma, Recurrence, Metformin

## PE-13

### Vascular Endothelial Growth Factor and Hepatocyte Growth Factors Predicts Prognosis Post Stereotactic Body Radiation in Advanced Hepatocellular Carcinoma

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**Aims:** To find more effective biomarkers for early detection of disease progression post SBRT.

**Methods:** Prospective blood samples were collected from the 18 advanced HCC patients with Child-Pugh score (CP) between A5-B8, along with a minimum liver reserve of ≥ 700cc (i.e. liver volume after subtraction of the gross tumour volume must be > 700 cc), and distance of tumour to luminal structure distance > 5 mm, who underwent SBRT in this study.

Kinetics of serum levels of hepatocyte growth factor, (HGF), vascular endothelial growth factor (VEGF) were analysed using sandwitch ELISA at the baseline (before SBRT, day 5 of SBRT and after 1 month of SBRT) and were correlated with progression free survival and overall survival.

**Results:** Total of 18 patients were analysed over a median follow up period of 12.5 months (4 - 30 months). In the entire cohort, the mean overall survival was 21.2 months (95% confidence interval [CI], 15.9 - 26.4) with SBRT. The median PFS was 8 months (95 % confidence interval [CI] 1.7-14.2). Patients with raised PIVKA-II at baseline and post SBRT showed increased concentrations of VEGF and HGF. Patients who were presented with metastasis had higher HGF ($P$=0.028) and VEGF-A ($P$=0.027) at baseline as compared to non-metastatic group. Additionally, patients with increased levels of VEGF and HGF at 30 days post RT as compared to day 5 of SBRT levels had poor PFS. The median progression free survival (mPFS) was 22 months vs 6 months ($P$=0.301) in patients with decrease in VEGF as compared to increase in VEGF. Similarly, mPFS in patients with increase in HGF was 6 months as compared to 22 months ($P$=0.326) in patients in whom HGF was reduced post SBRT

**Conclusions:** Along with PIVKA II, HGF and VEGF can be used as prognostic and predictive markers for the early progression of HCC patients post SBRT

**Keywords:** HCC, SBRT, Growth factors

## PE-14

### The Efficacy and Safety of Atezolizumab and Bevacizumab Therapy for Hepatocellular Carcinoma

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**Aims:** Atezolizumab-bevacizumab combination therapy has been approved for first-line systemic chemotherapy in advanced hepatocellular carcinoma. Real-world retrospective analysis was performed to evaluate the effectiveness and safety of the chemotherapy.

**Methods:** A single-center, retrospective cohort study was performed. Patients with advanced hepatocellular carcinoma who received atezolizumab-bevacizumab systemic therapy were enrolled. Response to the therapy was assessed with mRECIST criteria. Evaluation of first radiologic response, best overall response, progression-free survival, and overall survival was done. Also, prognostic factors for first radiologic response, progression-free survival, and overall survival were also assessed.

**Results:** A total of 70 patients were investigated. Baseline characteristics showed a median age of 63 years, male dominance (89%), and viral etiology (84%). Four patients achieved complete response and 19 reached partial response when evaluated by best overall response. Response duration was 4.7 months (range 1.5-25.5). Median progression-free survival was 4.1 months (95% CI, 3.7-6.7), and median overall survival was 24.6 months (95% CI, 11.6-). Age and tumor extent of over 50% of the liver was predictive of progression-free survival ($P$=0.009 and $P$=0.007, respectively) Tumor extent of over 50% of the

liver and ALBI score were predictive of overall survival (*P*=0.025 and *P*=0.004, respectively). A total of 120 adverse events occurred and event grades over 3 accounted for 24% (n=29).

**Conclusions:** Atezolizumab-bevacizumab therapy showed valuable outcomes and tolerable safety profiles in real-world advanced HCC patients. The outcome and safety results were comparable to previous studies

**Keywords:** Hepatocellular carcinoma, Ateozolizumab bevacizumab

## PE-15

### Comparison of Intrahepatic Metastasis and Multicentric Occurrence in Multiple Hepatocellular Carcinoma after Liver Transplantation

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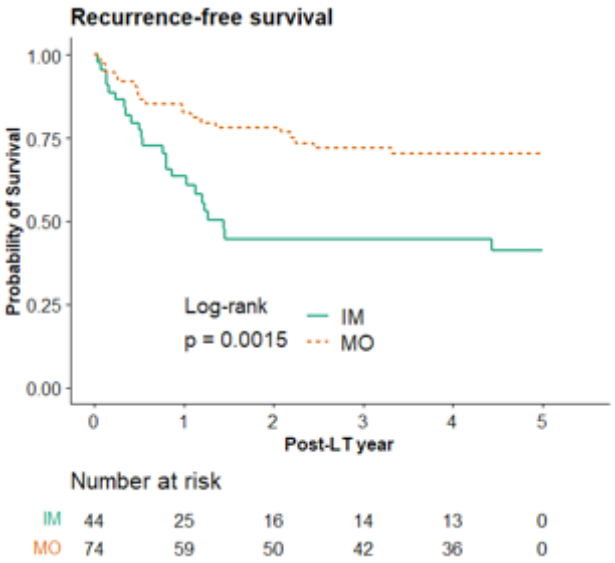
**Aims:** In the application of liver transplantation (LT) for multiple hepatocellular carcinoma (HCC), criteria such as Milan criteria, UCSF, and up-to-7 criteria emphasize tumor size and number when determining prognosis. However, these criteria do not consider whether the tumors are a result of intrahepatic metastasis (IM) or multicentric occurrence (MO). There is a lack of research on how these distinctions might affect recurrence rates. This study aims to compare prognosis and recurrence in multiple HCC patients after liver transplantation.

**Methods:** In this single-center retrospective study, 503 patients who underwent LT for HCC were categorized based on pathology results into two groups; intrahepatic metastasis (IM group, n=52) and multicentric occurrence (MO group, n=200). Recurrence free survival and overall survival were analyzed in entire and 1:2 propensity score-matched group with pre-operative baseline characteristics, tumor marker, size and number.

**Results:** In the entire study group, significant disparities were observed between the two groups in terms of the implementation of pretransplant locoregional treatments (IM vs. MO: 86.5% vs. 72%, *P*=0.002) and tumor markers levels (AFP: 27.5 vs. 8.4, *P*=0.001, PIVKA: 119 vs. 39.5, *P*=0.003). After propensity score matching, no statistically significant differences were found between the IM group and MO group except tumor differentiation (86.4% vs. 27%, *P*<0.001) and microvascular invasion (61.4% vs. 33.8%, *P*=0.006). In matched population, the five-year overall survival rate was notably lower in the IM group than in MO group (57.7% vs. 75.7%, *P*=0.04). The five-year recurrence free survival rate was significantly lower in the IM group than in the MO group (41.2% vs. 70.2%, *P*=0.002). The IM group was independently associated with recurrence even after adjusting for various factors related to tumor (HR 4.54, 95% CI 1.20-17.2, *P*=0.026).

**Conclusions:** This study revealed that patients with IM have poorer survival rates after liver transplantation compared to those with MO. This held true even when the pre-operation tumor markers and size were similar between two groups, indicating a worse prognosis for IM patients in comparison to MO patients.

**Keywords:** Hepatocellular carcinoma, Liver transplantation




## PE-16

### Early Bevacizumab Dose and Time Modifications Affect Efficacy of Atezolizumab Plus Bevacizumab Regimen for Advanced Hepatocellular Carcinoma Patients

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**Aims:** Atezolizumab (1200mg) plus bevacizumab (15mg/Kg) every 3 weeks (AtezBev) became a standard-of-care first-line treatment for advanced hepatocellular carcinoma (aHCC) following IMbrave-150. However, real-world data suggest milder

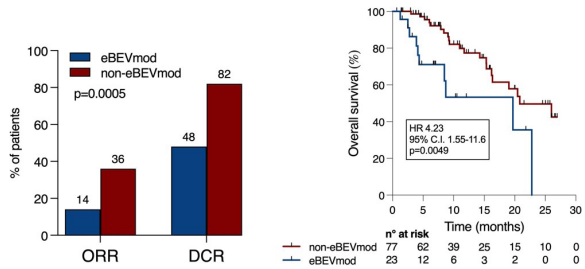
efficacy. Early bevacizumab interruption was described as frequent occurrence (~25%) in real-world scenario associated with poor prognosis. Additionally, early bevacizumab dose/time modifications (eBEVmod) may negatively impact outcome.

**Methods:** Data from n=100 AtezBev-treated aHCC patients in 5 Italian institutions were retrospectively analyzed. Cumulative bevacizumab dose (mg/Kg) received in the first 3 months of treatment was analyzed by ROC to identify a cut-off value (Youden's) to estimate survival and dichotomize the variable. Baseline clinical and laboratory characteristics were analyzed with uni-/multi-variate models to explore potential differences on overall survival (OS), objective-response and disease-control rates (ORR/DCR) based on eBEVmod. Progression-free survival was not evaluated due to inter-center variability in assessment timing.

**Results:** Median age was 69.5 (95CI: 65.7-73.0) years, 81%/19% were male/female, 96%/4% Child-Pugh A/B, 63%/37% ECOG-PS 0/≥ 1, 57%/43% ALBI-grade 1/2, 26%/74% BCLC-B/C, 62%/38% had viral/non-viral etiologies, 37% had macrovascular invasion, 35% alphafetoprotein > 400 ng/mL, and 34% received second-line treatments. Median follow-up was 11.4 (95CI: 9.1-26.9) months, mOS 20.5 (95CI: 16.2-26.0) months, ORR 31% and DCR 74%. ROC on 3-month cumulative bevacizumab dose revealed AUC 0.74 (*P*=0.001) and eBEVmod cut-off of < 45 mg/Kg/3 months (i.e. 10.5 mg/Kg/3 weeks) having 73% sensitivity and specificity in predicting death. 23% of patients had eBEVmod (9%/14% dose delay/reduction), with no differences in baseline characteristics nor second-line treatments compared to non-eBEVmod, except for sex (96% vs. 77% males, *P*=0.0423). eBEVmod patients had inferior ORR/DCR (14%/48% vs. 36%/82%, *P*=0.0005) and mOS (14.1 vs 20.8 months, HR 4.2, *P*=0.0049). eBEVmod was an independent negative prognostic factor of survival at multivariate analysis (HR 3.2, *P*=0.0134)

**Conclusions:** eBEVmod is an independent unfavorable prognostic factor of response and survival in AtezBev-treated aHCC patients. Optimization of bevacizumab-AEs management to reduce eBEVmod may substantially improve treatment outcome.

**Keywords:** Advanced HCC, Atezolizumab plus bevacizumab, Dose modification, Anti-VEGF




## PE-17

### Survival Outcomes According to the Timing of Switching to Atezolizumab plus Bevacizumab in TACE-Treated Patients with HCC

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**Aims:** Systemic treatment is recommended as a rescue therapy in hepatocellular carcinoma (HCC) patients with transarterial chemoembolization (TACE) failure or refractoriness. However, the proper switching timing has not been established. This study aimed to evaluate the impact of tumor response to repeated TACE when changing to Atezo/Bev on survival outcomes in patients with HCC.

**Methods:** We retrospectively analyzed patients with unresectable HCC who received TACE prior to the first-line systemic treatment with Atezo/Bev between 2018 and 2023 at Asan Medical Center. Responses to the last session of repeated TACE before Atezo/Bev were measured based on RECIST. TACE repetition was defined as consecutive sessions of the procedures every 6-8 weeks without on-treatment complete remission. Overall survival (OS) and progression-free survival (PFS) after Atezo/Bev were compared according to the last response of repeated TACE.

**Results:** Among a total of 107 patients included, 14 and 93 patients achieved stable disease (SD) and progressive disease (PD) at the last evaluation of repeated TACE. A median number of consecutive TACE sessions was 3.0. Objective response rates of Atezo/Bev as the best response were 23.1% and 16.1% for patients with SD and PD after TACE, respectively. During a 9.9-month median follow-up after Atezo/Bev, there were no significant differences in OS (median, not reached) and PFS (median, 7.0 and 5.6 months) between the two response groups. These trends for survivals were maintained after stratification by BCLC stages B and C at the switching time.

**Conclusions:** Last response of repeated TACE was not significantly associated with survival outcomes in patients with HCC receiving rescue Atezo/Bev. Nevertheless, given the potential hepatic and biliary damage from repeated TACE, the optimal timing for transitioning to systemic treatment should await further insights from randomized controlled trials.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization refractoriness, Atezolizumab plus bevacizumab, survival

## PE-18

### Limited Generalizability of Results of a Retrospective Single-Center Cohort Study of Prognosis of Hepatocellular Carcinoma

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**Aims:** We aimed to evaluate the validity of retrospective single-center versus multicenter research by comparing overall survival (OS) after various treatments in a nationwide multicenter cohort of hepatocellular carcinoma (HCC) patients with OS in a single-center cohort.

**Methods:** Patients newly diagnosed with HCC between January 2008 and December 2018 were analyzed using data from the Korean Primary Liver Cancer Registry (multicenter cohort, n=16,443), and the Asan Medical Center HCC registry (single-center cohort, n=15,655). Primary outcome was OS after initial treatment, which was compared between the two cohorts for both the entire population and for sub-cohorts with Child-Pugh A liver function (n=2,797 and n=5,151, respectively) treated according to the Barcelona-Clinic-Liver-Cancer (BCLC) strategy.

**Results:** Patients of BCLC stages 0 and A (59.3% vs. 35.2%) and patients who received curative treatment (42.1% vs. 32.1%) were more frequently observed in the single-center cohort (*Ps*<0.001). Multivariable analysis revealed worse OS in the multicenter cohort in patients receiving curative (adjusted hazard ratio [95% confidence interval], 1.48 [1.39–1.59]) and non-curative (1.22 [1.17–1.27]) treatments, and better OS in those receiving systemic therapy (0.83 [0.74–0.92]) and best supportive care (0.85 [0.79–0.91]). Subcohort analyses revealed differences in OS between the two cohorts in the subgroups undergoing chemoembolization (1.72 [1.48–2.00]) and ablation (1.44 [1.08–1.92]), with poorer OS in the multicenter sub-cohort.

**Conclusions:** Comparisons of treatment outcomes between single-center and multicenter cohorts revealed significant differences. Therefore, the results of retrospective single-center cohort studies of HCC treatments may not be generalizable to real-world practice.

**Keywords:** BCLC, UICC, Liver cancer, Retrospectic cohort

## PE-19

### Pre- and Postoperative Predictors of Extrahepatic Recurrence after Curative Resection for Hepatocellular Carcinoma

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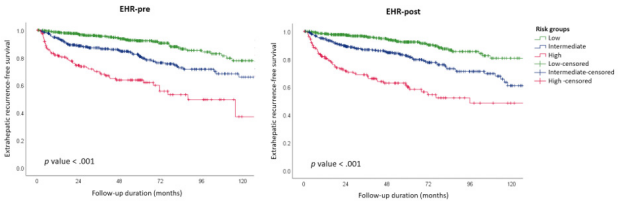
**Aims:** The factors associated with extrahepatic recurrence (EHR) after curative resection for hepatocellular carcinoma (HCC) have rarely been investigated. This study examined the pre- and postoperative predictors of EHR after curative resection in HCC patients over a ten-year follow-up period.

**Methods:** A retrospective review was conducted on treatment-naïve HCC patients who underwent curative resection between 2004 and 2019 at four tertiary hospitals in South Korea.

**Results:** Of 1,069 enrolled patients, the mean age was 59.1 years, and 85.8% were male. The majority of patients (98.6%) had compensated liver cirrhosis, and chronic hepatitis B was the prevalent etiology (73.7%). EHR developed in 175 patients (16.4%) and was associated with younger age, advanced tumor stages, and histological features including larger tumor size, a higher number of tumors, the presence of microvascular invasion, bile duct invasion, intrahepatic metastasis, and necrosis. According to multivariate Cox regression analyses younger age, a higher modified Union for International Cancer Control (UICC) stage, exceeding the Milan criteria, and an albumin–bilirubin (ALBI) grade ≥ 2 were independently significant preoperative factors associated with EHR. Similarly, age, the presence of microvascular invasion, necrosis, exceeding the Milan criteria, and an ALBI grade ≥ 2 were independently significant postoperative factors. Kaplan–Meier plots clearly differentiated EHR-free survival among the risk groups stratified by our EHR-preop and EHR-postop models.

**Conclusions:** Our study developed predictive models (EHR-preop and EHR-postop) to identify the risk of EHR after curative HCC resection. These models could potentially enhance clinical decision-making by identifying patients at elevated EHR risk thus advancing personalized HCC care.

**Keywords:** Carcinoma, Hepatocellular, Resection, Extrahepatic Recurrence




## PE-20

### Expression of Citrullinated Glial Fibrillary Acidic Protein Is Closely Associated with Poor Prognosis in Patients with Hepatocellular Carcinoma

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**Aims:** Citrullination is a posttranslational modification that abolishes the positive charges of arginine residues by conversion to citrulline residues via calcium-dependent peptidylarginine deiminases (PAD), leading to significant alterations in protein structure and function. Glial fibrillary acidic protein (GFAP), highly susceptible to the attack of PAD, was increased in activated hepatic stellate cells (HSCs) and GFAP-expressing HSCs, and myofibroblasts accumulated in and around hepatic fibrosis. Recently, the expression of citrullinated GFAP (cit-GFAP) is also increased in hepatic fibrosis, its expression and role of cit-GFAP in hepatocellular carcinoma (HCC) is unknown. This study investigated whether the expression of cit-GFAP affects recurrence and survival in HCC patients who underwent hepatic resection.

**Methods:** One hundred and sixty-eight HCC patients after hepatic resection were enrolled. The median follow-up was 39 months (range 0–183 months) in enrolled patients. To investigate an association between cit-GFAP expression level and the clinical characteristics of enrolled patients, the recurrence of HCC following surgical resection and survival of the patients were examined.

**Results:** Eighty-one cases (48.2%) of HCC demonstrated a higher expression of cit-GFAP. The expression of cit-GFAP was correlated with male sex, hepatitis B virus positivity, and higher Edmonson-Steiner grade. There was no association between cit-GFAP expression and age, diabetes mellitus, hypertension, liver cirrhosis, Child–Pugh class, major portal vein invasion, white blood cell counts, platelet counts, serum alanine transferase, total bilirubin, albumin, alpha-fetoprotein, HCC size or number. The mortality rates in HCC patients with higher cit-GFAP expression were worse than those with lower cit-GFAP expression. After multivariate cox analysis, larger tumors (HR 2.967, 95% CI 1.097-8.024, *P*=0.032) and higher cit-GFAP expression (HR 2.753, 95% CI 1.015–7.464, *P*=0.047) were independent risk factors for postoperative survival. The recurrence rates of patients with higher cit-GFAP expression were slightly higher than those of patients with lower cit-GFAP expression, but it was not statistically significant.

**Conclusions:** We report here, for the first time, the abnormal accumulation of cit-GFAP in patients with HCC. Also, cit-GFAP expression is closely associated with survival of HCC patients following surgical resection.

**Keywords:** Hepatocellular carcinoma, Citrullination, Glial fibrillary acidic protein, Prognosis

**Table 1.** Baseline characteristics of enrolled patients

| Variables | Total (n = 168) | Low (n = 87) | High (n = 81) | *p* Value |
|---|---|---|---|---|
| Age (years) | 62.49±12.15 | 63.03±10.76 | 61.91±13.53 | 0.601 |
| Sex (male), n (%) | 136 (81.0) | 76 (87.4) | 60 (74.1) | 0.028 |
| HBsAg-positive (+), n (%) | 115 (68.5) | 66 (75.9) | 49 (60.5) | 0.032. |
| DM, n (%) | 53 (31.5) | 28 (32.2) | 25 (30.9) | 0.854 |
| HTN, n (%) | 77 (45.8) | 40 (46.0) | 37 (45.7) | 0.969 |
| LC, n (%) | 91 (54.2) | 53 (60.9) | 38 (46.9) | 0.069 |
| Child-Pugh class (B/A) | 12/156 | 5/82 | 7/74 | 0.467 |
| Tumor size (≥ 5 cm/< 5 cm) | 46/122 | 24/63 | 22/59 | 0.951 |
| Tumor number | 1.24±0.612 | 1.22±0.53 | 1.26±0.08 | 0.230 |
| PVI | 65 (38.7) | 28 (32.2) | 37 (45.7) | 0.073 |
| Edmonson-Steiner (1,2/3,4) | 52/116 | 33/54 | 19/62 | 0.043 |
| WBC | 5750 (4625-7200) | 5700 (4300-7300) | 6000 (4800-7150) | 0.268 |
| Platelet | 167 (120.25-201) | 157 (106-197) | 175 (135-203) | 0.418 |
| Serum ALT (IU/L) | 28 (20-41) | 28 (21-41) | 27 (17.5-46.5) | 0.258 |
| Total bilirubin | 0.64 (0.52-0.898) | 0.64 (0.53-0.96) | 0.65 (0.400-0.875) | 0.301 |
| Albumin | 4.2 (3.8-4.5) | 4.2 (3.8-4.4) | 4.3 (3.85-4.6) | 0.406 |
| PT-INR | 1.04 (0.98-1.15) | 1.06 (0.98-1.16) | 1.02 (0.97-1.135) | 0.218 |
| AFP > 400, n (%) | 29 (17.3) | 14 (16.1) | 15 (18.5) | 0.678 |

**Table 2.** Univariate and multivariate cox analysis for recurrence following surgical resection.

| Variables | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p Value | HR | 95% CI | p Value |
| Age (years) | 1.002 | 0.982-1.022 | 0.845 | | | |
| Sex (male/female) | 0.932 | 0.487-1.787 | 0.833 | | | |
| DM | 0.864 | 0.512-1.458 | 0.583 | | | |
| HTN | 1.237 | 0.768-1.994 | 0.381 | | | |
| HBsAg-positive (+) | 0.965 | 0.576-1.617 | 0.892 | | | |
| LC | 0.959 | 0.592-1.552 | 0.863 | | | |
| Child–Pugh class (B/A) | 2.196 | 0.947-5.090 | 0.067 | | | |
| Tumor size (≥ 5 cm/< 5 cm) | 2.493 | 1.503-4.136 | <0.001 | 2.378 | 1.426-3.965 | <0.001 |
| Tumor number (single vs. multiple) | 1.173 | 0.650-2.120 | 0.596 | | | |
| Edmonson-Steiner (1, 2/3, 4) | 1.223 | 0.735-2.037 | 0.493 | | | |
| Platelet | 0.999 | 0.996-1.003 | 0.646 | | | |
| Serum ALT (IU/L) | 1.009 | 1.001-1.017 | 0.032 | 1.007 | 0.999-1.015 | 0.081 |
| AFP > 400 | 1.643 | 0.824-2.793 | 0.181 | | | |
| Cit-GFAP (high/low) | 1.456 | 0.895-2.369 | 0.130 | | | |

**Table 3.** Univariate and multivariate cox analysis for mortality following surgical resection.

| Variables | Univariate Analysis | | | Multivariate Analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p Value | HR | 95% CI | p Value |
| Age (years) | 1.021 | 0.981–1.062 | 0.312 | | | |
| Sex (male/female) | 1.274 | 0.363–4.475 | 0.705 | | | |
| DM | 0.871 | 0.308–2.461 | 0.794 | | | |
| HTN | 0.869 | 0.349–2.164 | 0.762 | | | |
| HBsAg-positive (+) | 0.494 | 0.199–1.221 | 0.127 | | | |
| LC | 0.954 | 0.387–2.349 | 0.918 | | | |
| Child–Pugh class (B/A) | 2.192 | 0.504–9.542 | 0.296 | | | |
| Tumor size (≥ 5 cm/< 5 cm) | 3.323 | 1.315–8.398 | 0.011 | 2.967 | 1.097–8.024 | 0.032 |
| Tumor number (single vs. multiple) | 2.270 | 0.882–5.842 | 0.089 | | | |
| Edmonson-Steiner (1, 2/3, 4) | 2.318 | 0.759–7.083 | 0.140 | | | |
| Platelet | 1.003 | 0.995–1.010 | 0.493 | | | |
| Serum ALT (IU/L) | 1.010 | 0.995–1.025 | 0.208 | | | |
| AFP > 400 | 2.736 | 1.025–7.303 | 0.045 | 1.696 | 0.5691-4.863 | 0.326 |
| Cit-GFAP (high/low) | 2.707 | 1.006–7.290 | 0.049 | 2.753 | 1.015-7.464 | 0.047 |

## PE-21

### Comparative Efficacy of Tenofovir Alafenamide, Tenofovir Disoproxil Fumarate, and Entecavir on Hepatocellular Carcinoma Incidence: Nationwide Data Analysis

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**Aims:** Previous research has demonstrated that oral antiviral therapy reduces the incidence of hepatocellular carcinoma (HCC) and improves survival rates for patients with chronic hepatitis B. Despite numerous studies on these drugs, the newer tenofovir alafenamide (TAF) lacks extensive research regarding its impact on HCC. This study aims to evaluate and compare the effects of TAF, tenofovir disoproxil fumarate (TDF), and entecavir (ETV) on HCC incidence in Korea.

**Methods:** We conducted a retrospective analysis of claims data from the Health Insurance Review and Assessment Service. Incidence rates of HCC were compared using 1:1:1 propensity score matching (PSM) among users of TAF, TDF, and ETV.

**Results:** Before PSM, the incidence of HCC was 74.14 per 1,000 person-years for TDF users, 62.14 for ETV users, and 61.12 for TAF users, with an incidence rate ratio (IRR) of 1.31 (95% CI 1.19-1.44, *P*<0.001) for TDF, and 1.24 (95% CI 1.12-1.37, *P*<0.001) for ETV, respectively. In patients with liver cirrhosis, the IRRs were significantly higher for TDF (IRR 1.66, 95% CI 1.46-1.89, *P*<0.001) and ETV (IRR 1.57, 95% CI 1.38-1.79, *P*<0.001) compared to TAF. In non-cirrhotic patients, only TDF showed a significant difference (IRR 1.24, 95% CI 1.08-1.42, *P*=0.002). Cox regression analysis confirmed that TDF was significantly associated with a higher HCC development compared to TAF (IRR 1.24, 95% CI 1.11-1.39, *P*<0.001), while ETV did not show significant differences (IRR 1.08, 95% CI 0.96-1.21, *P*=0.219). However, in the cirrhotic group, both TDF (IRR 1.31, 95% CI 1.11-1.54, *P*=0.0011) and ETV (IRR 1.27, 95% CI 1.08-1.50, *P*=0.0033) had significant *P*-values, indicating a lower incidence of HCC in TAF users after PSM.

**Conclusions:** TAF is associated with a lower incidence of HCC compared to TDF and ETV. No significant differences were

observed between ETV and TDF in HCC occurrence among chronic hepatitis patients. Notably, in patients with liver cirrhosis, TAF proves more effective in preventing HCC than both ETV and TDF.

**Keywords:** Tenofovir alafenamide fumarate, TAF, Hepatocellular carcinoma, Incidence, Claims data

## PE-22

### Comparative Analysis of Maliginant Hepatocellular Neoplasm, Not Otherwise Specified versus Hepatoblastoma and Pediatric Hepatocellular Carcinoma

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**Aims:** Hepatocellular neoplasm, not otherwise specified (HCN-NOS) is a provisional diagnostic entity known to represent intermediate or combined features of hepatoblastoma and pediatric hepatocellular carcinoma (p-HCC). We aimed to evaluate the characteristics of HCN-NOS and compare it with hepatoblastoma and p-HCC.

**Methods:** A total of 155 pediatric patients who were diagnosed with HCN-NOS, hepatoblastoma, or p-HCC after surgery were retrieved from the institutional database from 1998 to 2023. Clinical and radiologic parameters were retrospectively collected. Histopathology slides were reviewed to confirm and re-establish each patient's diagnosis.

**Results:** We identified 21 patients (13.5%) with HCN-NOS, 112 (72.3%) with hepatoblastoma, and 22 (14.2%) with p-HCC. The median age was 8.4 years (1.9—17.0) in HCN-NOS, 1.0 (0.1—11.7) in hepatoblastoma, and 9.0 (0.1—17.8) in p-HCC. There was no significant gender difference in all three groups. Background liver disease, such as hepatitis B, biliary atresia, portosystemic shunt, and progressive familial intrahepatic cholestasis, was frequently observed in p-HCC (14/22, 63.6%) but infrequent in HCN-NOS (2/21, 9.5%) and hepatoblastoma (2/112, 1.8%). On microscopic examination, HCN-NOS did not harbor distinct embryonal, cholangioblastic, small cell undifferentiated, mesenchymal or teratoid components observed in hepatoblastoma, but was exclusively composed of malignant cells showing hepatocellular differentiation, the morphology of which was intermediate between fetal hepatocellular carcinoma and hepatocellular carcinoma. HCN-NOS revealed the shortest event-free and overall survival rates among three groups, followed by p-HCC and hepatoblastoma ($P$<.001 and = .012, respectively).

**Conclusions:** The possibility of HCN-NOS should be considered in pediatric liver cancer patients, especially those older than 5 years with no background liver disease. Patients with HCN-NOS exhibit intermediate histologic features between hepatoblastoma and p-HCC but are associated with more aggressive behavior than hepatoblastoma and p-HCC. Therefore, patients with HCN-NOS need a different treatment strategy from those with hepatoblastoma or p-HCC.

**Keywords:** Liver neoplasms, Pediatrics, Hepatoblastoma, Diagnosis

## PE-23

### Exploring Prognostic Disparities of HCC Treatment in the Elderly: An Analysis of the Korean Nationwide Cancer Registry Data

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**Aims:** Although the incidence of hepatocellular carcinoma (HCC) is rising among the elderly population, there is a paucity of studies investigating the interplay between age and treatment diversity with respect to survival outcomes.

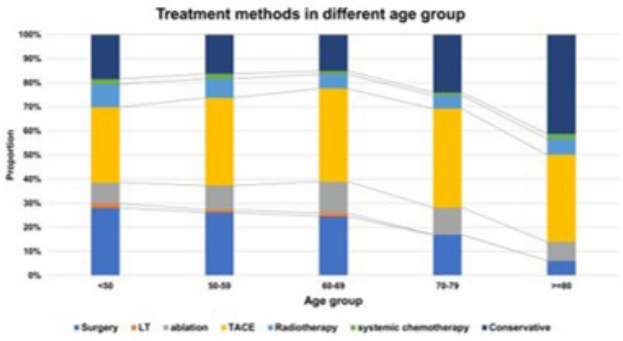
**Methods:** The study population consisted of 7,014 individuals aged 20 years and older, who were identified through the Korea Primary Liver Cancer Registry for the years 2014 and 2017. Baseline characteristics, hepatocellular carcinoma (HCC) stage, treatment modalities, and overall survival (OS) were evaluated. Participants were stratified into five age groups (< 50, 50-59, 60-69, 70-79, and ≥ 80 years), were stratified and compared by BCLC stage and treatment method. Cox regression model and restricted cubic spline (RCS) analysis were employed to establish the age cutoff at which the efficacy of curative and non-curative treatments diminished. Statistical significance was set at $P$<0.05 for all analyses.

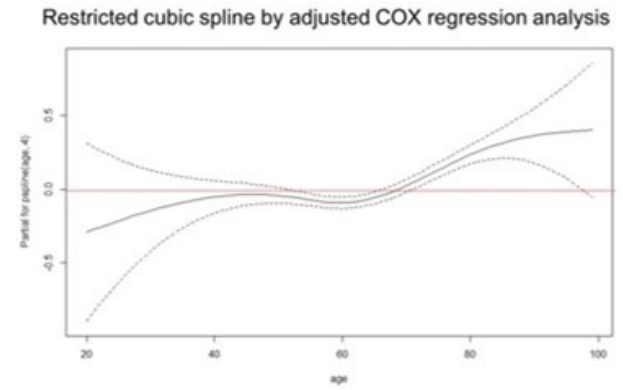
**Results:** The median age at the time of HCC diagnosis was 62 years with a male predominance (79.2%) and hepatitis B virus infection as the most common etiology (58.7%). The age distribution was 13.1% for < 50 years, 30.2% for 50-59 years, 28.4% for 60-69 years, 21.5% for 70-79 years, and 6.7% for ≥ 80 years. Patients aged 70 years and above showed a decline in surgical treatment rate (28% to 14.3%) and a marked increase in conservative treatment rate (18% to 28%) compared to those under 70 years of age (Fig 1). This trend persisted in the analysis stratified by Barcelona Clinic Liver Cancer (BCLC) staging and comparable patterns was observed in the curative and non-curative treatment cohorts. Among patients who received only conservative treatment, no statistical differences in survival rate by stage were observed in age groups 70-79 and ≥ 80 years. Restricted cubic splines analysis using adjusted Cox re-

gression results identified the age of 70 years as the threshold at which the potential treatment benefits began to diminish (Fig 2).

**Conclusions:** For patients diagnosed with HCC after their mid-70s, the potential for prognostic benefit attributable to the cancer stage or treatment modalities may be diminished relative to the younger age group. Age-based risk stratification may be necessary in the context of individual clinical scenarios, and further research is required to assess the optimal timing for terminating HCC surveillance.

**Keywords:** Hepatocellular carcinoma, Treatment, Prognosis, Elderly




## PE-24

### Impact of Lymphadenectomy for Patients with Clinically Node-Negative Intrahepatic Cholangiocarcinoma: A Multicenter Retrospective Cohort Study

Meng Sha[1], Jie Cao[1], Cheng-lin Qin[2], Jian Zhang[3], Zhe Li[1], De-fu Kong[1], Hua-lian Hang[1], Ying Tong[1], Qiang Xia[1]

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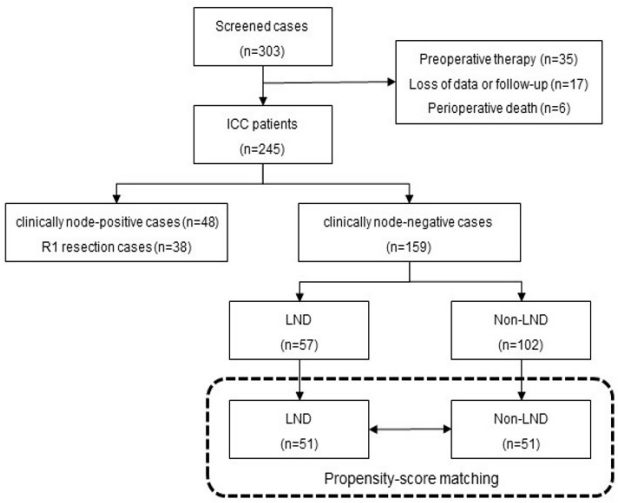
**Aims:** Lymph node status is a prominent prognostic factor for intrahepatic cholangiocarcinoma (ICC). However, the clinical value of performing lymphadenectomy (LND) in patients with clinical node-negative ICC remains controversial. The aim of this study is to determine whether lymphadenectomy improves long-term outcomes in this subgroup of patients.

**Methods:** We retrospectively analyzed patients who underwent radical liver resection for clinically node-negative ICC from three tertiary referral centers. A propensity score matching analysis based on clinicopathological data was conducted between patients with and without lymphadenectomy. Recurrence-free survival and overall survival were compared in the matched cohort.

**Results:** Among 303 patients who underwent radical liver resection for ICC, a total of 159 clinically node-negative ICC patients were eligible for the study with 102 in the LND group and 57 in the non-LND group. After propensity score matching, two well-balanced group of 51 patients each were analyzed. There was no significant difference of median RFS (12.0 vs. 10.0 months, *P*=0.37) and median OS (22.0 vs. 26.0 months, *P*=0.47) between the LND and non-LND group. Also, LND was not identified as one of the independent risks for survivals. On the other hand, postoperative adjuvant therapy was the independent risk factor for both RFS (HR 0.623, 95%CI 0.393-0.987, *P*=0.044) and OS (HR 0.585, 95%CI 0.359-0.952, *P*=0.031). Furthermore, postoperative adjuvant therapy was associated with prolonged survivals of non-LND patients (*P*=0.02 for RFS and *P*=0.03 for OS).

**Conclusions:** Based on the data, we found that LND did not significantly improve the prognosis of patients with clinically node-negative ICC. Postoperative adjuvant therapy was associated with prolonged survivals of ICC patients, especially in non-LND individuals.

**Keywords:** Intrahepatic cholangiocarcinoma, Liver resection, Lymphadenectomy, Lymph node metastasis



## PE-25

### Effect of Biliary Drainage on Prognosis of Patients with Hepatocellular Carcinoma and Bile Duct Invasion

**Keungmo Yang**, Hyun Yang, Chang Wook Kim, Hee Chul Nam, Ji Hoon Kim, Ahlim Lee, U Im Chang, Jin Mo Yang, Hae Lim Lee, Jung Hyun Kwon, Soon Woo Nam, Soon Kyu Lee, Pil Soo Sung, Ji Won Han, Jeong Won Jang, Si Hyun Bae, Jong Young Choi, Seung Kew Yoon, Hee Yeon Kim

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**Aims:** Bile duct invasion (BDI) is rarely observed in advanced hepatocellular carcinoma (HCC), leading to hyperbilirubinemia. However, the efficacy of pre-treatment biliary drainage for HCC patients with BDI and obstructive jaundice is currently unclear. Thus, this study aimed to assess the effect of biliary drainage on prognostic outcomes of these patients.

**Methods:** We retrospectively enrolled a total of 200 HCC patients with BDI from multicenter cohorts. Patients without obstructive jaundice (n = 99) and those who did not undergo HCC treatment (n = 37) were excluded from further analysis. Finally, 64 patients with obstructive jaundice (43 with drainage and 21 without drainage) were included. Propensity score matching (PSM) was then conducted.

**Results:** The biliary drainage group showed better overall survival (median OS: 10.1 months vs. 4.4 months, $P$=0.004) and progression-free survival (median PFS: 7.0 months vs. 2.0 months, $P$<0.001) than the non-drainage group. Multivariate analysis demonstrated that biliary drainage was a significantly favorable prognostic factor for OS (HR: 0.42, $P$=0.006) and PFS (HR: 0.30, $P$<0.001). Furthermore, biliary drainage presented beneficial results in the evaluation of first response after HCC treatment ($P$=0.005). Remarkably, OS ($P$=0.032) and PFS ($P$=0.004) were similar after PSM.

**Conclusions:** Biliary drainage is an independent favorable prognostic factor for HCC patients with BDI and obstructive jaundice. Therefore, biliary drainage should be contemplated in the treatment of advanced HCC patients with BDI for better survival outcomes.

**Keywords:** Hepatocellular carcinoma, Bile duct invasion, Hyperbilirubinemia, Biliary drainage

## PE-26

### Comparison of Atezolizumab plus Bevacizumab and Lenvatinib for Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

**Jeayeon Park**[1], Yun Bin Lee[1], Hyunjae Shin[1], Yunmi Ko[1], Youngsu Park[1], Moon Haeng Hur[1], Min Kyung Park[1], Dae-Won Lee[2], Eun Ju Cho[1], Kyung-Hun Lee[2], Jeong-Hoon Lee[1], Su Jong Yu[1], Tae-Yong Kim[2], Yoon Jun Kim[1], Tae-You Kim[2], Jung-Hwan Yoon[1]

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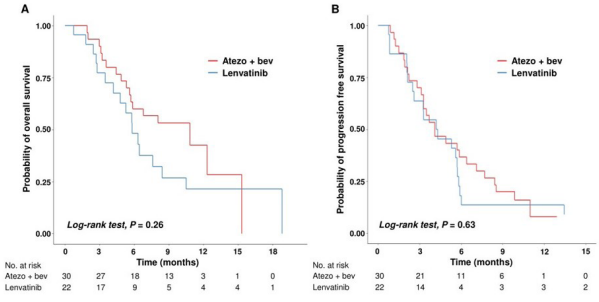
**Aims:** Atezolizumab plus bevacizumab and lenvatinib are currently available as first-line therapy for the treatment of unresectable hepatocellular carcinoma (HCC); however, comparative efficacy studies are still scarce. This study aimed to investigate the effectiveness of these treatments in HCC patients with portal vein tumor thrombosis (PVTT).

**Methods:** We retrospectively included patients who received either atezolizumab plus bevacizumab or lenvatinib as first-line systemic therapy for HCC with PVTT. Primary endpoint was overall survival (OS), and secondary endpoints included progression-free survival (PFS) and disease control rate (DCR) determined by Response Evaluation Criteria in Solid Tumors, version 1.1.

**Results:** A total of 52 patients were included: 30 received atezolizumab plus bevacizumab and 22 received lenvatinib. The median follow-up duration was 6.4 months (interquartile range, 3.9–9.8). The median OS was 10.8 months (95% confidence interval [CI], 5.7–not estimated) with atezolizumab plus bevacizumab and 5.8 months (95% CI, 4.8–not estimated) with lenvatinib ($P$=0.26 by log-rank test). There was no statistically significant difference in OS (adjusted hazard ratio [aHR], 0.71; 95% CI, 0.34–1.49; $P$=0.37). The median PFS was similar ($P$=0.63 by log-rank test), with 4.1 months (95% CI, 3.3–7.7) for atezolizumab plus bevacizumab and 4.3 months (95% CI, 2.6–5.8) for lenvatinib (aHR, 0.93; 95% CI, 0.51–1.69; $P$=0.80). HRs were similar after inverse probability treatment weighting. The DCRs were 23.3% and 18.2% in patients receiving atezolizumab plus bevacizumab and lenvatinib, respectively ($P$=0.74).

**Conclusions:** The effectiveness of atezolizumab plus bevacizumab and lenvatinib was comparable for the treatment of HCC with PVTT.

**Keywords:** Liver cancer, Immunotherapy, Immune checkpoint, PD-L1



## PE-27

### Clinical Outcomes of Transarterial Chemoembolization in Child-Turcotte Pugh Class A Patients with a Single Small (≤ 3 cm) Hepatocellular Carcinoma

Jungnam Lee[1], Young-Joo Jin[1], Seung Kak Shin[2], Jung Hyun Kwon[3], Sang Gyune Kim[4], Jung Hwan Yu[1], Jin-Woo Lee[1], Oh Sang Kwon[2], Soon Woo Nahm[3], Young Seok Kim[4]

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**Aims:** Transarterial chemoembolization (TACE) is one of the standard modalities used to treat unresectable hepatocellular carcinoma (HCC), but the effectiveness of TACE for treating patients with a solitary small (≤ 3 cm) HCC and well-preserved liver function has not been definitively established. This study aimed to determine the therapeutic impact of TACE in patients with these characteristics.

**Methods:** This multicenter (four university hospitals) retrospective cohort study analyzed the medical records of 250 patients with a solitary small (≤ 3 cm) HCC and Child-Turcotte-Pugh (CTP) class A liver function diagnosed over ten years. Post-treatment outcomes, including overall survival (OS), recurrence-free survival (RFS), and adverse events, were assessed following TACE therapy.

**Results:** 138 of the 250 patients (55.2%) treated with TACE achieved complete remission (CR). Overall median OS was 77.7 months, and median OS was significantly longer in the CR group than in the non-CR group (89.1 vs. 58.8 months, $P$=0.001). Median RFS was 19.1 months in the CR group. Subgroup analysis identified hypertension, an elevated serum albumin level, and achieving CR as significant positive predictors of OS, whereas diabetes, hepatitis c virus infection, and tumor size (> 2 cm) were poor prognostic factors of OS.

**Conclusions:** The study demonstrates the effectiveness of TACE as a viable alternative for treating solitary small (≤ 3 cm) HCC in CTP class A patients.

**Keywords:** Hepatocellular carcinoma, Transarterial chemoembolization, Overall survival, Child-turcotte pugh

## PE-28

### Inter-Reader Agreement for CT/MRI LI-RADS Category M Imaging Features: A Systematic Review and Meta-Analysis

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**Aims:** To systematically evaluate inter-reader agreement in the assessment of individual Liver Imaging Reporting and Data System (LI-RADS) category M (LR-M) imaging features in computed tomography/magnetic resonance imaging (CT/MRI) LI-RADS v2018, and explore the causes of poor agreement in LR-M assignment.

**Methods:** Original studies reporting inter-reader agreement for LR-M features on multiphasic CT or MRI were identified in MEDLINE, EMBASE, and Cochrane databases. The pooled kappa coefficient ($\kappa$) was calculated using the DerSimonian–Laird random-effects model. Heterogeneity was assessed using the Cochran Q test and $I^2$ statistic. Subgroup meta-regression analyses were conducted to explore study heterogeneity.

**Results:** In total, 24 eligible studies with 5163 hepatic observations were included. The pooled $\kappa$ values were 0.72 (95% confidence interval, 0.65–0.78) for rim arterial phase hyperenhancement, 0.52 (0.39–0.65) for peripheral washout, 0.60 (0.50–0.70) for delayed central enhancement, 0.68 (0.57–0.78) for targetoid restriction, 0.74 (0.65–0.83) for targetoid transitional phase/hepatobiliary phase appearance, 0.64 (0.49–0.78) for infiltrative appearance, 0.49 (0.30–0.68) for marked diffusion restriction, and 0.61 (0.48–0.73) for necrosis or severe ischemia. Substantial study heterogeneity was observed for all LR-M features (Cochrane Q test: $P$<0.01; $I^2$≥ 89.2%). Studies with a mean observation size of < 3 cm, those performed on 1.5-T MRI, and those with multiple image readers, were significantly associated with poor agreement for LR-M features.

**Conclusions:** Agreement for peripheral washout, delayed central enhancement, and marked diffusion restriction was limited. LI-RADS should focus on improving the agreement for LR-M features.

**Keywords:** Hepatocellular carcinoma, Radiology, Reproducibility of results, Meta-analysis, Systematic review

## PE-29

### Analysis of Factors Predicting the Real-World Efficacy of Atezolizumab and Bevacizumab in Patients with Advanced Hepatocellular Carcinoma

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**Aims:** Atezolizumab and bevacizumab has shown promising efficacy in clinical trials for advanced hepatocellular carcinoma (HCC). This study aims to validate these findings with com-

prehensive real-world data on their efficacy and safety in advanced HCC patients.

**Methods:** We conducted a retrospective cohort study at a tertiary cancer center in Korea, including 111 patients with advanced HCC treated with atezolizumab and bevacizumab as first-line therapy from May 2022 to June 2023. We assessed overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) according to RECIST v1.1, and safety profile.

**Results:** Of the patients, 38% had macrovascular invasion and 33% presented high risk features, including extensive portal vein tumor thrombosis, bile duct invasion, and significant liver infiltration (over 50%). The median OS was reported at 10.6 months (95% confidence interval 8.9-13.1 months). The ORR and DCR were 27% and 63%, respectively. Albumin-Bilirubin (ALBI) grade and Alpha-fetoprotein (AFP) levels were significant predictors of OS, with AFP also associated with PFS and ORR. Combined radiotherapy positively impacted PFS and ORR. Patients with peritoneal seeding exhibited a favorable response. The safety profile was consistent with that observed in clinical trials.

**Conclusions:** The real-world application of atezolizumab and bevacizumab for advanced HCC has validated its efficacy. The study identified ALBI grade, AFP levels, combined radiotherapy, and the presence of peritoneal seeding as significant prognostic factors affecting clinical outcomes.

**Keywords:** Hepatocellular carcinoma, Liver cancer, Systemic therapy, Immunotherapy

## PE-30

### Clinical Outcomes and Prognostic Factors of MRI-Guided Radiotherapy for Portal Vein Tumor Thrombosis in Hepatocellular Carcinoma Patients: A Single-Institutional Experience

**Myungsoo Kim**, So Jung Lee

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**Aims:** To evaluate the treatment outcome and prognostic factors for survival of the tumor tracking magnetic resonance imaging (MRI)-guided stereotactic body radiation therapy (SBRT) and hypofractionated radiotherapy (HFRT) for portal vein tumor thrombosis (PVTT) in hepatocellular carcinoma (HCC) patients.

**Methods:** We retrospectively reviewed thirty patients with unresectable HCC with PVTT treated with tumor tracking MRI-guided HFRT or SBRT using the ViewRay Linac MRIdian system between June 2019 and February 2023. Tumor thrombosis was located within the main trunk (n=18), first branch of the portal vein (n=10) or second branch of the portal vein (n=2). The HFRT was performed with a total of 50 Gy in 10 fractions (n=7), and SBRT performed in 36-50 Gy with 4-5 fractions (n=23). The median biologic effective dose (BED) with an a/b ratio of 10 was 100 $Gy_{10}$ (range, 64.4–100 $Gy_{10}$).

**Results:** The median follow-up duration was 7.2 months (range, 1.9–28.8 months). The median overall survival (OS) was 10.6 months, with 6-months,1-year, and 2-year OS rates of 72.8%, 38.6%, and 11.6%, respectively. The progression free survival at 6 months and 1-year were 42.5% and 24.3%, respectively. Multivariate analysis showed that ECOG performance status (PS) > 1 ($P$=0.040), HCC size > 5 cm or/and Multiple ($P$=0.031) and Transcatheter arterial chemoembolization (TACE) performed within 1 month of completion of radiotherapy (RT) ($P$=0.029) were significant prognostic factors for OS. There were no cases of grade 3 or higher treatment-related toxicity.

**Conclusions:** Tumor tracking MRI-guided SBRT and HFRT is an effective and safe treatment strategy for HCC patients with PVTT. ECOG PS, HCC size or/and multiplicity, and TACE performed within 1 month of completion of RT were the main factors affecting survival.

**Keywords:** Hepatocellular carcinoma, Portal vein tumor thrombosis, Radiotherapy, MRI-guided radiotherapy

## PE-31

### Outcomes between Liver Resection and Transarterial Chemoembolization in Patients with Multinodular BCLC-A Hepatocellular Carcinoma

**Sung Won Chung**[1], Jiwon Yang[1], Won-Mook Choi[1], Danbi Lee[1], Ju Hyun Shim[1], Kang Mo Kim[1], Young-Suk Lim[1], Han Chu Lee[1], Deok-Bog Moon[2], Dong-Hwan Jung[2], Jonggi Choi[1]

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**Aims:** We aimed to compare the outcomes between liver resection (LR) and transarterial chemoembolization (TACE) in patients with multinodular hepatocellular carcinoma (HCC) within the Milan criteria who are not eligible for liver transplantation.

**Methods:** We retrospectively analyzed consecutive 483 patients with multinodular HCC within Milan criteria receiving either LR or TACE as an initial therapy between 2013 and 2022. Overall survival (OS) in the entire population and recurrence-free survival (RFS) in the patients with LR and TACE with achievement of complete response were analyzed. Propensity score (PS)-matching analysis was also used for a fair comparison of the outcomes between the two groups.

**Results:** Among the 483 included patients, 107 (22.2%) and

376 (77.8%) received LR and TACE, respectively. The median size of the largest tumor was 2.0 cm, and 72.3% of the patients had two lesions of HCC. Median OS and RFS were significantly longer in the LR group than in the TACE group (Ps < 0.01 for both). In multivariate analysis, TACE (adjusted hazard ratio [aHR]:1.81, and aHR: 2.41) and large tumor size (aHR: 1.43, and aHR: 1.44) were significantly associated with worse OS and RFS, respectively. The PS-matched analysis also demonstrated that the LR group had a significantly longer OS and RFS than those of the TACE group (Ps < 0.05 for both).

**Conclusions:** In the present study, LR showed better OS and RFS than TACE in patients with multinodular BCLC stage A of HCC. LR could be considered an effective treatment option for these patients.

**Keywords:** Barcelona clinic liver cancer, Hepatocellular carcinoma, Transarterial chemoembolization, Survival outcomes

## PE-32

### X-Ray Vascular Chemoembolization of the Hepatic Artery for Focal Liver Lesions

Begimai Murzalieva

Kyrgyz State Medical Academy, Kyrgyzstan

**Aims:** To determine the most effective and safe method of X-ray endovascular chemoembolization of the hepatic artery in patients with hepatocellular cancer and metastatic lesions in colorectal cancer.

**Methods:** The study included 76 patients who underwent 245 hepatic artery chemoembolization procedures. Based on the results of magnetic resonance and/or computed tomography, as well as ultrasound, the topical characteristics of lesions in the liver were studied. To clarify the diagnosis, a percutaneous transhepatic fine-needle liver biopsy was performed. All patients were considered unresectable. Chemoembolization was carried out according to the scheme: one procedure every 2 months, at least 3 procedures per course. According to the etiology of liver damage, patients were divided into two groups: the first - patients with metastases of colorectal cancer, the second - patients with hepatocellular cancer. The chemotherapy drug doxorubicin (Teva, Israel) was used. Lipiodol (Guerbet, France) or saturable hepaspheres (Biospher Medical, France) were used as a carrier of chemotherapy drugs. Each patient underwent from 3 to 7 procedures.

**Results:** Post-embolization syndrome, noted in all patients, was treated with medication. There were no deaths during the hospital period. No complications were noted during the treatment process. The mean follow-up time was 15.3±7.6 months (range 6 to 28 months). The dynamics of liver formations were assessed according to RECIST criteria. In the group of patients with colorectal cancer metastases to the liver after the first 3 courses, partial response and stabilization were noted in 79%, progression - in 21%. In 3 patients, a recurrence of the primary tumor was detected during treatment, two refused further chemoembolization of the hepatic artery, and in 4 patients who underwent chemoembolization of the hepatic artery with hepaspheres, occlusion of the hepatic artery occurred, which led to loss of vascular access. In five patients, due to negative dynamics, a transition from hepaspheres to chemoembolization with lipiodol was required; subsequently, stabilization of the process was achieved. In the group of patients with hepatocellular carcinoma, after three courses, partial response and stabilization were observed in 83%, progression - in 17%. In 8 patients (36.4%), tumor necrosis was histologically confirmed after chemoembolization of the hepatic artery; there was no progression of the disease during dynamic observation. One patient underwent liver resection after reducing the size of the lesion, 4 patients continued treatment.

**Conclusions:** Chemoembolization of the hepatic artery for metastases of colorectal cancer to the liver during the 1st half of the year allows achieving 79% stabilization of the process. It is necessary to note the advantage of hepaspheres in the treatment of hepatocellular carcinoma, while chemoembolization with lipiodol is preferable in the treatment of colorectal cancer metastases for long-term preservation of vascular access.

**Keywords:** Chemoembolization of the hepatic artery, Colorectal cancer metastases, Hepatocellular carcinoma, Liver cancer

## PE-33

### Combined Portal and Hepatic Vein Embolization to Improve Liver Hypertrophy before Hepatectomy in Hepatocellular Carcinoma

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**Aims:** This study aimed to evaluate the portal and hepatic vein embolization (PHVE) outcome before hepatectomy in patients with hepatocellular carcinoma (HCC).

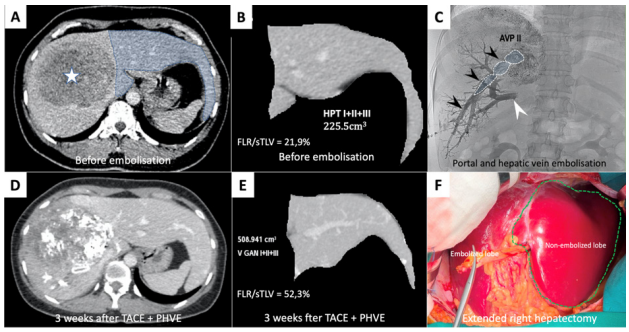
**Methods:** From January 2021 to November 2023, HCC patients with indications for hepatectomy but inadequate initial future liver remnant (FLR) were performed PHVE to increase FLR before surgery.

**Results:** Sixty-two HCC patients with a median age of 52.5 years underwent PHVE. Technical success was obtained in all cases. 1 case presented with grade A liver failure after PHVE (then recovered after 7 days), and another case presented with asymptomatic reflux glue into the biliary tree. The FLR volume before and after PHVE was 397.4 ml and 635.0 ml, respectively ($P$<0.001). The median percentage of FLR to standard liver

volume increased from 32.5% to 48.5% ($P$<0.001), with a hypertrophy rate of 54,8%. 61 patients demonstrated sufficient FLR after PHVE (56 patients at three weeks post-PHVE, three at six weeks, and two at ten weeks), but only 53 patients accepted surgery. Postoperative histopathology showed 30 patients with fibrosis F3-F4 and 23 with mild fibrosis F1-F2 (METAVIR). One patient presented with severe intraoperative bleeding due to damage of the left hepatic vein and developed grade C liver failure, then died on day 32 postoperation.

**Conclusions:** PHVE is a safe, effective, and feasible method of significantly increasing FLR in HCC patients. Randomized controlled clinical trials are needed to evaluate its efficacy and compare it with other methods.

**Keywords:** Portal and hepatic vein embolization, Liver hypertrophy, Hepatocellular Carcinoma, Hepatectomy




## PE-34

### Multidisciplinary Approach for HCC Management in Gastroenterology and Hepatobiliary Center, Bach Mai Hospital

Thuy Pham Thi Ngoc[1], Long Nguyen Cong[1,2,3], Diep Luu Thi Minh[1,2], Ngoc Nguyen Minh[1], Thuy Pham Thi[1]

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**Aims:** To describe the manifestations, treatment therapy, and outcome of HCC patients who are managed by a Multidisciplinary Team.

**Methods:** From 2020 to 2022, a total of 364 HCC patients were managed by MDTs and screened for complications of underlying conditions such as cirrhosis with varices bleeding, acute liver failure,. Patients were followed until the end of the study or died.

**Results:** 364 patients. The result showed a mean age of 61,6 ±10,9(17-89), the main underlying condition was hepatitis B (81%), the main complication was variceal bleeding (6 patients died), BCLC A (54,1%), BCLC B1 (14%), BCLC B2 (13,2%), BCLC B3 (3,6%). The mean follow-up time was 20±14,5 months and the mean survival time was 32,99±31,64 months, ranging from 1 to 234 months, depending on the classification of BCLC stage.

**Conclusions:** HCC in patients with underlying conditions such as cirrhosis, virus hepatitis, has various treatment therapies, and requires consulting multi-specialty. MDTs is one of the comprehensive and effective methods in treating HCC and managing complications, to improve outcomes. This model should be widely developed not only in Vietnam but also in the world.

**Keywords:** Hepatocellular carcinoma, Multidisciplinary therapy, Complication, Barcelona stage

## PE-35

### Analysis of Varix Bleeding after Atezolizumab Plus Bevacizumab for Advanced Hepatocellular Carcinoma Patients

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**Aims:** After the IMbrave150 trial, atezolizumab plus bevacizumab (AteBeva) became the gold standard for unresectable hepatocellular carcinoma (HCC). However, since this trial included well-selected patients without any history of acute variceal bleeding (AVB) nor high-risk esophageal varices, real-world data from advanced HCC patients with any history of AVB or large varices were unknown under this new combination of treatment. We aimed a study to provide real-life data on the therapeutic effect and the safety of AteBeva and to identify risk factors of AVB during treatment in Korea.

**Methods:** We conducted a prospective study including all patients diagnosed with advanced HCC and received AteBeva from seven centers of Catholic Medical Center between September 2020 to December 2022. We followed up on these patients until December 2023 and analyzed therapeutic efficacy and safety, especially AteBeva-related variceal bleeding. Time-to-events were estimated by Kaplan-Meier with the log-rank test, along with Cox models.

**Results:** One hundred fifty-four patients treated with AteBeva were included. In baseline characteristics, the median age was 64.0(56.0-73.0), the male sex was 85.1%, the most common etiology was hepatitis B virus infection (62.2%) and alcohol-related liver disease(26.5%). Child-Pugh class was A or B, and Barcelona Clinic Liver Cancer stage was B or C. The Objective response rate of AteBeva was 38.3% and the Disease control

rate was 70.9%. Median overall survival (OS) 14.000±2.788(95% CI: 8.536-19.464), median progression-free survival 5.000±0.570(3.882-6.118), median time-to progression was 3.000±0.352(2.310-3.690). In multivariable analysis, variables associated with OS were the Eastern Cooperative Oncology Group performance scale, liver cirrhosis, Child-Pugh class, largest intrahepatic tumor size, and treatment duration. The patient underwent all grades of gastrointestinal bleeding events after AteBeva was 40(26.0%), varix bleeding was 23(14.9%), and 18(11.7%) received endoscopic band ligation (EBL). In multivariable analysis, variables associated with varix bleeding after AteBeva were Child-Pugh score and ulceration from prophylactic EBL before AteBeva.

**Conclusions:** In this study, the most common adverse event after AteBeva was all grades of gastrointestinal bleeding events. Risk factors for varix bleeding after AteBeva were Child-Pugh score at baseline and ulceration from prophylactic EBL before AteBeva. Therefore, for patients with prophylactic EBL before AteBeva, ulceration monitoring and management are needed after EBL. Further studies on large scale are needed.

**Keywords:** Hepatocellular carcinoma, Atezolizumab-bevacizumab, Varix bleeding

## PE-36

### The First-Line Utilization of Atezolizumab Combined with Bevacizumab in Unresectable Hepatocellular Carcinoma: A Single-Center Retrospective Study in Vietnam

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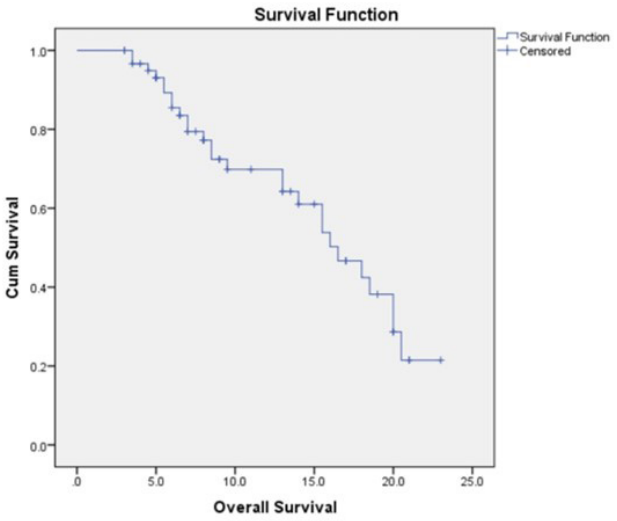
**Aims:** Hepatocellular carcinoma is one of the most common and fatal cancers in Vietnam. Our study aims to evaluate the real-life results of Atezolizumab-Bevacizumab (AT) regimen in the first-line treatment for patients with Barcelona Clinic Liver Cancer (BCLC) B or C who no longer require surgery and local intervention.

**Methods:** 61 patients with hepatocellular carcinoma, BCLC B or C stages, no longer indicated surgery and local intervention, well-preserved liver function (Child-Pugh class A), were enrolled in this study. Patients were treated with AT regimen every 3 weeks: Atezolizumab 1200 mg and Bevacizumab 15 mg/kg. The primary endpoints included: Response rate, progression-free survival, and overall survival. The secondary endpoint was toxicity.

**Results:** From 2020 to 2023, there were 61 patients receiving first-line treatment with AT regimen at National Cancer Hospital. The average age was 53.7 years (ranger 35-78), with 12.9% of patients at stage B and 87.1% of patients at stage C. The proportion of patients infected with hepatitis B, hepatitis C, and co-infected with both was 77.4%, 3.2%, 3.2%, respectively. The overall response was observed in 41.9% of patients, in which, two patients had a complete response (3.3%). The median progression-free survival was 7 months (95% confidence interval [CI], 5.5 to 8.5) and the median overall survival was 16.5 months (95% CI, 12.9 to 20.1). Grade 3 or 4 adverse events occurred in 12 patients (19.7%), including hypertension in 5 patients (8.2%), elevated liver transaminases in 5 patients (8.2%) and thrombocytopenia in 2 patients (3.3%).

**Conclusions:** The AT regimen showed good efficacy as a first-line treatment for advanced hepatocellular carcinoma in Vietnamese patients, with good tolerability.

**Keywords:** Hepatocellular carcinoma, Atezolizumab combined with bevacizumab, First line




## PE-37

### Laparoscopic versus Open Major Hepatectomy for The Management of Hepatocellular Carcinoma in a Vietnamese Tertiary Hospital: A Five-Year Retrospective Comparative Study

Tran Manh Thang

Vin University, Vietnam

**Aims:** This study aimed to compare the results between laparoscopic and open major hepatectomy for managing hepatocellular carcinoma (HCC) in a Vietnamese tertiary hospital over a five-year period.

**Methods:** A retrospective comparative study between two groups of patients with HCC who underwent major liver resection either by laparoscopic or open approach at Departments of Hepatopancreatobiliary Surgery, Military Central Hospital

108, from January 2019 to December 2023.

**Results:** A total of 262 major hepatectomies were consecutively performed to manage HCC. One hundred fifty-nine resections were performed in the open approach group (60.7%), and 103 resections were performed in the laparoscopic surgery group (39.3%). There was a statistical difference favorable to the laparoscopic group regarding postoperative complications, intraoperative blood loss, shortening operating times, and length of hospital stay. Resection rate R0 was similar between both groups. There was no difference regarding mortality rate, overall survival, and recurrence-free survival.

**Conclusions:** Laparoscopic major hepatectomy for HCC provides the same long-term results as the open approach, with favorable for short-term outcomes. Laparoscopic major hepatectomy could be considered an alternative and become the gold standard in selected patients.

**Keywords:** Hepatectomy, Hepatocellular carcinoma

## PE-38

### Hepatocyte Nuclear Factor 1 Alpha Variants as Risk Factor for Hepatocellular Carcinoma Development with and without Diabetes Mellitus

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**Aims:** HNF1A gene variants have been reported to be involved in developing mature onset diabetes mellitus (DM). Many studies reported the role of DM as a risk factor for hepatocellular carcinoma (HCC) development. To date, it has not been reported whether HNF1A gene variants are associated with the risk of DM in cirrhotic patients and their subsequent HCC. Objective: To evaluate the HNF1A (the hepatocyte nuclear factor 1 homeobox A) genetic variants as a cofactor with DM for HCC development in HCV-infected patients.

**Methods:** : This study was conducted on 140 subjects; 30 had HCC without DM, 30 HCC with DM, and 40 patients had DM with no HCV infection or had HCC; in addition, 80 healthy volunteers with matched ages and genders were enrolled in the study as a control group. Liver function tests, hepatitis viral markers, alpha-fetoprotein (AFP), fasting sugar and HBA1c and HNF1A (rs2464196 and rs1169310) using real-time polymerase chain reaction (PCR) were done for all participants.

**Results:** : The frequency of HNF1A rs2464196 (AA) genotype in patient groups (DM, HCC, HCC+DM) was significantly higher compared to the control group ($P$=0.006, $P$=0.018, $P$<0.001respectively). The combined dominant model (AA + GA) of rs 2464196 was significantly higher than the (GG) genotype in patient groups (DM, HCC, HCC+DM) than the control group. In addition, the frequency of the AA genotype is more prevalent in HCC+DM (73%) compared to the group of DM or HCC patients. In contrast, the HNF1A rs 1169310 (TT, TC or CC genotypes) showed no significant difference among the four studied groups and their T or C allele distributions.

**Conclusions:** This finding suggested that the HNF1A rs2464196 (AA) genotype could be associated with DM and may raise the possibility of HCC development among HCV-infected patients who harbour this genotype more than (GG). On the contrary, the HNF1A rs 1169310 polymorphism was of no significance as a risk factor in the current study. Large scale studies are recommended on other variants of HNF1A to clarify the role of this gene in HCC development.

**Keywords:**, Hepatocyte; Nuclear Factor 1 homeobox A; Hepatocellular carcinoma

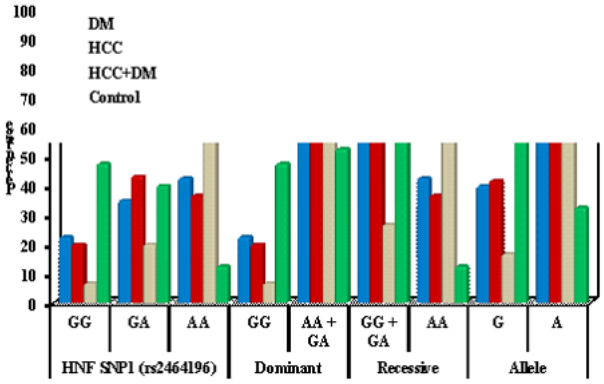


**Figure 1.** Comparison between the studied groups according to HNF SNP1 (rs2464196) genotypes and allele freq uencies.

## PE-39

### Evaluation of Circular RNA SMARCA5 as a Novel Biomarker for Hepatocellular Carcinoma

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**Aims:** Hepatocellular carcinoma (HCC) is the fourth most prevalent type of cancer in Egypt and the sixth globally. Most patients with HCC are typically diagnosed during the advanced

stages of the disease due to the absence of biomarkers for early detection. Consequently, these patients miss the optimal timeframe for receiving therapy. Objective: we aimed to assess the circular RNA SMARCA5 level and SMARCA5 mRNA gene expression as a potential biomarker for early detection of HCC.

**Methods:** The present study utilized a case-control design comprising 159 participants. Participants were selected from both inpatient and outpatient hepatology and gastroenterology clinics at the National Liver Institute Hospital, Menoufia University. They were evenly distributed among three groups: Group I: 53 control subjects, Group II: 53 HCV cirrhotic patients, and Group III: 53 HCC patients. Tumor staging was done using BCLC staging system. Each patient underwent a thorough clinical examination, radiological examination, complete history taking, and serum Alpha-fetoprotein (AFP) assessment and detection of circular RNASMARCA5 and SMARCA5mRNA gene sutilizing quantitative real-time polymerase chain reaction.

**Results:** Statistically substantial differences were observed in the examined groups in terms of AFP, SMARCA5, and CircSMARCA5 (*P*-value = 0.001, 0.001 & 0.001). CircSMARCA5 and SMARCA5mRNA were markedly down regulated in the HCC group compared to HCV cirrhotic patients and controls. ROC analysis for early HCC diagnosis demonstrated that the CircSMARCA5 area under the curve (AUC) at cut-off point 4.55 yielded a specificity of 83.8% and sensitivity of 91.7%. The AUC for AFP at a cut-off point of 515 ng/ml yielded a specificity of 89.2% and a sensitivity of 91.3%.

**Conclusions:** CircSMARCA5 has the potential to be a more sensitive predictor of HCC disease compared to AFP.

**Keywords:** Alpha-fetoprotein, CircSMARCA5, Hepatocellular Carcinoma

## PE-40

### Outcomes in Liver Recipients with Hepatocellular Carcinoma and Combined Portal Vein Tumor Thrombosis, Multicenter Study

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**Aims:** Liver transplant (LT) recipients facing an increased risk of hepatocellular carcinoma (HCC) recurrence due to concurrent portal vein tumor thrombosis (PVTT) often undergo liver transplantation, despite general discouragement. This study aims to investigate and offer insights into the practice of liver transplantation in such cases, given the absence of a standardized consensus.

**Methods:** A retrospective analysis of 371 LT recipients diagnosed with HCC and PVTT across six major Korean hospitals evaluated patient demographics, pre-transplant characteristics, and post-transplant outcomes. Prognostic factors, including tumor stage, vascular invasion, PVTT level, tumor marker, and treatment modalities, were examined for their impact on overall survival (OS) and disease-free survival (DFS).

**Results:** OS and DFS rates demonstrated variations based on the extent of PVTT. Independent risk factors for HCC recurrence included microvascular invasion (HR 2.536, 95% CI 1.637-3.929, $P<0.001$), adjacent organ or hepatic vein invasion (HR 2.220, 95% CI 1.402-3.515, $P<0.001$), sum of HCC size ≥ 9 cm (HR 2.094, 95% CI 1.470-2.984, $P<0.001$), and disease progression in image response (HR 1.864, 95% CI 1.186-2.932, $P=0.007$). OS and DFS rates varied significantly based on the number of risk factors (both $P<0.001$). Even in PVTT patients with zero risk factors, the 10-year OS and DFS rates after liver transplantation were 69.9% and 62.1%, respectively.

**Conclusions:** This study identified risk factors for LT recipients with HCC and PVTT, emphasizing the prognostic significance of preoperative factors like HCC size, adjacent organ and hepatic vein invasion, disease progression in image response, and PVTT level.

**Keywords:** HCC, Liver transplantation, Portal vein tumor thrombosis

## PE-41

### Clinical and Radiologic Predictors of Response to Atezolizumab-Bevacizumab in Advanced Hepatocellular Carcinoma

Se Jin Choi[1], Sung Won Chung[2], Jonggi Choi[2], Kang Mo Kim[2], Hyung-Don Kim[3], Changhoon Yoo[3], Baek-Yeol Ryoo[3], Seung Soo Lee[1], Won-Mook Choi[2], Sang Hyun Choi[1]

[1]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [2]Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [3]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

**Aims:** This study aimed to identify clinical and radiologic characteristics that could predict response to atezolizumab-bevacizumab combination therapy in patients with liver-dominant advanced hepatocelluar carcinoma (HCC).

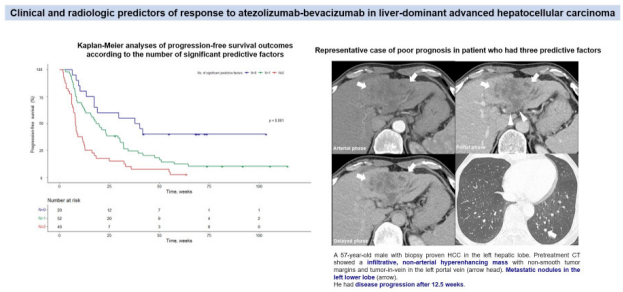
**Methods:** This single-center retrospective study included 108 patients with liver-dominant advanced HCC who were treated with atezolizumab-bevacizumab. Predictive factors associated with progressive disease (PD) at the best response based on Response Evaluation Criteria in Solid Tumors, Version 1.1) were

evaluated using logistic regression analysis. Progression-free survival (PFS) was estimated by the Kaplan-Meier method and compared with the log-rank test.

**Results:** Of 108 patients with a median PFS of 15 weeks, 40 (37.0%) had PD during treatment. Factors associated with PD included the presence of extrahepatic metastases (adjusted odds ratio [aOR], 4.13; 95% confidence interval [CI], 1.19–14.35; *P*=0.03), the infiltrative appearance of the tumor (aOR, 3.07; 95% CI, 1.05–8.93; *P*=0.04), and the absence of arterial phase hyperenhancement (APHE) (aOR, 6.34; 95% CI, 2.18–18.47; *P*<0.001). Patients with two or more of these factors had a PD of 66.7% and a median PFS of 8 weeks, indicating a significantly worse outcome compared to the patients with one or fewer of these factors.

**Conclusions:** In patients with liver-dominant advanced HCC treated with atezolizumab-bevacizumab treatment, the absence of APHE, infiltrative appearance of the tumor, and presence of extrahepatic metastases were associated with poor response and survival. Evaluation of early response may be necessary in patients with these factors.

**Keywords:** Hepatocellular carcinoma, Liver, Liver imaging, Chemotherapy




## PE-42

### Huge Ruptured Hepatocellular Carcinoma in Case of Dubin-Johnson Syndrome

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**Aims:** Dubin-Johnson syndrome (DJS), a rare autosomal recessive liver disorder, is characterized by hyperbilirubinemia. We would like to report a case in which a left hemihepatectomy was performed on a patient with DJS presenting with a massive ruptured hepatocellular carcinoma (HCC)

**Methods:** A 54-year-old male who presented to the emergency room with sudden upper abdominal pain. Vital signs were stable and laboratory analysis revealed with a white blood cell count of 10,100/L, hemoglobin of 12.7 g/dL, platelets of 178,000/L, total bilirubin (TB) of 2.45 mg/dL, direct bilirubin (DB) of 1.26 mg/dL, AST of 42 U/L, ALT of 20 U/L, and PT of 1.24 INR. Imaging studies demonstrated a 13cm ruptured mass in the left hemiliver, prompting emergency angiography and subsequent embolization with gelfoam. Post-procedure, the patient exhibited fluctuating bilirubin levels (TB:2.5~10.7), eventually stabilizing at TB 2.5~3.5. Follow-up MRI revealed a necrotic, but partially viable tumor in the left hemiliver without cirrhosis, biliary problem, or metastatic findings.

**Results:** Considering the elevated TB levels observed in past health screenings, a suspicion of DJS, guiding the decision to proceed with left hemihepatectomy. Operative findings included a black liver color and omental adhesions around the ruptured tumor area. Postoperatively, the patient's peak TB levels was 5.5 but subsequently decreased. Pathological examination confirmed an 11x10cm HCC and DJS findings in the non-tumor liver area. The patient was discharged on the 12th hospital day without complications.

**Conclusions:** This case emphasizes the importance of considering DJS in cases of conjugated hyperbilirubinemia and the successful performance of hepatectomy for ruptured HCC.

**Keywords:** Dubin-johnson syndrome, The cahepatocellular carcinoma, hyperbilirubinemia

## PE-43

### Higher Objective Responses by Hepatic Arterial Infusion Chemotherapy Following Atezolizumab and Bevacizumab Failure than as the Initial Therapy in Hepatocellular Carcinoma

Ji Hoon Kim[1], Hee-Chul Nam[1], Chang-Wook Kim[1], Ji Won Han[2], Jeong Won Jang[2], Jong Young Choi[2], Seung Kew Yoon[2], Hyun Yang[3], Si Hyun Bae[3], Pil Soo Sung[2]

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**Aims:** Atezolizumab/bevacizumab (atezo-bev) is the first-line chemotherapy for patients with unresectable hepatocellular carcinoma (HCC). However, hepatic artery infusion chemotherapy (HAIC) can be used as an alternative. Our aim was to compare the prognosis of HAIC treatment between newly diagnosed patients and patients treated after failure of atezo-bev.

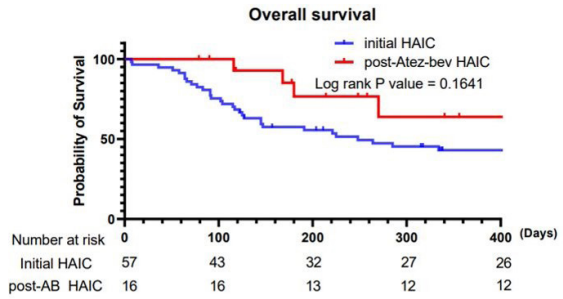
**Methods:** We retrospectively assessed 73 patients with HCC treated with HAIC between January 2022 and September 2023. Fifty-seven patients were treated with HAIC at initial diagnosis, while 16 were treated with HAIC after firstline atezo-bev combination chemotherapy. We evaluated tumor responses such as overall survival (OS), progression-free survival (PFS), and ob-

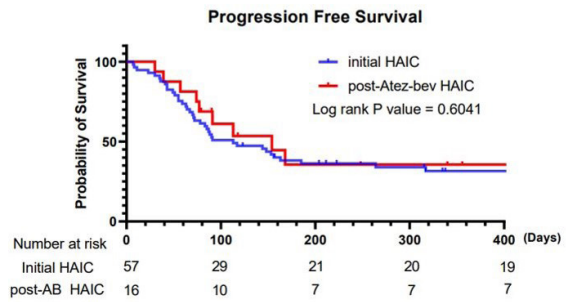
jective response rate (ORR).

**Results:** No significant difference was observed in either OS or PFS between patients with HCC treated with HAIC at the initial diagnosis and those treated after atezo-bev treatment failure. However, the ORR of the initial HAIC group was 19.6% and that of the HAIC group after atezo-bev therapy failure was 43.6%, which was a statistically significantly difference.

**Conclusions:** Although no significant difference was observed for OS and PFS, the ORR of patients in the HAIC group after the failure of atezo-bev therapy was superior to that of newly diagnosed patients. HAIC may prolong survival in patients with HCC after atezo-bev treatment failure.

**Keywords:** HCC, Atezolizumab-bevacizumab, HAIC, Prognosis




## PE-44

### Impact of Skeletal Muscle Mass on Long-Term Outcomes in Hepatocellular Carcinoma Treated with Hepatic Artery Infusion Chemotherapy

Ji Hoon Kim[1], Hee-Chul Nam[1], Chang-Wook Kim[1], Jae-Sung Yoo[2], Ji Won Han[2], Jeong Won Jang[2], Jong Young Choi[2], Seung Kew Yoon[2], Pil Soo Sung[2*]

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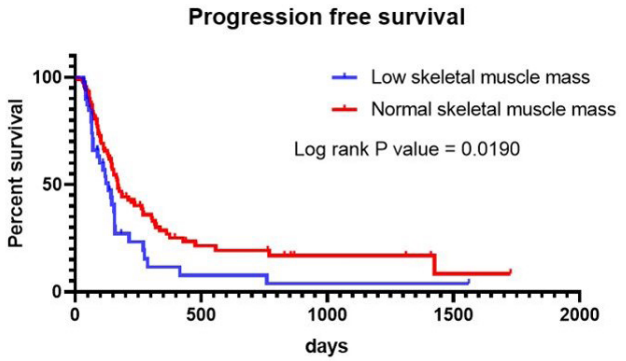
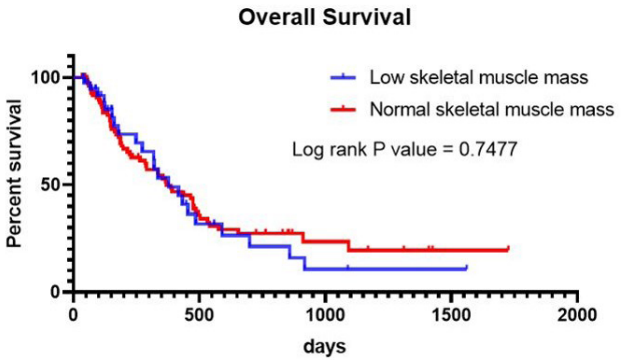
**Aims:** Hepatic artery infusion chemotherapy (HAIC) is a regional chemotherapy used to treat hepatocellular carcinoma (HCC) in patients whom atezolizumab plus bevacizumab combination chemotherapy (AB CTx), currently the first-line chemotherapy, is contraindicated or the patient is infeasible for AB CTx . We aimed to explore the correlation between the skeletal muscle mass and long-term outcomes of HCC patients being treated with HAIC.

**Methods:** We retrospectively enrolled 143 patients with HCC who had undergone HAIC from January 2018 to January 2024. The tumor response, progression-free survival(PFS), disease control rate (DCR) and overall survival (OS) were evaluated. The muscle mass of the patients was measured via open-source software (BMI measurement tools, version 1.0). Low skeletal muscle mass (LSMM) was defined as the following: for men, the SMI cut-offs were < 43 $cm^2/m^2$ for underweight or normal-weight patients (BMI < 25 $kg/m^2$) and < 53 $cm^2/m^2$ for overweight (BMI ≥ 25 $kg/m^2$) or obese patients (BMI ≥ 30 $kg/m^2$). For women, the cut-off value was < 41 $cm^2/m^2$, regardless of weight.

**Results:** 143 HCC patients treated with HAIC were enrolled. Median age was 63 and 124 patients were of male sex. 102 patients had PVTT. 40 patients were classified as LSMM (low skeletal muscle mass). The median overall survival was 186 days and median progression free survival was 122 days. When OS and PFs were compared, patients with LSMM had a significantly worse prognosis than those with normal skeletal muscle mass. However, OS showed no significant difference in prognosis.




**Conclusions:** In our retrospective single-center study, we sought to evaluate the difference in prognosis in HCC patients

treated with HAIC with LSMM and no LSMM. There seemed to be no significant difference in OS but there was a significant difference in PFS; patients with LSMM had a significantly worse prognosis compared to patients with no LSMM.

**Keywords:** HCC, Prognosis, HAIC, Skeletal muscle mass

## PE-45

### Reduced Occurrence of Hepatocellular Carcinoma in Hepatitis C Patients Following Direct-Acting Antiviral Therapy

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**Aims:** Direct-acting antivirals (DAAs) have transformed the management of chronic HCV-related disease, achieving high rates of sustained virological response (SVR), even in advanced cirrhosis, with minimal contraindications and low rates of adverse events. This prospective study aimed to evaluate the incidence and risk factors of HCC following DAA therapy in patients with HCV-related advanced fibrosis (F3) and cirrhosis (F4).

**Methods:** The incidence of HCC was assessed in 973 patients with HCV-related F3 and F4 treated with DAAs, prospectively followed for up to 48 months in a single referral center and compared to historical controls. Additionally, risk factors associated with incident HCC were determined.

**Results:** The crude incidence rate was 2.8/100 person-years, significantly lower than a similar historical cohort (5.9/100 person-years). The risk of developing HCC was higher in patients with cirrhosis (F4 vs F3, AHR 3.79) and treatment failure (vs achieving SVR, AHR 3.47). Decompensated cirrhosis, platelet count < 100× 103/mL, and elevated AFP were identified as independent risk factors for developing HCC.

**Conclusions:** The incidence of HCC was markedly lower in patients with HCV-related advanced fibrosis and cirrhosis treated with DAAs compared to untreated historical controls.

**Keywords:** HCV- Related disease, Direct acting antiviral therapy, Hepatocellular carcinoma

## PE-46

### Frailty and Sarcopenia as a Predictor of Mortality in Hepatocellular Carcinoma Patients with Transarterial Chemoembolization

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**Aims:** The existing prognostic indicators for the well-being of patients with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE), like the Child-Pugh-Turcotte (CTP) class or Model for End-Stage Liver Disease (MELD), currently offer an insufficient assessment of an individual's likelihood of death. In this study, we investigate whether incorporating frailty or sarcopenia into standard prognostic indicators enhances the predictive accuracy for the prognosis of hepatocellular carcinoma (HCC) patients undergoing transarterial chemoembolization (TACE).

**Methods:** A systematic review search through Pubmed/MEDLINE, Scopus, Cochrane Library, and EBSCO was conducted to find this topic. The studies were selected and critically appraised. Data were then analyzed and summarized descriptively.

**Results:** A study by Rebi et al (2023) with retrospective analysis concluded that increasing frailty, as assessed by mFI-5, independently forecasts complications within 30 days and a reduced TFS after chemoembolization ($P$=0.01). A retrospective study by Vakil et al (2020) showed that increasing frailty is an independent predictor of SAEs ($P$<0.01) but not 1-year mortality following TACE. Another study from Chien et al (2022) showed that sarcopenia also significantly impaired OS in HCC patients receiving TACE (18 vs. 25 months, $P$=0.011).

**Conclusions:** A straightforward evaluation of frailty or sarcopenia indicators upon admission significantly influences predicting the prognosis of individuals with hepatocellular carcinoma (HCC) who later undergo transarterial chemoembolization (TACE) therapy.

**Keywords:** Frailty, Transarterial chemoembolization, Hepatocellular carcinoma

## PE-47

### Lipid Metabolic Reprogramming in Tumor Microenvironment : Clostridium Cluster Cocktail Attenuate High-Fat Diet Induced Hepatocellular Carcinoma

Seol-Hee Song, Jeong-Su Kim, Jeong-Ha Park, Min-Ju Kim, Jung A Eom, Dong-Hoon Yang, Satya Priya Sharma, Hyunjoon Park, Jin-Ju Jeong, Sung-Min Won, Dong Joon Kim, Ki Tae Suk

Institute for Liver and Digestive Disease, Hallym University College of Medicine, Chuncheon, Republic of Korea

**Aims:** Metabolic reprogramming for adaptation to the tumor microenvironment (TME) has been recognized as a hallmark of cancer. In recent studies, lipid metabolism reprogramming has been shown to play an important role in TME. TME of progressed hepatiocellular carcinoma (HCC) revealed inflammation-based lipid-rich background and deteriorated lipid metabolism. *Clostridium* cluster is known for reducing liver in-

flammation. This study focused on the regulatory mechanism of *Clostridium* cluster in lipid pathway of HCC TME.

**Methods:** For the hypothesis establishment, we collected fecal samples from healthy control (n=66), non-alcoholic fatty liver (n=67), hepatitis (n=100), and cirrhosis and cancer patients (n=21). We compared microbial diversity among human groups. In the HCC-animal study, C57BL/6J male mice received 20 mg/kg (i.p) of diethylnitrosamine (DEN) at 14 days of age. To accelerate the development of HCC, mice were fed a 60% high-fat diet and drinking water with 300 mg/L thioacetamide (TAA). *Clostridium* cluster cocktail was orally administered at a concentration of 109 CFU/day from 7 weeks to 32 weeks of age. We compared liver weight, body weight, liver enzymes, cholesterol, and triglyceride. We conducted the histopathological examination, fecal analysis, and markers for inflammation, lipogenesis, cell growth factor, hypoxia pathway and $\beta$-oxidation in the liver.

**Results:** In the human stool analysis, genus *Clostridium* abundance was increased according to the progression of liver disease. In the analysis of hypoxia relating markers, expression of HIF1a, FABP and IDH were significantly increased in HCC patients. In HCC patients, HCC development was increased in *Clostridium* cluster group. *Clostridium* cluster group showed significant improvement in liver enzymes (AST 99.6± 31.9, $P$<0.01; ALT 67.3±13.3, $P$<0.01), and compared with the untreated group (AST 148.1±52.6; ALT 223.6±25.8; $P$<0.01). Moreover, *Clostridium* cluster cocktail downregulated the expression of hepatic steatosis and inflammation biomarkers (TNF-$\alpha$ and TGF-ß; $P$<0.01) by regulating the fatty acid uptake (LIPIN, AGPAT2, IDH1; $P$<0.01), cell growth factor (KI67, CCNB2, CXCL10, and CXCL2; $P$<0.01) and oxidation (CPT1A. $P$<0.01) marker. *Clostridium* cluster cocktail ameliorates HCC development, dysbiosis, and gut-microbiota derived metabolites through modulation of gut-liver axis resulting in reduced hepatic inflammation, steatosis, and fatty acid synthesis.

**Conclusions:** This study revealed that hypoxia pathway plays an important role in the development of HCC. Oral administration of *Clostridium* cluster cocktail inhibited hypoxia pathway in murine liver disease model. The result of this study will contribute to the development of novel prevention method of HCC.

**Keywords:** HCC, Gut-liver axis, Probiotics, *Clostridium* cluster, Hypoxia pathway, Lipid metabolism

## PE-48

### A Margin Morphology-Based Gross Classification System for Stratifying Hepatocellular Carcinoma

Zhong-Qi Fan[1], Xiao-Dong Sun[1], Ming-Yue Li[1], Mei-Shan Jin[2], Lei Zhang[3], Nan-Ya Wang[4], Tian Yang[5], Guo-Yue Lv[1]

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**Aims:** The selection of interventions for patients with solitary hepatocellular carcinoma (HCC) continues to pose challenges. While gross classification has been suggested as a potential prognostic predictor, its widespread adoption has been limited by insufficient studies involving an adequate number of patients and the absence of established mechanisms. Therefore, we aim to examine the prognostic implications of gross subtypes in HCC patients and evaluate their associated molecular landscapes.

**Methods:** A prospective cohort study consisting of 400 patients who underwent hepatectomy for solitary HCC was conducted, and the gross classification was assessed. Additionally, multiomics analyses were carried out on tumors and non-tumor tissues obtained from 49 patients to explore the underlying mechanisms associated with gross classification. To account for confounding factors, IPTW was employed.

**Results:** Overall 3-year survival rates varied significantly among the four gross subtypes (Type I: 91%, Type II: 80%, Type III: 74.6%, Type IV: 38.8%). Specifically, Type IV was identified as an independent predictor of poor prognosis in both the entire cohort and the IPTW cohort. The four gross subtypes demonstrated distinct transcriptional modules, with Type IV tumors exhibiting increased angiogenesis and immune scores, decreased metabolic pathways, and the highest frequency of TP53 mutations. Patients with Type IV HCC may benefit from adjuvant intra-arterial therapy compared to the other three subtypes. A modified trichotomous margin morphological gross classification system was established.

**Conclusions:** Different gross subtypes of HCC exhibited distinct prognosis and molecular characteristics, highlighting the potential of gross classification in facilitating the development of precise individualized treatment strategies for HCC.

**Keywords :** Gross classification, Hepatocellular carcinoma, Multiomics analysis

# Liver Transplantation

## PE-01

### Anti-Thymocyte Globulin (ATG) Use after Steroid Resistant Acute Rejection (SRAR) in Liver Transplantation: 1st Experience in Asan Medical Center (AMC)

Eun-Kyoung Jwa

Surgery, Asan Medical Center, Democratic People'S Republic of Korea

**Aims:** High MELD increased, we can't use enough immunosuppressant due to sepsis fear. When we meet SRAR, we usually plan to re-transplantation. I reported the first case of ATG use after SRAR in AMC

**Methods:** The medical records were reviewed.

**Results:** 47 year old men did Desead donor Liver Transplantation due to alcoholic liver cirrhosis. At that time His mentality was drowsy and MELD score was 39. Intra-operative steroid injection was 3mg/kg. He discharge POD #67. When He discharged, his FK TDM was 3.6 ng/ml. when he come to the center for regular check His total bilirubin elevated, we did liver biopsy at POD#134 The pathology reported Acute cellular rejection (ACR) (RAI=7). We high dose steroid therapy with FK level above > 10 ng/ml. His liver function not recovery and we did rebiopsy on POD#144 The pathology reported also ACR (RAI=7). His general condition was good, so we decided try to ATG therapy. Before injected the ATG, We check chest CT for rule out pneumonia, we planned to ATG 1.5mg/kg for 12hr. we check CD 3 count before injection and 3rd day and 6th day. CD 3 count was below 25, we stop injection after 7th ATG injection. After injection He feel chilling at first day after then He did well. Finish injection 7days. Although inject ATG, the patient's liver function was aggravated we plan to re-transplantation.

**Conclusions:** Unfortunately my 1st experience did not success. But He did not suffer from thymoglobulin side effect. We know the ATG was tolerable used in LT patient.

**Keywords:** Asan medical center, Steroid resistant acute rejection, Liver transplantation

## PE-02

### Child's Condition after Liver Transplantation Surgery

Derizal Derizal[1], Roland Helmizar[2], Siska Azizah[3]

[1]Tourism, IP of Trisakti, Indonesia, [2]Health, Baiturrahmah University, Indonesia, [3] Health, Baiturrahmah University, Indonesia

**Aims:** Liver transplantation is the final therapy performed if liver failure occurs. This study aims to identify the condition of pediatric patients with liver failure after liver transplantation in Indonesia.

**Methods:** The method used is a literature review of RSUD reports and scientific journals. The results show that there are still few open reports regarding pediatric liver transplantation in Indonesia.

**Results:** The result show that the research at RSUPN dr. Cipto Mangunkusumo, patients suffering from 2011-2017 found that 36 pediatric patients with liver failure (33.3%) were on the liver transplant waiting list, some of whom had poor nutritional conditions, high PELD scores, high Laennec scores, and mortality before liver transplantation 42. 6%. Of the 34 liver transplant patients, the most common indication was biliary atresia. The causes of death of patients on the transplant waiting list vary with the most common causes being poor nutrition and infection. Sucinta's research in 2018-2020 at the same RSUP showed that Graft-to-recipient weight ratio (GRWR) was inversely correlated with the length of post-hospitalization of children. transplant. Silva's research revealed that the factors that influence patient survival after liver transplantation are a pediatric end-stage liver disease (PELD) score of 20 and an operation duration of more than 16 hours which determines the child's survival.

**Conclusions:** So, the child's condition before surgery had poor nutrition, a poor PELD score and was specified as biliary atresia. The child's survival depends on the PELD results and the duration of the operation and length of hospital stay.

**Keywords:** Liver, Transplantation, Child

## PE-03

### Review of the Long-Term Quality of Life after Liver Transplantation

Mega Dwi Septivani

Business Administration, Politeknik Negeri Padang, Indonesia

**Aims:** The sole option for therapy for terminal liver disease is liver transplantation. Precise long-term quality of life (QOL) data are necessary when discussing better surgical outcomes and higher rates of survival following transplantation. In Indonesia liver transplantation beginning in May 2010, both adult and pediatric patients at Cipto Mangunkusumo Hospital received liver transplants through the establishment of the FKUI-RSCM Liver Transplant Team. This study reviews the long-term QOL after primary liver transplantation in adult patients surviving few years after surgery.

**Methods:** A comprehensive review of the database was carried out with relevant keywords related to quality of life and liver transplantation. The scope of the search was restricted to articles published in the years 2013 through 2023. Using VOSviewer software, co-authorship and co-occurence analyses were conducted.

**Results:** Long-term benefits in functional domains include mobility and self-care independence. The employment rates for different liver disease aetiologies vary greatly and recover in the short term, but deteriorate beyond five years. When compared to the general population, overall QOL improves to a similar degree, but physical function doesn't improve. Liver transplant recipients who engage in post-operative physical exercise have better quality of life outcomes than individuals in the general community. Improvements in QOL were comparable to those obtained from kidney, lung, and heart transplants.

**Conclusions:** In compared to preoperative status, liver transplantation gives particular long-term quality of life and functional improvements. With the use of these data, a more thorough assessment of the general health and surgical success of liver transplant recipients may be made.

**Keywords:** Liver transplantation, Quality of life, Indonesia

## PE-04

### The Impact of Age on Liver Regeneration after Living Donor Right Hemihepatectomy in Elderly Donors

Na Reum Kim, Gi Hong Choi, Dai Hoon Han

Department of Surgery, Department of Hepato-Biliary and Pancreatic Surgery, Severance Hospital, Republic of Korea

**Aims:** The expanding donor pool includes marginal donors with steatosis, small-for-size grafts, and elderly donors. This study aimed to investigate liver volumetric regeneration after living donor right hepatectomy(LDRH) in elderly and younger donors

**Methods:** From March 2012 to December 2022, 38 elderly(≥ 55years) and 291 younger donors (< 30 years) underwent LDRH. Donors without preoperative liver fibroscan or postoperative follow-up CT after three months were excluded. Propensity score matching resulted in a final cohort of 55 younger and 30 elderly donors. Remnant liver volume was assessed via CT within one-year after surgery. Clinical characteristics and liver volumetric regeneration was compared between two groups. Binary logistic regression was used to analyze risk factors for poor liver regeneration.

**Results:** The mean age was 58.0 and 24.0 years for elderly and younger donor, respectively. Preoperative factors were similar. Rapid liver regeneration occurred within the first months (median 465.9mL, 77.8% of initial total liver volume(iTLV)), but elderly donors showed significantly lower liver regeneration rates than younger age donors throughout all time points (around 1 month: 83.5 vs. 75.5%, $P$=0.001; 3 months: 89.9 vs. 79.2%, $P$<0.001; 6 months: 94.7 vs.86.2%, $P$=0.001). Multivariate logistic regression analysis identified old age and low preoperative phosphate level (< 3.5 mg/dL) as risk factors for liver regeneration below 80% of iTLV.

**Conclusions:** After LDRH, liver regeneration within one year reaches over 95% of the original volume in young donors but is less, at approximately 86% of the original volume, in elderly donors. Therefore, more conservative criteria for the remnant liver volume need in elderly donors compared to younger donors.

**Keywords:** Liver regeneration, Elderly, Donor hepatectomy

## PE-05

### Mesenchymal Stem Cell Therapy for Enhancing Liver Regeneration Post-Hepatectomy: A Review

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**Aims:** The regenerative capacity of the liver plays a crucial role in recovering from injuries, especially after surgical procedures such as partial hepatectomy. However, enhancing post-hepatectomy liver regeneration remains challenging. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic option for various liver diseases due to their ability to migrate to injured tissues, undergo hepatogenic differentiation, and regulate inflammatory responses. Several studies have highlighted the potential of MSC-based therapy in promoting liver regeneration and repairing liver injuries. This review aims to explore the role of MSCs in liver regeneration after partial hepatectomy, examining their mechanisms of action and therapeutic efficacy.

**Methods:** A comprehensive literature search was conducted across multiple databases, including PubMed, ProQuest, clinicaltrial.gov, Science Direct, and the Cochrane. Studies investigating the effects of MSC transplantation on liver regeneration after partial hepatectomy were included. Animal models or clinical trials were considered.

**Results:** Several studies have demonstrated the beneficial effects of MSC transplantation on liver regeneration after partial hepatectomy. These effects include enhanced hepatocyte proliferation, improved liver synthesis function, modulation of inflammatory responses, and promotion of glycogen synthesis. Mechanistically, MSCs exert their regenerative effects through various pathways, including the AKT/glycogen synthase kinase-3$\beta$ (GSK-3$\beta$)/$\beta$-catenin pathway, modulation of inflammatory cytokines such as IL-6 and IL-10, TNF-$\alpha$, and activation of signaling pathways involved in cell proliferation like STAT3 and Hippo-YAP. Besides IL-10 modulation, MSCs also play a role in metabolic regulation such as increased AKT activity and survivin secretion. Furthermore, MSCs have been shown to reduce ischemia-reperfusion injury and acute inflammation, further supporting their role in liver regeneration after hepatectomy.

**Conclusions:** MSC transplantation offers promise for enhancing liver regeneration post-hepatectomy by regulating inflammation, promoting hepatocyte proliferation, and activating regeneration pathways. Further research is needed to optimize dosage, timing, and delivery methods, aiming to translate these findings into clinical practice for liver disease and post-hepatectomy liver failure treatment.

**Keywords:** Liver regeneration, Mesenchymal stem cell, Post-hepatectomy

## PE-06

### Comparative Analysis of Immune Cells and Gut Microbiome in Patients Exhibiting Tolerance and Rejection Following Liver Transplantation: A Preliminary Study

Soon Kyu Lee[1], Jong Young Choi[1], Ho Joong Choi[2], Dong Jin Joo[3], Hye Won Lee[4], Young Rok Choi[5], Byungjin Hwang[6], Kwang-Woong Lee[5*]

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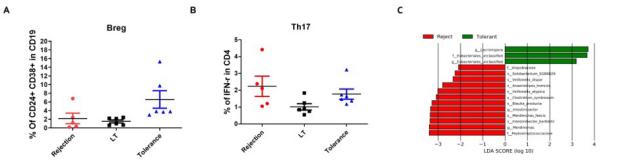
**Aims:** Liver transplantation (LT) patients are at risk of rejection during post-operative follow-up, while some achieve a state of tolerance, maintaining stability without immunosuppression (IS). This study aims to investigate the differential profiles of immune cells and gut microbiomes between patients exhibiting tolerance and those experiencing rejection post-LT.

**Methods:** In this prospective study, 17 liver transplantation (LT) patients were enrolled, categorized into three groups: five with rejection, six exhibiting tolerance, and six stable on immunosuppression (IS). Blood samples were collected from rejection patients at the time of diagnosis, prior to steroid treatment. We compared the proportions of various immune cells, including Tregs, Bregs, Th1, and Th17 cells, across these groups. Additionally, fecal microbiome analyses were performed and compared between the rejection and tolerant patients.

**Results:** Among the six patients with rejection, median levels of aspartate transaminase (AST) and alanine transaminase (ALT) were 158 and 160 mg/dL, respectively. In immune cell comparisons, patients exhibiting tolerance showed a higher proportion of Breg and Th1 cells compared to those with rejection (Figure A). Conversely, the proportion of Th17 cells was higher in rejection patients (Figure B). Regarding gut microbiome, rejection patients exhibited lower $\alpha$-diversity than tolerant patients. Notably, distinct microbial differences were observed between the two groups, with Lacrimispora being the most notably increased bacterial genus in the tolerant patients (Figure C).

**Conclusions:** Our preliminary study suggested significant immunological differences between tolerant and rejection patients, notably in Breg and Th17 cell populations. Additionally, we observed marked variations in gut microbial diversity and composition between these groups.

**Keywords:** Liver transplantation, Regulatory B cells, T helper 17 cells, Gut microbiome




## PE-07

### Effects of Graft Anatomy on Outcomes of Living Donor Liver Transplantation using Right Liver: Donor Safety and Long-Term Recipient Results

Sang-Hoon Kim, Gil-Chun Park, Sung-Gyu Lee, Shin Hwang,Chul-Soo Ahn, Ki-Hun Kim Deok-Bog Moon, Tae-Yong Ha, Gi-Won Song, Dong-Hwan Jung, Young-In Yoon, Woo-Hyoung Kang, Eun Kyung Jwa

Division of Liver Transplantation and Hepatobiliary Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

**Aims:** The anatomical characteristics of liver grafts in living donor liver transplantation (LDLT) and their impact on donor and recipient outcomes are not well understood. This study aimed to investigate the influence of graft anatomy on donor safety and long-term recipient outcomes in LDLT using the right liver.

**Methods:** This retrospective study included 3480 living donors undergoing living donor right hepatectomy (LDRH) from November 2013 to August 2023 at Asan Medical Center in Seoul. Donor complications were assessed based on Clavien-Dindo classification and significant factors associated with major complications and biliary complications were identified by logistic regression analyses considering anatomical factors of right liver graft. Recipient overall survival (OS) and graft survivals (GS) were analysed according to graft anatomical factors.

**Results:** The 30-day complication rates for donors undergoing LDRH were as follows: 3.3% for overall complications, 2.0% for major complications, and 0.9% for biliary complications. Multivariate analyses identified multiple portal veins ($P$=0.011, odds ratio [OR] 2.275, 95 % confidence interval [CI]1.204 – 4.300) as a significant risk factor for major complications. For biliary complications, multiple portal veins ($P$=0.002, OR 3.578, 95 % CI 1.599-8.005) and preoperative moderate steatosis ($P$=0.001, OR 4.953, 95 % CI 1.870-13.119) were significant risk factors. Recipient survival analyses showed that graft with multiple inferior hepatic veins related with worse OS ($P$<0.001) and GS ($P$<0.001), whereas recipients with separated two bile ducts undergoing ductoplasty to achieve a single biliary anastomosis showed improved OS ($P$=0.014) and GS ($P$=0.005).

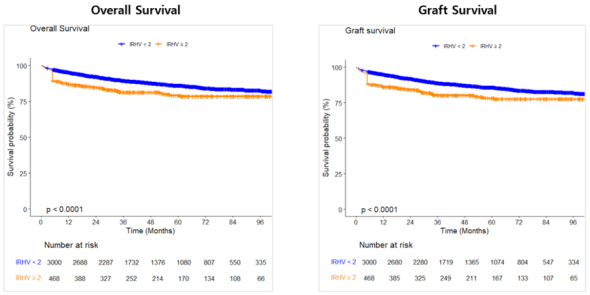
**Conclusions:** In LDLT using right liver, portal vein variation and steatosis were associated with significant donor complications, whereas multiple inferior right hepatic veins and multiple

biliary anastomoses reduced recipient long-term survival. Therefore, careful donor selection and surgical strategies considering vascular and biliary structures of the graft are essential for both donor and recipient safety.

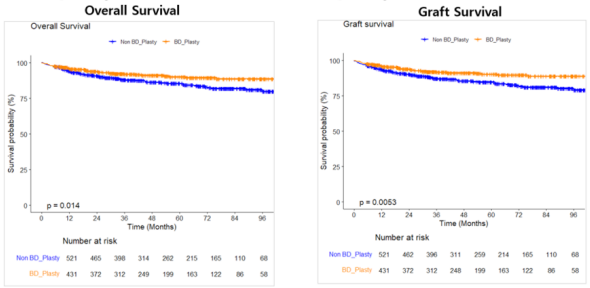
**Keywords:** Right liver, Anatomy, Living donor liver transplantation

**Long-term outcomes of recipients**

- **Multiple IRHV < 2 (N=3012) vs ≥ 2 (N=468)**




- **For separated two bile ducts (N=952)**
- **Ductoplasty for single anastmosis**
- **Ductoplasty (N=431) vs Non-ductoplasty (N=521)**




## PE-08

## Associations between Clinical Factors and Biliary Complications among Liver Transplant Recipients in Mongolia

**Myagmarjargal Sodjamts**[1], Enkh-Oyun Boldbaatar[1], Chinzorig Altankhuyag[1], Misheel Boldbaatar[1], Uuriintuya Gantumur[1] ,Anar Ganbold[1], Bayarmaa Ochirkhuree[1], Bat-Ireedui Badarch[1], Altangagnuur Albanch[1], Urnultsaikhan Ganbold[1], Munkhtsetseg Chimedtseren[2], Odontungalag Norovrenchin[2], Bolormaa Buuveibaatar[2], Sumiya Bayarsaikhan[1]

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**Aims:** Biliary complications (BC) stands among the foremost surgical challenges encountered by liver transplantation recipients, constituting a significant problem after transplantation. These complications, which encompass biliary stenosis, leakages, biloma, among others, can precipitate severe consequences, including recipient mortality. This study aimed to show potential factors associated with BC in liver transplant recipients in Mongolia.

**Methods:** This study encompassed 47 patients diagnosed with BC out of a total cohort of 251 individuals who underwent liver transplantation at our center from September 2011 to February 2024. Kaplan-Meier survival analyses were done to estimate the survival rates of patients with BC. The assessment of clinicopathological characteristics was conducted via chi-square or Fisher's exact test, with a *P*-value of less than 0.05 considering statistical significance.

**Results:** Within the study timeframe, 47 out of 251 transplant recipients developed BC (18.7%), of which 8 dead, leaving 39 survivors during the observation period. The breakdown of BC types included 2 cases of biloma, 4 of biliary leaks, and 41 of biliary stenosis. Survival analysis did not reveal a statistically significant difference in outcomes among recipients with any of the three complications. Univariate analysis suggests a potential correlation between male gender and the development of biliary stenosis; while combined hepatitis B and D viral infections appeared to be associated with biliary leaks although there were some statistical tendencies in other variables as well with the complications as well.

**Conclusions:** This study reveals the importance of identifying risk factors for biliary complications in liver transplant recipients in Mongolia. Preliminary findings suggest associations between male gender and biliary stenosis, hepatitis B and D co-infections and biliary leaks development. These insights necessitate further research to confirm these associations and enhance prevention and management strategies for biliary complications post-transplantation in liver transplant recipients.

**Keywords:** Biliary complications, Liver transplantation, Biliary stenosis, Biliary leakage

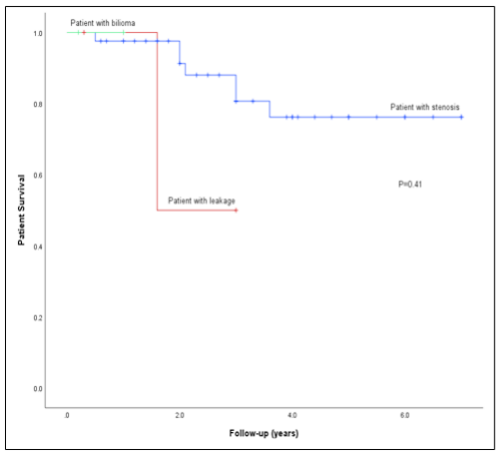


**Figure 1.** Impact of Biliary Complications on Patient Survival (Kaplan-Meier) in Years.

## PE-09

### Laparoscopic Donor and Recipient Explant Hepatectomy in Living Donor Liver Transplantation: A Single Center Experience in Vietnam

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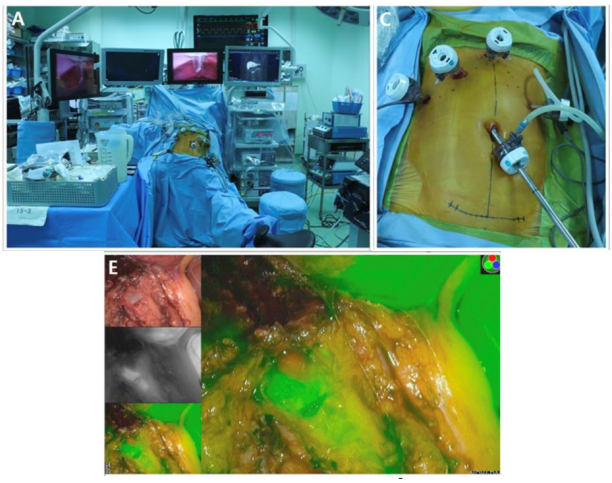
**Aims:** Laparoscopic donor and recipient explant hepatectomy in living donor liver transplantation has been successfully performed in a few high-volume centers around the world, proving feasibility, safety, fast recovery, and aesthetics for liver donors and recipient.

**Methods:** We reported 27 first cases of pure laparoscopic donor hepatectomy and 8 cases underwent total laparoscopic explant hepatectomy in Vietnam performed at Department of Hepatopancreato-biliary Surgery at 108 Military Hospital from November 2017 to December 2023.

**Results:** In 27 donors, the mean operative time was 255,3 minutes, mean time for parenchyma resection was 71,6 minutes, mean blood loss was 245,3 mL. The patients were followed up for 3-20 months after surgery, complication rate was witnessed in 3 cases (11,1%), all of which were biliary leak, managed successfully with percutaneous drainage in 2 cases and reoperation in 1 case. In 8 recipients, mean time for laparoscopic explant hepatectomy 120,5 minutes. We noted no complication related with laparoscopic phase.

**Conclusions:** Our short-term outcome of pure laparoscopic donor hepatectomy proved this technique as a feasible and safe strategy for liver living donor and laparoscopic explant hepatectomy is indicated in selected recipients only.

**Keywords:** Laparoscopic donor and, Recipient explant hepatectomy




## PE-10

### Diaphragmatic Hernia after Living-Donor Hepatectomy: A 10-Year Single-Center Case Series

Minha Choi, Sung-Gyu Lee, Shin Hwang, Chul-Soo Ahn, Ki-Hun Kim, Deok-Bog Moon, Tea-Yong Ha, Gi-Won Song, Gil-Chun Park, Young-In Yoon, Woo-Hyoung Kang, Eun-Kyoung Jwa, Byeong-Gon Na, Sung-Min Kim, Rak-Kyun Oh, Hyo Jung Ko, Sang-Hoon Kim, I-Ji Jeong, Dong-Hwan Jung

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**Aims:** Acquired diaphragmatic hernia (DH) is a rare and potentially fetal complication after living-donor hepatectomy (LDH). This study aims to evaluate the incidence and clinical outcomes of diaphragmatic hernia after LDH.

**Methods:** Cases of 3989 living-donors who underwent LDH in Asan Medical Center in Seoul between January 2014 and December 2023 were retrospectively reviewed. Demographic information, operative data, admission types (emergency or elective), imaging methods used for diagnosis, surgical methods for repair of DH, and follow-up data were recorded from electronic medical records. The incidence of DH was analysed in periods before and after use of Aquamatis, a saline-coupled bipolar sealer.

**Results:** Postoperative DH was occurred in 14 patients (0.35%) in our study. Thirteen patients underwent right LDH and developed right-sided DH, and one patient underwent left LDH and developed left-sided DH. The incidence of DH was 0.25% in the pre-Aquamatis period and more than doubled to 0.6% in the post-Aquamatis period. The median time from the first surgery to diagnosis of DH was 15.8 months (range, 2.9-95.3 months). Eleven patients with severe abdomen pain or ileus underwent emergent operation for DH repair, and small bowel resection and anatomosis was performed to one patient due to severe bowel ischemia.

**Conclusions:** Early recognition and surgical repair of DH following LDH should be considered for living-donor with unexplained abdominal or thoracic symptoms. In addition, care should be taken when using Aquamatis around the diaphragm in LDH to minimise potential thermal damage.

**Keywords:** Diaphragm Hernia, Living-donor hepatectomy,

## PE-11

### A Learning Curve for Laparoscopic Living Donor Hepatectomy Using Cusum Analysis

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Korea University College of Medicine, Department of Liver Transplantation And Hepatobiliary Surgery, Korea University Anam Hospita, REpublic of Ko-

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**Aims:** Living donor liver transplantation plays an important role in the treatment of liver disease as an alternative to the lack of liver grafts. However, donors' safety remains a subject of controversy. Minimally invasive living donor hepatectomy is also receiving attention to reduce liver donor's post-operative pain and aid recovery. This study is for evaluating the learning curve of laparoscopic living liver donor hepatectomy performed by a single surgeon.

**Methods:** Living liver donors from 2014 to 2023 were listed in operation date order and operation time of each case was checked. Cusum analysis was performed on the operation time.

**Results:** In total 46 cases of laparoscopic donor hepatectomy, 9 cases were left and 37 cases were right graft donors. Among those right graft cases, 6 were hand assisted procedures which was performed in the very early period (1st - 6th donor). There were 54 cases of laparoscopic hepatectomy before the first laparoscopic living donor hepatectomy. The learning curve for the laparoscopic living donor hepatectomy was divided in to 3 phases; phase 1 (3 initial donors), phase 2 (6 intermediate donors), and phase 3 (the subsequent donors). There was no open conversion case.

**Conclusions:** To perform a safe and skillful laparoscopic living liver donor hepatectomy, adequate previous laparoscopic liver resection experience may be important. Because phase 1 in the learning curve appears very short, once proficient laparoscopic hepatectomy becomes possible, laparoscopic living donor hepatectomy also rapidly reaching the learning phase.

**Keywords:** Donor

## PE-12

### Short-Term External Biliary Drainage in Living Donor Liver Transplantation Using Duct-to-Duct Anastomosis: A Single-Center Experience

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**Aims:** In living donor liver transplantation(LDLT), biliary complication (BC) is most common and intractable complication. There is no optimal method of reconstruction to reduce these complication. The most common biliary reconstruction is duct-to-duct anastomosis (DDA) in LDLT. And placing external biliary drainage (EBD) across the biliary anastomosis is good method to reduce BC. Unlike the general method of maintaining the drainage tube for 3 months to 12 months, our institution tried a short-term placement method of 6 weeks. This study reported the single institutional experience of short-term EBD in LDLT.

**Methods:** A total of 123 patients underwent LT from January 2013 to November 2022 in The Catholic University of Korea Incheon St. Mary's hospital. 53 patients who underwent deceased donor liver transplantation and 11 patients who lack of data were excluded. A retrospective cohort study was conducted on total 59 patients who underwent a LDLT with EBD and DDA. EBD was placed across the biliary anastomosis during operation. EBD was naturally drained for the first 1 to 3 weeks and was removed after 6 weeks.

**Results:** The overall BC was occurred in 22 patients (37.3%). 3 (5.1%) of early biliary fistula, 5 (8.5 %) of early biliary stricture, and 14 (23.7%) of late biliary stricture was occurred. All of BC was resolved by intervention (ERBD, PTBD). There was no re-operation for resolving BC. There was no mortality related to BC. There was no bile leakage after removal of the drainage tube.

**Conclusions:** A single institutional experience showed the effectiveness and safety of short-term EBD.

**Keywords:** Living donors, Liver transplantation, External drainage

## PE-13

### Patient Survival Prediction Analyzing Pathological Images after Liver Transplantation

**Seung Hyoung Ko**[1,2], Jie Cao[1], Yong-kang Yang[1], Zhi-feng Xi[1], Hyun Wook Han[2], Qiang Xia[1], Meng Sha[1]

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**Aims:** Predicting patient survival after liver transplantation is important for determining treatment. Data such as pathological images, CT, and MRI can be used for predicting patient survival. Recently, predicting survival using artificial intelligence has been receiving attention. In this study, the five years survival is predicted based on the pathological images of liver transplant. To improve the prediction, we combine structured data and verify performance through comparative indicators.

**Methods:** Images were acquired for 67 patients who received liver transplantation from 2015 to 2018 at the Shanghai Renji Hospital Liver Transplant Surgery Center. We acquired two pathological images for each patient. One of the images is used for training the classification model. The other is used to test the classification model, from which the probability of the patient's survival is calculated. For survival analysis, the probability calculated from the classification model is combined with the structured data, including gender and age. To verify the performance of the classification model in tracking patient

survival, the model was compared with the AFP(Alpha-Fetoprotein) and tumor number. The comparison indices were C-Index (Concordance index), AUC (Area Under Curves) and Hazard ratio.

**Results:** Classification accuracies for images of patients who underwent liver transplant were 65%. C-index (classification model / AFP / tumor number) for liver transplantation were calculated 0.617, 0.421, 0.606 respectively. AUC were 0.657(CI: 0.525 ~ 0.789), 0.391(0.271 ~ 0.51), 0.596(0.476 ~ 0.716) respectively. Hazard ratio was 39.91(1.284 ~ 1241), 0.9707(0.8945 ~ 1.053), 2.195(1.043 ~ 4.619) respectively.

**Conclusions:** In most cases, to predict a patient's survival, an expert decides how to treat the patient. However, as the number of patients being diagnosed become more complex and larger, experts may make misjudgments. Our proposed methods can solve this problem. We expect that our methods will help clinician make treatment decisions for patients.

**Keywords:** Deep learning, Post liver transplantation, Patient survival prediction, Multi-modal data

**Table 1.** Clinicopathological characteristics of HCC patients who received LT.

| Clinicopathological characteristics | n (%) |
|---|---|
| Total patients | 67 |
| Age (years) (median, range) | 43 (5 - 79) |
| Gender (Male)<br>Gender (Female) | 56 (83.6)<br>11 (16.4) |
| Presence of HBV infection | 63 (94) |
| Presence of HCV infection | 3 (4.5) |
| Preoperative AFP level (ng/ml) (median, range) | 29 (1.3 – 60500) |
| Preoperative CA199 level (U/ml) (median, range) | 27.5 (0.7 – 150.8) |
| Presence of cirrhosis | 55 (82.1) |
| Multiple tumor numbers | 40 (59.7) |
| Presence of satellite lesions | 4 (6) |
| Tumor max diameter (median, range) | 4.5 (0.5 – 24) |
| Poor differentiation of tumor grade | 41 (61.2) |
| Presence of microvascular invasion | 14 (20.9) |
| Presence of portal vein tumor thrombus | 14 (20.9) |
| Presence of biliary tumor thrombus | 1(1.5) |
| Presence of vena cava invasion | 3(4.5) |
| TACE | 14(20.8) |
| RFA | 10(14.9) |
| Operation history | 30(44.7) |
| Presence of laparotomy | 15(22.3) |
| Liver resection | 11(16.4) |
| Splenectomy | 4(5.9) |

**Table 2.** Time-dependent AUC values (95% CI) for each condition

| Duration (months) | Deep model score | AFP | Tumor number |
|---|---|---|---|
| 10 | 0.647(0.464 ~ 0.831) | 0.476(0.286 ~ 0.666) | 0.594(0.399 ~ 0.788) |
| 20 | 0.606(0.458 ~ 0.754) | 0.4(0.259 ~ 0.541) | 0.667(0.53 ~ 0.803) |
| 30 | 0.63(0.492 ~ 0.768) | 0.398(0.275 ~ 0.522) | 0.623(0.5 ~ 0.746) |
| 40 | 0.641(0.504 ~ 0.778) | 0.418(0.296 ~ 0.537) | 0.601(0.479 ~ 0.716) |
| 50 | 0.657(0.525 ~ 0.789) | 0.391(0.271 ~ 0.51) | 0.596(0.476 ~ 0.716) |

**Table 3.** C-index / Hazard ratio / p-value for each condition

| | Deep model score | AFP | Tumor number |
|---|---|---|---|
| C-index | 0.617 | 0.421 | 0.606 |
| HR (95% CI) | 39.91 (1.284-1241) | 0.9707 (0.8945-1.053) | 2.195 (1.043-4.619) |
| P-value | 0.0355 | 0.476 | 0.0384 |

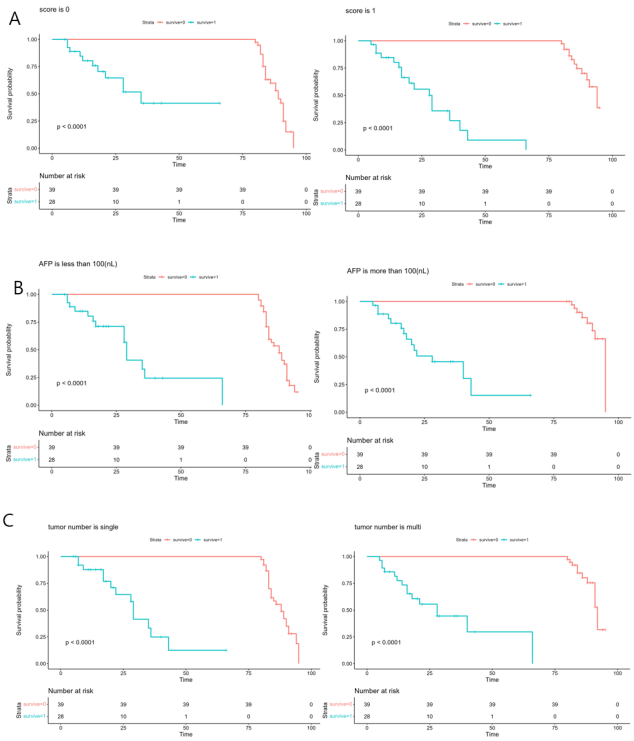


**Figure 1.** Survival analysis plot of each condition. (A) Classification model (Threshold: 0.3). (B) AFP (Threshold: 100nL). (C) Tumor number (Single or Multi cancer).

## PE-14

### Comparison of Survival Outcomes in Liver Transplantation Recipients with Refractory Ascites(RA) or Hydrothorax(RH)

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**Aims:** In previous studies comparing groups of patients with refractory hydrothorax(RH) and refractory ascites(RA), there was a tendency for higher liver-related deaths in the RH group. Additionally, the number of thoracentesis procedures performed was cumulatively associated with the survival outcomes. Therefore, we aimed to investigate the impact of hydrothorax and ascites on outcomes in liver transplantation recipients.

**Methods:** A single-center cohort of liver transplant recipients data was merged between June 2006 and December 2022. The RA group included patients who had more than 1000cc of ascites drained during surgery, or those who underwent paracentesis from three months prior to surgery up until one month post-surgery. The RH group encompassed patients who underwent therapeutic thoracentesis for pleural effusion in the three months leading up to the surgery. We conducted a 1:7 propensity score matching(PSM) analysis for the two groups.

**Results:** Among the matched 206 liver transplantation patients, there were 35 patients(17.0%) with RH and 171 patients(83.0%) with RA. Between the two groups, there was no statistically significant difference in 1-year survival($P$=0.073). However, in the 5-year survival analysis, the RH group showed significantly lower mortality rates ($P$=0.042). Also, there was no difference between the two groups in terms of hospital stay duration or the length of stay in the post-operative intensive care unit stay ($P$=0.115, $P$=0.191, respectively).

**Conclusions:** Our study reveals that patients with refractory hydrothorax exhibit significantly reduced survival rates. While various scoring systems assign weight based on the presence of ascites, pleural effusion is also important mortality factor in liver transplantation recipients.

**Keywords:** Liver transplantation, Hydrothorax, Ascites, Survival outcome

## PE-15

### The Figure out of Live Donor Liver Transplantation (LDLT) in Asia Using Bibliometrics Analysis

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[1]Management, Universitas Andalas, Indonesia, [2]Music Education, Alumnus of Padang State University, Indonesia

**Aims:** Live Donor Liver Transplantation (LDLT) is an essential life-saving procedure for patients suffering from acute liver failure and hepatocellular carcinoma. The success of liver transplantation worldwide has brought increased demand for liver grafts. In Asia, the focus has been on living donor liver transplantation (LDLT), as this procedure is more acceptable in most Asian cultures. This study aims to provide a specific overview of LDLT in Asia research using a bibliometric framework.

**Methods:** This research uses the bibliometric analysis method using the VOSViewer application to analyze the data. Data was taken from Lens.org from 2002 until early 2024, with 77 articles analyzed. The keywords are Live Donor Liver Transplantation and Asia.

**Results:** Liver transplant centres in Asia have been the pioneers, innovators and catalysts of technical advancements followed by the world, especially in terms of LDLT (Chen et al. 2013). The analysis showed that in Asia, most LDLT patients were from India, with the gender being male and aged around 18-26 years (young adults). The process of performing transplantation begins with patient selection and then proceeds with methods such as antineoplastic agents and blood transfusion. The five countries that have contributed the most to research on LDLT are Japan, the United States, India, Hong Kong and China.

**Conclusions:** Based on the explanation above, it can be concluded that bibliometrics analysis can provide an overview of the literature review in research on LDLT in Asia. This will provide insight into the therapy, treatment, and development of LDLT.

**Keywords:** Asia, Bibliometrics analysis, Live donor liver transplantation (LDLT)

## PE-16

### Single Centre Experience of Acute and Chronic Rejection after Liver Transplantation

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**Aims:** Liver transplantation has been recognized as one of the most effective treatment for patients with end stage liver diseases that increases annually in Kazakhstan. Acute and chronic rejection following LTx continues to influence transplant recipients. This study aimed to establish predisposing factors, histological characteristics and evaluate treatment response.

**Methods:** Clinical records of patients with ACR and CR following LTx, between 2013 and 2024, were retrospectively reviewed.

**Results:** 96 cases (LDLT - 73, DDLT - 23 cases) were considered.

25 patients (35 cases) were diagnosed with ACR (20 cases) and CR (15 cases) at a median 2.4 years (7 days–9 years) after LTx. Among the patients in the study group, there were 12 men and 13 women aged 24 to 71 years (mean age 45 years). Prior to the diagnosis of rejection, everyone had an increase cholestatic liver function tests. The biopsy confirmed with Banff criteria in 23 cases (ACR-15; CR-8), not performed in 12 cases for different reasons. Rejection activity index (RAI) was as follows: borderline – 2 (13.3 %), mild – 6 (40%), moderate – 7 (46.7%) and none of severe ACR. 9 ACR cases were responsive to steroid boluses, 6 cases to escalation of immunosuppression, no response in 3. CR were treated by correcting immunosuppression. One patient received re-Tx and died after 6 month due to multi-organ failure. 5 of them require retransplantation. Overall mortality was at 4 (16%).

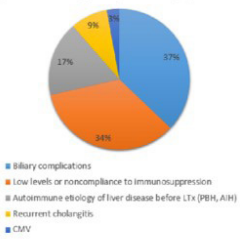
**Conclusions:** In our study, most episodes of acute and chronic rejection occurs within late period of post-transplantation. According to histological findings, severe biopsy-proven rejection was not revealed. In over half of cases, etiology of cirrhosis before LTx was hepatitis B and D. Biliary complications were the most common predisposing factor (37%) of rejection and they had several episodes of rejection. Patients with CR had poor prognosis, 42% of them need retransplantation.

**Keywords:** Acute rejection, Chronic rejection, Liver transplantation, Immunosuppression

**Table 1.** Etiology of cirrhosis before liver transplantation in patients with rejections.

| Primary indication for transplant | N (total = 25) |
|---|---|
| Hepatitis B and D viruses | 13 (52%) |
| Cryptogenic | 4 (16%) |
| Primary biliary cirrhosis | 3 (12%) |
| Autoimmune hepatitis | 3 (12%) |
| Hepatitis B virus | 1 (4%) |
| Non-alcoholic steatohepatitis | 1 (4%) |

**Figure 1.** Predisposing factors (%)



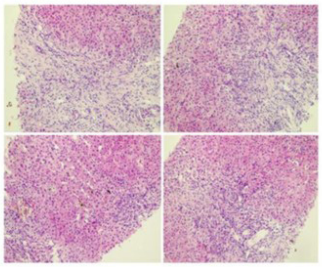



**Figure 2.** Histologic findings of acute rejection after liver transplantation. The histologic characteristics indicated acute injection, including normal structure of hepatic lobules, fibrous proliferation of interlobular portal area, small bile-duct hyperplasia, visible lymphocyte infiltration around the small bile-duct wall, liver cell mild edema with cholestasis, and point necrosis.

# Biliary and Pancreatic Disease

## PE-01

### Feasibility of Laparoscopic Hepatectomy for Hepatolithiasis

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**Aims:** Hepatolithiasis is a still a common disease in Vietnam and many countries in Asia with high rates of residual stones and recurrence after treatment. Treatment of hepatolithiasis requires a careful selection and combination between surgical, endoscopic and interventional treatment. The role of laparoscopy, especially in hepatectomy for hepatolithiasis remains unclear and controversial due to technical difficulties.

**Methods:** Between October 2020 and April 2023, 35 consecutive patients with hepatolithiasis undergoing laparoscopic hepatectomy were enrolled. The general characteristics, intraoperative, and postoperative data were analyzed.

**Results:** Mean age was 55.9±12.6 years; female/male ratio was 2.3; 14.3% patients had previous biliary surgery. Acute cholangitis occurred in 68.6% patients. 28.6% patients had both intra- and extrahepatic duct stones. Left lateral sectionectomy was performed in (25 cases), followed by left hepatectomy (5 cases), right posterior sectionectomy (3 cases), right hepatectomy (2 cases). 46.7% patients underwent common bile duct exploration. Cholangioscopic exploration with/without laser lithotripsy was used in 37.1%. The median surgery time is 170 (120 - 200) minutes. Intraoperative blood transfusion was required in only 3 cases (8.5%). Mean time to bowel movement was 2.3±0.7 days. Mean post-operative hospital stay was 7.7 ±2.2 days. Post-operative complications occurred in 14.3%; including wound infection 8.5%; residual abscess 2.9%, and bile leak 2.9%. Complete stone clearance rate was 91.2%.

**Conclusions:** Laparoscopic liver resection, especially left lobectomy, is safe and effective treatment for patients with hepatolithiasis.

**Keywords:** Hepatolithiasis, Laparoscopy, Liver resection

## PE-02

### Cancer Stem Cells-Derived Exosomal MiR-675-3p Promotes Epithelial-Mesenchymal Transition in Human Pancreatic Cancer Cells by Targeting the STAT3 Pathway

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**Aims:** Exosomes mediate the intercellular communication by transporting information cargo between cancer stem cells (CSCs) and pancreatic cancer cells (PCCs) to regulate pancreatic cancer progression. This study aimed to assess the role of CSCs-derived exosomal miR-675-3p in the regulation of EMT in PCCs.

**Methods:** Serum-free floating culture systems were used to harvest the CSCs. Exosomes was isolated by the standard ultracentrifugation method. Migration and invasion ability was evaluated by transwell assays. The expression of EMT markers and the status of STAT3 signaling were detected by qPCR and Western blot.

**Results:** CSCs-derived exosomes enriched large amounts of miR-675-3p. CSCs-derived exosomes led to increased miR-675-3p expression in PANC-1 and promoted the EMT, migration and invasion of PANC-1 cells, while PCCs-derived exosomes couldn't yield the similar results at the same concentration. Meanwhile, we observed that miR-675-3p inhibitor could restore CSCs exosomes-induced changes in cell migration and invasion. Additionally, we identified that the modulation of miR-675-3p on EMT was conducted via activation of STAT3 pathway by targeting SOCS5, up-regulating miR-675-3p expression in PCCs promoted tumor cells migration and invasion, and the EMT process and the expression of STAT3 pathway were significantly enhanced, while SOCS5 overexpression could counteract the effects of miR-675-3p up-regulation.

**Conclusions:** This is the first study to identify exosomal miR-675-3p as a crucial miRNA released by CSCs that promotes EMT of PCCs. These data provide new insights into the oncogenic function of miR-675-3p in human pancreatic cancer and reveal potential targets to develop optimal treatment approaches for this disease.

**Keywords:** Pancreatic cancer, Cancer stem cells, Cancer stem cells

## PE-03

### Comparison of Intraperitoneal Nebulization with Instillation of Ropivacaine in Reducing Post-Operative Pain after Laparoscopic Cholecystectomy: A Double Blinded, Randomized Control Trial

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**Aims:** Although Laparoscopic cholecystectomy (LC) is minimally invasive with less morbidity, postoperative pain remains a significant burden to health care. Various pharmacological and non-pharmacological interventions have been tried to reduce the postoperative pain. In this study, we compared the efficacy of intraperitoneal nebulization with the instillation of ropivacaine in decreasing postoperative pain after LC.

**Methods:** The study was single-center, double-blinded, RCT. Fifty-six patients were randomized to receive intraperitoneal nebulization or instillation of ropivacaine. Static, dynamic, and shoulder pain were measured using a visual analog scale (VAS) at 6, 24, and 48 hours after surgery. Also, time to unassisted walking, postoperative nausea and vomiting (PONV), and postoperative length of hospital stay (PLOH) were measured.

**Results:** The static pain at 6,24 and 48 hours (p-0.007, 0.016, 0.04) and Dynamic pain up to 24 hours (p-0.002, 0.026) were significantly lower in the nebulization group. Patients in the nebulization group had decreased postoperative vomiting (p-0.023) and ambulated early (p-0.003). There was no statistically significant difference in shoulder pain (p-0.87, 0.69, 0.32), incidence of nausea (p-0.076) & PLOH (p-0.48) between the groups.

**Conclusions:** Intraperitoneal nebulization of ropivacaine results in decreased postoperative pain, time to unassisted walking, and the incidence of postoperative vomiting when compared to intraperitoneal instillation of ropivacaine in patients undergoing laparoscopic cholecystectomy.

**Keywords:** Intraperitoneal nebulisation of ropivacaine, Instillation of ropivacaine, Post-operative pain in laparoscopic cholecystectomy

## PE-04

### Role of Circulating miRNA as Diagnostic and Prognostic Biomarkers for Biliary Tract Cancer

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**Aims:** Biliary tract cancer (BTC) is a highly aggressive malignant tumor, and its incidence has been on the rise in recent years. However, the underlying pathogenetic mechanisms and predisposing factors remain unclear, leading to challenging early diagnosis and poor prognosis. Current diagnostic methods such as imaging, biopsy, and biomarkers are deemed ineffective due to their high cost, technical difficulties, invasiveness, and low specificity and sensitivity for BTC detection. Traditional surgical puncture biopsy is a complex and invasive procedure, causing physical and psychological discomfort in patients. Therefore, there is an urgent need to develop non-invasive methods to identify specific molecular markers for early detection of BTC. Currently, certain types of Circulating MicroRNAs

(MiRNAs), a class of small non-coding RNAs expressed by various cancer cells into biofluids, have been identified as potential non-invasive indicators for the diagnosis and prognosis of BTC. The aim of this study is to assess the diagnostic and prognostic value of circulating MiRNAs in BTC compared to healthy individuals.

**Methods:** This review collects literature from Science Direct, PubMed, NLM, Epistemonikos, clinicaltrials.gov, and applies standard review methods to evaluate the diagnostic value of circulating MiRNAs as biomarkers for BTC based on sensitivity, specificity, and AUC scores.

**Results:** The results of the reviewed studies indicate that circulating MiRNAs have the potential to serve as non-invasive diagnostic and prognostic biomarkers for BTC. Isolated from plasma, serum, and human blood, these MiRNAs show adequate sensitivity, specificity, AUC, and OS scores, distinguishing BTC from healthy individuals.

**Conclusions:** This review suggests that circulating MiRNAs can be utilized as non-invasive diagnostic and prognostic biomarkers for BTC, providing opportunities for the development of more effective early detection methods that are less intrusive for patients.

**Keywords:** Biliary tract cancer, Circulating micrornas, Diagnostic, Prognostic

## PE-05

### Obstructive Jaundice of Non-Tumor Genesis: State of Immunity and Methods of Correction

**Nodirjon Ruzimurodov**[1], Tamara Aripova[1], Tokhir Askarov[2]

[1]Department of Cell Therapy, Institute of Immunology and Human Genomics of the Academy of Science of the Republic of Uzbekistan, Uzbekistan; [2]Department of General Surgery, Tashkent Pediatric Medical Institute, Uzbekistan

**Aims:** The study is aimed at analyzing changes in integral hematological parameters in patients with obstructive jaundice of non-tumor origin, in order to determine the relationship between changes in these parameters, the severity of the disease and the immunological status.

**Methods:** All patients had blood taken for a detailed hematological analysis, counting the number of erythrocytes, leukocytes, platelets and determining the erythrocyte sedimentation rate. In addition, the level of enzyme markers of liver failure was determined in all patients: bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gammaglutamine transpeptidase (GGT), lactate dehydrogenase (LDH).

To assess the immune status of patients, indicators of leukogram, cellular, humoral immunity, circulating immune complexes (CIC) and phagocytosis activity were used. Statistical processing of the material was carried out on a personal PC-compatible computer with the Windows XP Pro operating system installed. using the statistical software package "STATISTICA 6" from StatSoft Inc. (2003) Microsoft office applications for the environment

**Results:** We studied the dependence of changes in integral hematological parameters and liver enzymes on the time of admission to the hospital, age, gender, type of operation and bilirubin level in patients with obstructive jaundice of non-tumor origin.

The majority of patients - 83.1% - were admitted to the hospital later than 24 hours from the onset of the disease, 11.3% were admitted before 24 hours, and 5.6% - before 6 hours.

The distribution of patients by gender showed that women accounted for 68.6%, and men - 31.4% (71.3%, and men - 28.7%). 75.2% of patients were 66 years of age or older and were hospitalized.

60 patients were operated on, of which 68 (27) underwent open interventions (laparotomy, choledocholithotomy, drainage of the common bile duct, in case of bile duct obstruction - application of biliodigestive anastomosis) and 37 (33) patients underwent endoscopic operations (ERCP + EPST).

Based on laboratory data, we have developed a method for determining the severity of obstructive jaundice depending on integral hematological parameters and the level of liver enzymes, which allows us to assess the patient's condition at an early stage of the disease and determine the principles of initial therapy.

With mild severity, the parameters of integral hematological parameters were as follows: leukocyte intoxication index 1 - up to 2.5, leukocyte intoxication index 2 - up to 2.75, stress index - up to 1.0, segmented neutrophil to lymphocyte ratio index - up to 7.0, - index of the ratio of neutrophils to lymphocytes - up to 12.0, index of the ratio of lymphocytes to eosinophils - up to 18.

The average severity of the pathological process was confirmed by the following values of integral hematological indicators: leukocyte intoxication index 1 from 2.6 to 4.5, leukocyte intoxication index 2 from 2.76 to 5.0, stress index from 1.1 to 2.0, index the ratio of segmented neutrophils to lymphocytes is from 7.1 to 10.0, - the neutrophil to lymphocyte ratio index is from 12.1 to 16.0, the lymphocyte to eosinophil ratio index is from 18.1 to 22.0.

In severe cases of mechanical meltdown, the hematological parameters were as follows: leukocyte intoxication index1 over 4.5, leukocyte intoxication index2 over 5.0, stress index over 2.0, segmented neutrophils to lymphocytes ratio index over 10.0, - neutrophils to lymphocytes ratio index over 10.0, lymphocytes over 16.0 and the lymphocyte to eosinophil ratio index over 22.0.

To clarify the intracellular mechanisms of the formation of im-

munological disorders, data on the immune status of patients with mechanical meltucha were compared with similar indicators of healthy people. As a result, 30 patients were identified depending on the severity of mechanical meltucha.

In patients with mild severity, moderate T-immunodeficiency was revealed while the function of the humoral part of the immune system was preserved during the acute period of the disease. The indicators of the CEC and phagocytic link were within normal values.

In patients with moderate severity, along with a decrease in the number of T-helpers, the number of T-suppressors was also reduced, as a result of which the immunoregulatory index was close to the level of healthy people, but did not reach it.

In patients with severe degrees, a marked decrease in both T-helper and T-suppressor levels and a critical level of the immunoregulatory index were found.

**Conclusions:** The analysis of integral hematological indices in patients with mechanical jaundice of non-tumorous origin has revealed significant correlations between endotoxemia levels, immune status, and disease severity. It was found that elderly patients are most susceptible to substantial changes, and there exists a direct relationship between the degree of auto-intoxication and the timing of patients' admission to the surgical ward.

The application of a method for determining the severity of mechanical jaundice using integral hematological parameters proves to be an effective screening and diagnostic tool for determining the level of initial therapy.

An important criterion for assessing the development of hepatic cell insufficiency is the level of hepatic enzymes, which increases during the acute phase of the disease and decreases as the inflammatory process subsides.

The immune status of patients with mechanical jaundice is associated with secondary immunodeficiency, with the depth of these disturbances depending on the severity of the disease.

Immunocorrection in mechanical jaundice of non-tumorous origin, including the use of the immunomodulator glutocim, has a positive effect on normalizing the immune system and improving treatment outcomes, thus confirming the necessity of its application in clinical practice.

**Keywords:** Mechanical jaundice, Non-tumor genesis, Immunocorrection, Surgical treatment

## PE-06

### Idiopathic Vanishing Bile Duct Syndrome in a Young Female: A Case Report

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**Aims:** Vanishing Bile Duct Syndrome (VBDS) is a rare disease characterized by the progressive disappearance and destruction of intrahepatic bile ducts within the portal tract, leading to cholestasis and resulting in symptoms such as jaundice and liver failure. However, the underlying mechanisms of the disease are not fully understood.

**Methods:** This study presents a rare case of a young female patient who was diagnosed with idiopathic Vanishing Bile Duct Syndrome after undergoing a liver biopsy to investigate unexplained jaundice.

**Results:** The patient's liver function partially improved after ursodeoxycholic acid and prednisolone treatment.

**Conclusions:** A better understanding and prompt diagnosis of VBDS can lead to effective treatment, and it is crucial to recognize that delays in diagnosis and treatment can increase mortality. Through this case, we aim to provide insights into managing patients suffering from VBDS using a comparable approach.

**Keywords:** Vanishing bile duct syndrome; Jaundice; Cholestasis

## PE-07

### High Expression of Senescence Marker Protein-30 (SMP-30) Is Associated with 3-year Mortality in Cholangiocarcinoma

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**Aims:** SMP-30 (senescence marker protein-30) is a calcium (Ca2+)-binding protein known as regucalcin, abundantly expressed in hepatocytes. SMP-30 plays a crucial role in intracellular calcium homeostasis and protects cells from apoptosis. There are only a few studies that have reported its value as a prognostic indicator or therapeutic target for hepatocellular carcinoma; however, there is no study for cholangiocarcinoma (CCA). In this study, we aimed to investigate changes in hepatic SMP-30 expression in patients with CCA and to examine its relationship with clinical prognosis.

**Methods:** Patients who underwent surgical resection for CCA at Hallym University Sacred Heart Hospital (in Anyang, Korea) from January 2011 to November 2021 were included in the study. To examine hepatic SMP-30 expression, representative slides of CCA are selected, and immunohistochemical staining for SMP-30 is performed. To assess the level of SMP-30 expres-

sion, the Immunoreactive Score (IRS) was determined by multiplying the expression ratio and intensity of SMP-30 across all tumor cells.

**Results:** Total of 75 patients were included in the study. The average age was 66.6 years, and 49 patients (65.3%) were male. In-hospital mortality was 8% (6/75); 45 patients (60%) were died during observation period (971.2±880.6 days). When investigating factors associated with 1-year and 3-year mortality after surgical resection, we found that high expression of SMP-30 in tumor tissue was significantly associated with 3-year mortality. In multivariate analysis, prolonged INR (≥ 1.13) and lymph node (LN) metastasis were associated with 1-year mortality, while high expression of SMP-30 (≥ 100), a long hospitalization period (≥ 3 weeks), and LN metastasis were related to 3-year mortality.

**Conclusions:** High expression of SMP-30 in CCA tissue was an independent predictive factor for 3-year mortality. Investigating the intensity of SMP-30 expression in CCA could help estimate the patient's long-term prognosis.

**Keywords:** Senescence marker protein-30, Cholangiocarcinoma

## PE-08

### Diagnostic Efficacy of Preoperative Biopsy in Distinguishing Gallbladder Cancer from Cholecystitis

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**Aims:** Distinguishing between gallbladder cancer (GBC) and GB cancer mimicking cholecystitis remains a clinical challenge due to their shared clinical and radiological features. Accurate preoperative differentiation is crucial for guiding appropriate surgical management.

**Methods:** This retrospective study, conducted at Keimyung University Dongsan Hospital from 2008 to 2023, aimed to assess the role of preoperative biopsy in diagnosing GBC and differentiating it from GB cancer mimicking cholecystitis. Among 55 initially suspected cases, 17 benign cases were excluded, focusing the analysis on the remaining 38 cases to evaluate the impact of preoperative biopsy on surgical decision-making.

**Results:** Of the 38 cases, 29 patients underwent preoperative biopsy, while 9 did not. The biopsy group showed a significantly lower rate of unnecessary surgeries, with only 1 out of 29 cases (3.4%) undergoing such procedures. In contrast, the non-biopsy group had a markedly higher rate, with 7 out of 9 cases (77.8%) undergoing unnecessary surgeries, including 4 cases identified as benign during intraoperative frozen section biopsies. Statistical analysis revealed a significant difference ($P$=0.0000163) between the two groups.

**Conclusions:** This study underscores the importance of preoperative biopsy in differentiating GBC from GB cancer mimicking cholecystitis. The findings advocate for the routine use of preoperative biopsy in surgical decision-making for these complex gallbladder pathologies. Implementing preoperative biopsy can significantly reduce the incidence of unnecessary surgeries, leading to improved patient care and more efficient utilization of medical resources. These results have significant implications for surgical practices worldwide, emphasizing the necessity of comprehensive preoperative evaluation in optimizing patient outcomes.

**Keywords:** GB Cancer mimicking cholecystitis

## PE-09

### Early Predictors of Successful Kasai Portoenterostomy

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**Aims:** To identify early predictors of successful Kasai Portoenterostomy (KPE)

**Methods:** Retrospective analysis of 49 infants who underwent KPE between January 2018 to October 2023. Successful KPE was defined as total bilirubin < 1 mg/dl by 6 months of age. None of the patients received post KPE steroids and none were tested for concomitant CMV.

**Results:** The median age at KPE was 71 (59-83) days, with 21 (42.9%) less than 65 days. Median follow up was of 11 (6-36) months with native liver survival in 27 (55.1%).Thirty six (73.5%) were type III biliary atresia and 2 (4%) were associated with other congenital anomalies. Successful KPE was in 22 (44.9%). Age less than 65 days at the time of KPE was significantly associated with successful KPE (42.9% vs 57.1%, OR 5, 95% CI 1.472 -16.988, $P$=0.009). Weight ($P$=0.932), total bilirubin ($P$=0.907), direct bilirubin ($P$=0.667), AST ($P$=0.837), ALT ($P$=0.937), Total protein ($P$=0.051), albumin ($P$=0.201) and INR ($P$=0.220) at the time of surgery did not affect outcome. Ishak fibrosis grade ($P$=0.267) and inflammation grade ($P$=0.743) were not associated with outcome. Post surgery, lower total bilirubin (7.95 mg/dl vs 10.1 mg/dl, MD 0.07 to 4.66, $P$=0.043) and direct bilirubin (4.92 mg/dl vs 6.5 mg/dl, MD 0.16 to 3.03, $P$=0.03) by post operative day 7 were associated with a successful outcome. Parameters like ascites for more than 7 days ($P$=0.071), albumin ($P$=0.431), AST ($P$=0.091), ALT ($P$=0.108) and INR ($P$=0.241) at 7 days post KPE did not affect the outcome. Seventeen patients suffered from complications post KPE with sepsis in 17, bowel

perforation in 3 and biliary ascites in 2. Presence of complications post KPE did not affect the outcome (*P*=0.825). Twenty (40.8%) patients suffered from a median of 1 (1-3) cholangitis episodes. However, cholangitis was not associated with outcome (*P*=0.374). On logistic regression analysis age less than 65 days (OR 8.024, 95% CI 1.865 to 34.530, *P*=0.005) and lower total bilirubin at day 7 post KPE (OR 0.789, 95% CI 0.642 to 0.970, *P*=0.028) were found to be significantly associated with successful KPE increasing the correctness of classification of model from 55.1% to 73.5%

**Conclusions:** There is a 8 folds increase in successful outcome if KPE is done at less than 65 days of age. Bilirubin at post operative day 7 is an early predictor of successful KPE

**Keywords:** Biliary atresia, Kasai portoenterostomy, Early predictors of success

## PE-10

### Clinico Pathological Profile, Surgical Outcome and Survival Analysis after Pancreaticoduodenectomy: 7 Year Experience from Tertiary Care Teaching Hospital in Odisha

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**Aims:** Despite advances in multimodality treatment, morbidity after pancreaticoduodenectomy (PD) remains high. This study aimed to analyze the clinico-pathological profile, surgical outcomes, and survival of patients undergoing PD in a single tertiary care center.

**Methods:** Retrospective analysis was conducted using prospectively compiled data from 2016 to 2022. Patients who underwent PD and completed one year of follow-up were included. Survival analysis was performed using Kaplan-Meier analysis.

**Results:** Of 104 patients who underwent PD, age range was 15 to 77 years (median: 53), with most being male (61.5%) and having CCI score - 0 (77.9%). Jaundice was the common presenting complaint. Preoperative stenting was performed in 47% of patients mainly for cholangitis. Most patients underwent pancreaticojejunostomy(92%). Total morbidity was 77.1%, with pancreatic fistula (62.5%) as most common complication, followed by delayed gastric emptying (35.6%). Postoperative hemorrhage ()7%, bile leak(5.8%), and surgical site infection(18%) were also observed. The 30-day and 90-day mortality rates were 3.8% and 9.6%, respectively. Adenocarcinoma was the most common histopathological finding (79.8%), followed by benign disease. Most adenocarcinomas were T3 stage (49.3%) with no lymph node involvement (62%) (N1: 26.5%). Only 66.2% of adenocarcinoma patients received or were on chemotherapy. The median survival for adenocarcinoma was 45 months, with no significant difference among subtypes. However, significant survival improvement was observed in patients who received chemotherapy. The one-year, three-year, and five-year survival rates were 79.4%, 51.2%, and 35.7%, respectively.

**Conclusions:** Pancreaticoduodenectomy remains a high-risk surgery with significant morbidity and mortality. Adenocarcinoma was the most common diagnosis, and chemotherapy showed a significant survival benefit.

**Keywords:** Pancreaticoduodenectomy, 5 yr survival, POPF

## PE-11

### Demographic, Clinicopathological Profile & Surgical Outcome in Chronic Calcific Pancreatitis Patients in Eastern India (Odisha) : 7 Yrs Experience from a Teritary Care Teaching Hospital

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**Aims:** Surgical intervention in the management of pain in Chronic pancreatitis(CP) usually sought late. Frey procedure has become standard surgical intervention because of its hybrid character, combining resection and drainage. Aims & objectives :To determine the short and medium-term outcomes of surgical treatment for CP & To Analyse the demographic and clinicopathological profiles of patients with chronic pancreatitis from eastern part of India.

**Methods:** Methods: Retrospective review of prospectively collected database over 7-year period who underwent surgery for CP between 2016-2023 at IMS & SUM Hospital.

**Results:** Of 110 patients 73(66.36%) were < 40 years. Mean age is 36.42. Males were affected more 62.7%(M/F=1.8:1) Mc cause was Idiopathic 68(61.8%) .Mc presenting symptom was pain in103(93.63%). 44(40%) pts had diabetes . Mean MPD diameter is 9mm. Complications noted in 40(36.3%) of which 36 (90%) had > 3yrs index episode, Most common is Biliary stricture 18(16.6%). 73 underwent freys, LPJ in 27, Whipples in 10, Freys+Gj in 8, freys+HJ in 8 cases. 85 (77%) had wt gain - Avg Wt gain 4.8 kgs(*P*<0.0017) . 32(96.9%) pts has decrease insulin requirement- mean preop 34.5U, mean postop 18.68U(*P*<0008). Izbicki score preop-51.91, postop–19(*P*<0.013). 11(10%) were diagnosed with malignancy postsurgery. 9 showing Adenocarcinoma, 2 NET. Low albumin levels have been shown to be associated with increased complications, icu stay, increased bleed, DGE . (*P*<0.027)

**Conclusions:** Early surgery < 3yrs from index episode is associated with reduced pain scores, decrease insulin requirement and better preservation of pancreatic function and less com-

plications.

**Keywords:** Chronic calcific pancreatitis, Early surgery, Freys procedure

## PE-12

### Biological Effects of Atractylodin on Migration and Autophagy of Cholangiocarcinoma Cell through Its Different Molecular Mechanism

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**Aims:** Atractylodes lancea rhizome has been extensively used for the treatment of night blindness, digestive disorders, rheumatic diseases, and influenza in Chinese traditional medicine. Further, Atractylodes lancea has also been used for the treatment of common cold, fever, nausea, dyspepsia, flatulence, and noninfectious diarrhea in Thai traditional medicine. However, in Japan, it is an effective component of several Kampo medicines such as Juzen-taiho-to and Saireito. Atractylodin is an important phytochemical of the root of Atractylodes lance which is soluble in ethyl acetate and acetone but insoluble in water.

**Methods:** Biological potential and health beneficial aspects of atractylodin have been investigated in the present work through scientific data analysis of different scientific research work. In the present work, biological effect of atractylodin on cholangiocarcinoma has been investigated through scientific data analysis of different research work. However, in some of the research work, biological potential of atractylodin in the cholangiocarcinoma for their cytotoxic potential has been investigated.

**Results:** Biological effects of atractylodin on cholangiocarcinoma has been investigated and found that atractylodin inhibited the migration and invasion of cholangiocarcinoma cells. Further, in another scientific research work, combination of atractylodin with other constituents produced additive and synergistic effect. In some other research work, biological potential of atractylodin for their effectiveness on cholangiocarcinoma cell has also been investigated with its molecular target of action of atractylodin and found that atractylodin may involve the destruction of the DNA of cancer cells.

**Conclusions:** Present work revealed the biological effects of atractylodin on migration and autophagy of cholangiocarcinoma cell.

**Keywords:** Atractylodin, Cholangiocarcinoma, Autophagy

## PE-13

### The Non-Invasive Approach to Pancreatic Fibrosis Assessment by Multidetector Computed Tomography: The Intermediate Results

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**Aims:** Pancreatic fibrosis (PF) non-invasive diagnosis may facilitate the preventing pancreatic disease progression. Aim was to clarify relationships between PF grade and results of multidetector computed tomography (MDCT).

**Methods:** This study was conducted within the healthcare research project "Assessment of pancreatic fibrosis as a prognostic factor for its diseases course" funded by Autonomous non-profit organization "Moscow Center for Innovative Technologies in Healthcare" administered by the Moscow Healthcare Department. Results of contrast-enhanced 128-row MDCT from 119 patients (mean age 58.2±13.9) who underwent surgery from April 2022 to October 2023 due to pancreatic tumors and advanced chronic pancreatitis were analyzed. We calculated contrast enhancement ratio (CER) between venous phases (VP) and non-contrast MDCT, and normalized CER (NCER) during the pancreatic phase (PP) and VP. PF morphological grade was assessed according to Klöppel & Maillet's scoring system.

**Results:** CER value was higher ($P$=0.005) in patients with severe PF (mean CER=1.1), than in patients with mild PF (mean CER=0.86). We received a significant ($P$=0.003) moderate growth of NCER VP in patients with severe PF (mean NCER $VP$=0.6) compared with NCER VP in patients with mild pancreatic fibrosis (mean NCER $VP$=0.49). NCER PV and CER ($P$=0,002 and $P$=0.0001, respectively) were higher in patients with morphological signs of inflammation (0.49 and 0.76, respectively), than in patients without these signs (0.58 and 1.15, respectively).

**Conclusions:** MDCT post-processing indicators, NCER VP and CER, increased in patients with severe PF as well as in those who had morphological signs of inflammation. It could be useful for noninvasive PF diagnosis and prognosis.

**Keywords:** Pancreas, Fibrosis, Pancreatitis

## PE-14

### X-Ray Endobiliary Methods in the Treatment of Patients with Liver Alveococcosis Complicated with Obstructional Jaundice

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**Aims:** To improve the results of treatment of patients with obstructive jaundice of alveococcal etiology by optimizing the tactics of surgical treatment using the method of percutaneous transhepatic interventions

**Methods:** Of the 280 patients who were hospitalized in the clinic named after. I.K. Akhunbaeva NG Ministry of Health of the Kyrgyz Republic for the period from April 2009 to April 2016, 31 (11%) were admitted with obstructive jaundice.

**Results:** In 21 patients, the bilirubin level was more than 124 μmol/l, and therefore they underwent PCCG and PCHS. Of these, 12 (57.1%) were women, 9 (42.9%) were men, aged from 16 to 62 years, the average age was 33.2±9 years. The average bilirubin level upon admission was 252.4±35 μmol max-543, min- 124. In the postoperative period, an improvement in the general condition was observed already on the 2nd day, and the average bilirubin level in the postoperative period was 149 ±24 mmol/l with a tendency to decrease with further dynamic, and in subsequent dispensary observation. The length of stay in the hospital was 4 days - 2 patients, 7 days - 6 patients, 10 days - 9 patients, 20 days - 2 patients. Due to cholangitis, patients stayed for more than 10 days.

Subsequently, after the bilirubin level decreased to normal levels, four patients underwent radical liver resection.

**Conclusions:** Percutaneous transhepatic cholangiostomy is one of the publicly available, widespread and effective methods of surgical treatment of patients with obstructive jaundice of alveococcal origin, allowing to achieve adequate drainage of the bile ducts. At the moment, surgery is one of the stages of treatment for patients with liver alveococcosis. In the first case, this is preparation before radical liver resection, in the second case, this is a palliative operation in inoperable patients who are indicated for liver transplantation.

**Keywords:** Jaundice, Comon hepatic duct, Endobiliary methods, Treatment of patients

## PE-15

### Risk Factor for Conversion Additional Port in Single-Incision Laparoscopic Cholecystectomy in Patients with Acute Cholecystitis

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**Aims:** Laparoscopic cholecystectomy has been perceived as the standard operation of benign gallbladder diseases. Single-incision laparoscopic cholecystectomy (SILC) is also considered safe and feasible surgical methods that provides comparable results. However, some patients with acute cholecystitis require conversion additional port during the surgery, we focus on risk factor for conversion additional port in SILC with acute cholecystitis patients.

**Methods:** From March 2020 to September 2023, totally 104 acute cholecystitis patients underwent SILC. During this period, ten patients required an additional port, and no patient required conversion to open cholecystectomy.

**Results:** Conversion to one additional port rate was 9.62%. In logistic regression analysis for the risk of additional port, high C-reactive protein (CRP) values (> 8.0 mg/dl) (odd ratio=6.09, *P*-value=0.040), intraoperative much bleeding (> 15ml) (odd ratio=5.40, *P*-value=0.014) and bile spillage event (odd ratio=6.93, *P*-value=0.029) were significantly correlated with the need for an additional port.

**Conclusions:** SILC is a feasible and safe method for acute cholecystitis. Acute cholecystitis with severe inflammation indicated by high CRP predicts the need for an additional port. Intraoperative much bleeding and bile spillage is also predictive factors for additional port insertion, because of inadequate visualization of the Calot's triangle.

**Keywords:** Cholecystectomy, Silc, Additional port

## PE-16

### Features of Choosing a Method for Emergency Laparoscopic Cholecystectomy in Patients with Chronic Diffuse Liver Diseases

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**Aims:** To determine the features of choosing the method of emergency laparoscopic cholecystectomy in patients with chronic diffuse liver diseases.

**Methods:** The results of laparoscopic cholecystectomy in 88 patients with acute calculous cholecystitis against the background of chronic diffuse liver diseases, operated on during the period 2005-2022, are summarized. Alcoholic liver disease occurred in 13 (17.8%), viral hepatitis (C and B) - in 52 (59.1%) and liver cirrhosis (16 - viral and 7 - alcoholic etiology) - in 23 (26.1 %) of patients. The destructive form of calculous cholecystitis occurred in 67.0% (n=59) of patients.

**Results:** Emergency laparoscopic cholecystectomy was performed in 26.1% of patients, urgent – 46.6% and delayed – 27.3%. Laparoscopic cholecystectomy in 20.4% was accompanied by increased bleeding from the gallbladder bed. Conversion was performed in 3.4% patients. In other cases, bleeding from the gallbladder bed was stopped using Tacho-Comb plates and application of Tugin a solution. In all cases, the operations are completed by taking a biopsy from the liver tissue. In the postoperative period, 19.3% patients had complications characteristic of diffuse liver pathologies, in the form of various stages of hepatocellular insufficiency, hypocoagulation disorders, worsening dysproteinemia, hypoalbuinemia and increased transaminase activity. Death was observed in 1.1% patient. In the pre- and postoperative periods, patients underwent targeted correction of the functional state of the liver.

**Conclusions:** Laparoscopic cholecystectomy in patients with chronic diffuse liver diseases helps reduce complications and postoperative mortality. However, it is necessary to observe the specifics of the method and the corresponding pre- and postoperative corrections.

**Keywords:** Atypical laparoscopic cholecystectomy, Chronic diffuse liver diseases, Liver cirrhosis

## PE-17

### Indicator for Prevention Elderly Disease of "Silent Disease" Pancreatic Cancer in Indonesia: Systematic Review

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**Aims:** In Indonesia itself, there are many cancer patients. GLOBOCAN 2018 recorded at least 4,940 patients and ended with the death of 4,812 people. This cancer is often nicknamed the "silent disease" because it has no specific signs or symptoms. But apart from that, pancreatic cancer can be recognized early in its development by consulting a doctor. This study aims to describe the reduction in pancreatic cancer patients by knowing early prevention methods.

**Methods:** This research is a review using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA METHOD) Systematic Mapping Study model. The first step was to collect several journals with the keyword Hematology as the focus of discussion. The journals collected were journals published from 2010-2023.

**Results:** Based on a study provides results regarding the pattern of pancreatic cancer patients, showing that the number of patients aged 50-60 is an age that is vulnerable to experiencing pancreatic problems with symptoms of fever accompanied by body heat (Oktavia et al. 2020). A similar study was also carried out by (Irmayani et al. l 2017), who analyzed a 58-year-old patient with initial symptoms of fever accompanied by yellow eyes. The physical condition showed that the patient was in average condition without any significant indications.

**Conclusions:** Nutritional therapy is an excellent method to help prevent and keep the pancreas healthy. A balanced intake of supplements and calories can help stabilize the function and work of the pancreas in producing enzyme glands, which are channelled to the human body's digestive tract.

**Keywords:** Pancreas disease, Surgery, Cancer

## PE-18

### To Identify the Cause of Gallstones and Conduct a Chemical Analysis of Them

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**Aims:** Gallbladder may develop hardened deposits of digestive fluid called gallstones.Determining the chemical makeup of gallstones in the local environment is crucial for identifying aetiopathogenic variables, which are then helpful in putting preventative and therapeutic measures into action.

**Methods:** Between 2021 and 2023, a cross-sectional study was carried out at the central diagnostic laboratory and research center. Personal demographic information, including daily routines, was collected with the appropriate authorization. Following a cholecystectomy, 117 patients with gallstone disease were included in the research. The precipitation method, x-ray diffraction (XRD), and fourier-transform infrared (FTIR) spectroscopy were used to evaluate the chemical composition of stones.

**Results:** Female patients had a higher frequency of gallstones (65.7%) compared to male patients (34.3%). Ten of the 107 patients declined to provide their personal demograpic information and gallstones for examination. A total of 58 patients presented with mixed stones consisting of calcium carbonate, calcium bilirubinate, and cholesterol; 42 patients had cholesterol stones, and 7 individuals had pigmented stones having the same chemical composition.In 22% of the stones, bilirubin was detected, but cholesterol made up the majority of the chemical composition (78%).Gall stones was confirmed by FTIR and XRD analysis

**Conclusions:** Cholesterol is frequently present in gall stones, either by itself or in conjunction with bilirubin or calcium carbonate. There was no statistically significant correlation seen between cholecystectomy and hypertension. We may change our lifestyles to prevent gallstones by using this info. Even though serum cholesterol is within normal limits, we still need

to be aware of this and use advanced screening techniques.

**Keywords:** FESEM, XRD, GALL STONE,

## PE-19

### Gallbladder Clear Cell Carcinoma: A Case Report

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**Aims:** Incidence of 6500 cases annually in the United States, gallbladder cancer is the fifth most common gastrointestinal tract malignancy in this country. Incidence increases with age and is two to six times higher in women than in men.

**Methods:** Case Presentation: A 54 years old female, with no prior medical conditions presented with a 10 days history of upper abdominal pain. Last 4 days ago right abdomen upper quadrant pain, vomiting. Routine hematological leukocytosis and biochemical tests were CRP increased. An abdominal ultrasound revealed the gallbladder is enlargement, about 6.0 cm × 3.0 cm like the mudstone in the gallbladder. GB wall thickening/double. Common bile duct is dilated 1.2 cm. Computed tomography imaging: Moderate thickening with surrounding mild edematous changes in wall of the gallbladder. Size of the GB is moderated dilated with diffuse sludges. IHBD is no dilated; CBD is mild dilated 1.2 cm and no sign of biliary tract obstruction. An open cholecystectomy, upon pathologic investigation, the morphologic and immunophenotypic features supported a diagnosis of clear cell variant of gallbladder carcinoma.

**Results:** Clear cell gallbladder carcinoma was first reported in 192. Clear cell carcinoma represents on average over 90% of all malignancies of the kidney. Approximately 20% to 30% of patients with clear cell carcinoma have metastatic disease at presentation and nearly 50% of patients with advanced disease die within 5 years of diagnosis.

**Conclusions:** Our team diagnosed during surgery and histological analysis. As a result of the surgery patient was completely healed and discharged from hospital.

**Keywords:** Clear cell carcinoma, Intraoperative cholangiogram, Gallstone disease

## PE-20

### Muscle Splitting Mini Cholecystectomy

Ashish Prasad Rajbhandari

GI And General Surgery, Stupa Hospital, Nepal

**Aims:** Muscle splitting mini cholecystectomy is an alternative option for open cholecystectomy. It offers less postoperative pain. In our hospital, muscle splitting technique was done in 40 consecutive open cholecystectomy cases.

**Methods:** June 2016 to December 2022, 40 consecutive patients underwent the open muscle splitting cholecystectomy. 33 were female. Age range: 19-83 years. 1 patient had BMI:44 kg/m$^2$. 8 of preoperatively diagnosed complicated cholelithiasis: 2 cases each of empyema gallbladder, chronic cholecystitis and pancreatitis & 1 each of acute calculous cholecystitis and perforated gallbladder. Transverse skin incision in the right upper quadrant around the tip of 9th costal cartilage of 5 cm (mini cholecystectomy) except for complicated cases (up to 7 cm). After cutting the anterior rectus sheath, the rectus muscle was split and retracted before incising the posterior sheath and adjacent internal oblique, transversus abdominis and peritoneum. Drain was placed in the complicated cases.

**Results:** Duration of surgery ranged from 35-65 mins. Pain scale on 1st postoperative day: 4-6. Regular IV analgesia was stopped after 1st 24 hrs. Pain scale on 2nd postoperative day: 2-5. 6cases were discharged on the 1st post operative day; 31cases on the 2nd postoperative day. In 6 of the complicated cases (acute and chronic cholecystitis, empyema gall bladder and perforated gallbladder), drains were removed on the 3rd post operative day and were discharged after completion of a course of IV antibiotics for 5 days.

**Conclusions:** Muscle splitting cholecystectomy is an alternative to traditional open cholecystectomy with shorter convalescence period.

**Keywords:** Muscle splitting, Mini cholecystectomy

## PE-21

### Intraductal Papillary Neoplasm of the Bile Duct (Ipnb) With Invasion to the Stomach and Lef Lobe Atrophy - Case Presentation

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Departament of HBP surgery and Liver Transplantation, National Research Oncology Center, Kazakhstan

**Aims:** Intraductal papillary neoplasm of the bile duct (IPNB) is a rare neoplasm of the biliary tract. IPNB develops in any part of the biliary tree, displays papillary exophytic growth pattern. Here we present the clinical case of the patient with IPNB with invasion to the serous layer of the stomach and atrophy of the liver left lobe.

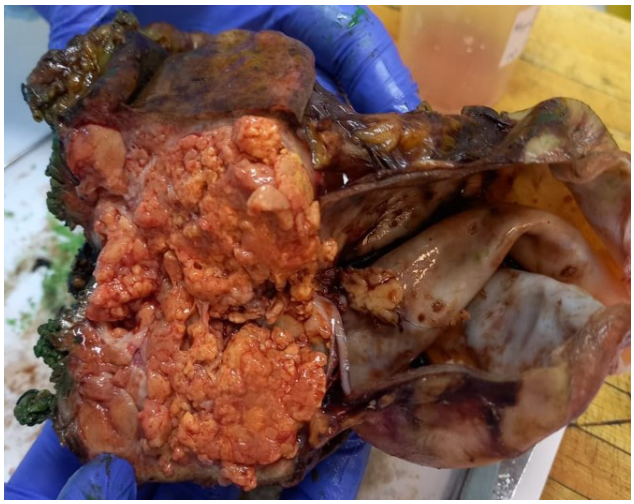
**Methods:** All data regarding patients were retrieved from electronic records

**Results:** 66-year-old male with a history of abdominal pain was admitted to our hospital. 12 month prior to hospitalization, he

was found with the lesion in the left lobe of the liver on abdominal ultrasonography. Abdominal computed tomography (CT) and magnetic resonance imaging (MRI) revealed solid soft tissue mass of the left lobe of the liver, irregular in shape, a cystic mass with a walled soft tissue continuing to the left of the lesion. Left liver parenchyma was almost completely atrophied. Resection of the left lateral sector of the liver with gastric serous layer desection, cholecystectomy, and standard lymphadenectomy were performed. Histological examination showed an intraductal papillary liver tumor associated with invasive G2 carcinoma (in the invasive component), biliary type. Invasive component within liver tissue. Retention cyst of the liver The resection margin is negative (R0). Lymph nodes without metastatic lesions. The postoperative period show no complications. The patient was discharged from the hospital on the 7th day after surgery. 3 month follow up showed no reccurence.

**Conclusions:** Intraductal papillary biliary neoplasm carries a risk of biliary obstruction and increases the risk of progression to invasive carcinoma. Radical liver resection is the treatment of choice, showing better survival. Accurate preoperative imaging evaluation and thorough intraoperative cholangioscopy evaluation are key to curative resection.

**Keywords:** IPMN-B, Liver resection, Cholangiocarcinoma,



## PE-22

### Percutaneous Transhepatic Endobiliary Interventions in Patients with Unresectable Cholangiocarcinomas Complicated by Mechanical Jaundice

Anastasiia Sochnieva[1],Valeriy Boyko[2,3], Yuriy Avdosyev[3], Volodymir Tkachenko[1,3], Vasyl Kritsak[1,3], Volodymir Ponomaryov[1], Pavlo Korzh[1,3]

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**Aims:** Literature sources describe the development of mechanical jaundice (MJ) in 40-67% of patients with malignant tumors of the biliary tract.

The purpose of this work is to study the results of using PTBD in patients with unresectable cholangiocarcinomas complicated by MJ.

**Methods:** The results of using PTBD in 62 patients with unresectable cholangiocarcinomas complicated by MJ, classified according to Bishmuth-Corlette were analyzed: I type was observed in 9 (14.52%), II - in 16 (25.81%), IIIA - in 10 (16.3%), IIIB – in 8 (12.9%), IV – in 13 (20.97%), distal cholangiocarcinoma in 6 (9.68%) patients. In 36 (58.1%) cases were performed external-internal PTBD (group 1), 26 (41.9%) – external PTBD (group 2).

**Results:** Complications directly related to PTBD were found in 13 patients (21.0%). In 7 (26.9%) patients after external PTBD and in 6 (16.7%) after external-internal PTBD. PTBD migration was observed in 5 (8.06%) patients, from the left lobe duct in 1 (1.6%) and from the right in 4 (6.4%) patients. Cholangitis developed in 2 (3.2%) patients after external-internal PTBD. Bile leakage into the abdominal cavity after PTBD in 1 (1.6%) patient. Hemobilia development was noted in 2 (3.2%) patients. In 3 (4.8%) cases, external PTBD placement was ineffective. External-internal PTBD was accompanied by a lower frequency of complications - 16.7% (group 1) compared to external PTBD - 26.9% (group 2). The mortality rate in group 1 was 8.33% compared to patients in group 2 - 11.54%.

**Conclusions:** In the absence of anatomical and technical limitations, it is more effective to use external-internal PTBD in the treatment of patients with unresectable cholangiocarcinomas complicated by MJ, which is more physiological and functional.

**Keywords:** Mechanical jaundice, Cholangiocarcinoma, Percutaneous transhepatic endobiliary interventions

# Surgery, Technical Issues

## PE-01

### Comparative Study of Proficiency Improvement in ArtiSential Instruments According to Conventional Laparoscopic Surgery Experiences

Seoung Yoon Rho[1], Munseok Choi[1], Sung Hyun Kim[2], Seung Soo Hong[2], Hung Il Kim[2], Chamg Moo Kang[2]

[1]Surgery, Yongin Severance Hospital, Republic of Korea, [2]Surgery, Severance Hospital, Republic of Korea

**Aims:** ArtiSential Instrument

**Methods:** From June to November 2023, 18 participants with experience in conventional laparoscopic surgery enrolled in PEG transfer and Suture training using ArtiSential instruments. Participants were categorized into three groups: Novice, Intermediate, and Expert. We assessed the time taken to accomplish PEG transfer and suturing in various directions and compared the results among the three groups.

**Results:** There were 6 surgeons in the novice group, each having experience with conventional laparoscopic surgery of fewer than 50 cases. All surgeons were right-hand dominant. In terms of PEG transfer timing analysis, there are significant differences between the three groups in the 1st and 2nd trials. In all three groups, the suture times at 3 o'clock and 5 o'clock were consistently lower compared to the 1 o'clock and 12 o'clock directions. As the trials progressed in all three groups, the time decreased for suturing in all directions. Among them, all participants in the novice group had reduced suture times at 3 o'clock and 5 o'clock direction.

**Conclusions:** The ArtiSential instrument is relatively easy to adapt to, even if you have novice surgeon with conventional laparoscopic surgery. With its articulating movement, sutures in the 3 o'clock and 5 o'clock directions, which can be challenging for right-handed surgeons, can be easily performed. Future research on large cohort e learning curve study is needed.

**Keywords:** Artisential instrument

## PE-02

### Tumor Thrombectomy via Surgically Reopened Umbilical Vein as a Palliative Treatment for Patient with Advanced Hepatocellular Carcinoma

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National Hospital of Tropical Diseases, Vietnam

**Aims:** Portal vein tumor thrombosis is an ominous prognosis factor in patients with HCC. It can cause deadly complications such as liver failure, GI bleeding due to portal hypertension

**Methods:** We present a case of a patient with huge right liver tumor and multinodular in the left with an extensive portal venous tumor thrombus extending into the main trunk and left portal branch. He had already been resistance to immunotherapy (Atezolizumab plus Bevacizumab) and HAIC. The CT Scanner showed that the tumor thrombosis increased rapidly, to prevent the complications, we performed the surgical tumor thrombectomy using a balloon catheter push to push the thrombus via reopened umbilical vein and ligated the right portal vein.

**Results:** The operated time was 200 minutes with estimated blood loss 550ml. The patient recovered well with no complication. The post-operation CT Scanner show no thrombus in the main portal trunk and the left branch, with the left liver volume increase from 552ml to 705ml after 17 days. He was continued to treat with Levatinib and Radiotherapy. 10 months after the operation, he is treated with HAIC again and his health is stable.

**Conclusions:** Tumor thrombectomy via the umbilical vein is safe and can be apply as a palliative treatment for patients with advanced HCC.

**Keywords:** Portal vein tumor thrombectomy, Advanced hepatocellular carcinoma

## PE-03

### Systematic Assessment of Surgical Techniques for Complex Liver Resections

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**Aims:** This systematic review aims to evaluate the efficacy, safety, and perioperative outcomes of various surgical techniques for complex liver resections. The primary research question is: What are the comparative outcomes of laparoscopic and robotic-assisted techniques versus traditional open surgery in complex liver resections?

**Methods:** A comprehensive literature search was conducted using PubMed, Scopus, and relevant databases up to January 2024. Studies comparing laparoscopic, robotic-assisted, and open surgical techniques for complex liver resections were included. Data extraction included surgical outcomes such as operative time, blood loss, length of hospital stay, morbidity, mortality, and oncological outcomes. Quality assessment was performed using appropriate tools.

**Results:** 18 studies met the inclusion criteria and were analyzed. Findings indicate that laparoscopic and robotic-assisted techniques offer shorter operative times, reduced blood loss, and shorter hospital stays compared to open surgery. Moreover, robotic-assisted techniques may provide improved surgical precision and dexterity. However, open surgery remains preferred in certain cases due to technical complexities and patient factors.

**Conclusions:** This systematic assessment highlights the advantages of laparoscopic and robotic-assisted techniques over traditional open surgery in complex liver resections, including decreased operative time, blood loss, and hospital stay. However, individual patient factors and technical considerations should guide the selection of the most appropriate surgical approach. Further research is warranted to refine surgical management strategies and optimize patient outcomes.

**Keywords:** Surgical techniques, complex liver resections, Laparoscopic surgery, Robotic-assisted surgery

## PE-04

### Early Outcomes of Single Port Robotic Left Lateral Sectionectomy

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**Aims:** Laparoscopic left lateral sectionectomy (L-LLS) is a cornerstone procedure in minimal hepatobiliary surgery that is frequently employed for various benign and malignant liver lesions. But, The advantages of robotic platforms for left lateral sectionectomy (LLS) remain controversial. Therefore, this study aimed to contribute to the existing body of knowledge by conducting a comprehensive evaluation of the surgical outcomes in patients who underwent LLS using either a single-port robotic or laparoscopic technique.

**Methods:** Between January 2020 and June 2023, 12 patients underwent Single-port robotic LLC(SPR-LLS) and 30 underwent Laparoscopic LLS(L-LLS). Patients with Child-Pugh class A or B cirrhosis and lesions without major vessel or hilar structure invasion were selected for surgery. In total, 12 patients in the SPR-LLS group were matched in a 1:2 ratio with 24 patients in the L-LLS group using Propensity score matching analysis. The same surgeon performed all laparoscopic and robotic surgeries.

**Results:**

Table 1. Patients' baseline characteristics after propensity score matching

| Characteristic | SPR-LLS group | L-LLS group | P-value |
|---|---|---|---|
| No. of patients | 12 | 24 | |
| Age (yr) | 59.6 ± 8.7 | 61.0 ± 11.8 | 0.723[a] |
| Sex, male:female | 7:5 | 15:9 | >0.999[b] |
| Body mass index (kg/m$^2$) | 23.6 ± 2.3 | 24.3 ± 2.7 | 0.445[a] |
| ICG-R15 | 12.2 ± 4.1 | 14.0 ± 7.5 | 0.362[a] |
| Total bilirubin (mg/dL) | 0.64 ± 0.3 | 0.71 ± 0.6 | 0.810[a] |
| PT (INR) | 1.0 ± 0.1 | 1.1 ± 0.2 | 0.357[a] |
| Platelet count (×10$^3$/μL) | 187.6 ± 42.9 | 179.3 ± 65.0 | 0.839[a] |
| α-FP | 17.2 ± 7.1 | 76.7 ± 183.9 | 0.127[a] |
| PIVKA | 25.6 ± 12.6 | 36.2 ± 183.9 | 0.171[a] |
| Albumin (mg/dL) | 4.2 ± 0.4 | 4.1 ± 0.3 | 0.247[a] |
| Liver cirrhosis | | | 0.797[a] |
| CTP A | 12 (100) | 22 (91.6) | |
| CTP B | 0 (0) | 2 (8.4) | |
| ASA PS classification | | | 0.994[c] |
| I | 8 | 17 | |
| II | 4 | 7 | |
| III | 0 | 0 | |
| Previous abdominal surgery | 2 (16.7) | 5 (20.8) | >0.999[b] |

Table 2. Peri- and postoperative details of patients after propensity score matching

| Variable | SPR-LLS group (n = 12) | L-LLS group (n = 24) | P-value |
|---|---|---|---|
| Operative time (min) | 151.8 ± 36.5 | 115.1 ± 32.7 | 0.004[a] |
| Estimated blood loss (mL) | 121.2 ± 29.9 | 175.4 ± 104.4 | 0.025[a] |
| Pringle maneuver | 9 (75.0) | 12 (50.0) | 0.282[a] |
| Transfusion | 0 (0) | 2 (8.3) | 0.797[a] |
| Tumor size (cm) | 2.5 ± 1.3 | 2.8 ± 1.5 | 0.077[a] |
| Negative of resection margin | 12 (100) | 24 (100) | >0.999[a] |
| Pathology | | | |
| HCC | 11 | 22 | |
| CCC | | 1 | |
| Combine HCC and CCC | 1 | 1 | |
| Overall complication, CD grade | 1 (8.3) | 3 (12.5) | 0.966[b] |
| ≤II | 1 (8.3) | 3 (12.5) | |
| ≥III | 0 (0) | 0 (0) | |
| Complication details | | | |
| Ascites | 0 | 0 | |
| Pleural effusion | 0 | 0 | |
| Wound infection | 0 | 2 | |
| Fluid collection at operation site | 1 | 1 | |
| Incisional hernia | 0 | 0 | |
| Postoperative hospital stay (day) | 5.1 ± 1.6 | 6.2 ± 1.6 | 0.045 |

**Conclusions:** SPR-LLS using the da Vinci SP system was comparable to L-LLS in terms of surgical outcomes. Robotic procedures are associated with less blood loss and shorter postoperative length of stay. These findings suggest that minor hepatic resection with the da Vinci SP system is technically feasible and safe for selected patients.

**Keywords:** Robotic surgery, Liver cancer, Minimal Invasive surgery, Surgical outcome

## PE-05

### Our Experience in the Surgical Treatment of Liver Alveococcosis and Its Complications

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**Aims:** Analysis of the results of surgical treatment of alveococcosis

**Methods:** From April 2009 to February 2024, there were 573 patients with liver alveococcosis in the Department of Surgical Gastroenterology and Endocrinology of the National Hospital, of which 512 were operated on. The age of the patients ranged from 9 to 73 years, the average age was 37±2.3.

**Results:** Out of 512 operated patients, 18 cases were explorative, resectability was 86.2%. Extensive liver resections - 234 (47.3%), of which right-side hemihepatectomy (RHHE) - 127 (54.3%), extended right-side hemihepatectomy (ERHHE) - 43 (18.3%), extended left-side hemihepatectomy (RLHHE) - 22 (9.4%), LHH E – 42 (18%). Non-anatomical liver resections (segmentectomy and bisegmentectomy) – 260, which amounted to 52.7%.

Average volume of blood loss: for the period 2009-2013. – 2812±205 ml, for the period 2014-2018. – 1725±198ml, for the period 2019-2023. - 1145±110ml.

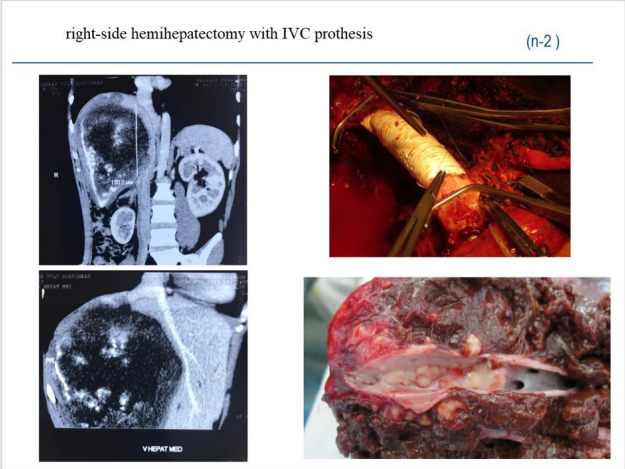
342 (61.4%) patients underwent radical surgery. Palliative surgery was performed in 215 patients (38.6%). There was no intraoperative mortality.

The overall frequency of complications is 69 (29.5%): reactive pleurisy - 22 (9.3%), liver failure - 20 (8.8%), bilateral pneumonia - 4 (1.6%), biloma - 7 ( 3.1%), bile leakage - 14 (5.7%), gastrointestinal bleeding - 1 (0.5%), portal vein thrombosis (during surgery) - 1 (0.5%), hospital mortality - 4 (1.7%).

Patients with a complicated form of alveococcosis and those who underwent non-radical surgery in the postoperative period received antiparasitic therapy with the drug albendazole at 10-12 mg per kg/body weight per day, in two doses after meals, according to the traditional regimen.

**Conclusions:** The relevance of liver alveococcosis increases

annually due to the high infection rate of the population in endemic areas of Kyrgyzstan. The percentage of complicated forms of the disease is high - 52%. The only and radical method of treatment remains resection of the liver within healthy tissue. In complicated forms of liver alveococcosis, palliative liver resections and palliative operations (PPS) prolong and improve the quality of life.




**Keywords:** liver Alveococcosis, Surgical treatment of alveococcosis, Liver resections, Liver

## PE-06

### Radical Liver Resections during Repeated Surgical Intervention of Liver Alveococcosis

**Edir Surov**, Bebezov B.Kh., Umetaliev T.M., Mamashev N.D., Murzaliev E.M., Marshankulov R.I.

Department of Hospital Surgery, Kyrgyz-Russian Slaivc University, Kyrgyzstan

**Aims:** To study the result of repeated surgical treatment of patients with liver alveococcosis

**Methods:** The paper presents repeated surgical treatment of 38 patients who were hospitalized in the Department of Surgical Gastroenterology and Endocrinology of the National Hospital from 2009 to 2023 for liver alveococcosis and its complications. During repeated surgical interventions, we performed radical liver resections in 13 cases (34.2%). Radical liver resections during repeated interventions were performed at various times after the first operation - from 1 month to 6 years. In 13 cases of radical liver resection during repeated interventions, exploratory laparotomies were performed among primary operations in 4 cases (30.8%), and palliative laparotomies were performed in 7 cases (53.8%). In 2 cases (15.4%) lumps of the parasitic tumor and marsupialization (drainage) of the cavities were performed.

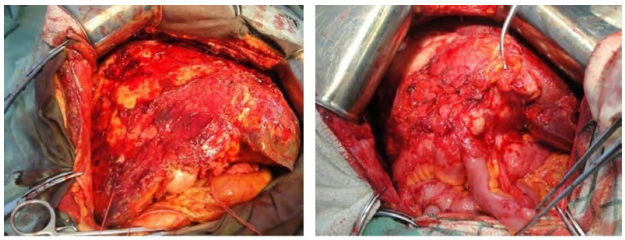
Upon admission to the hospital, 5 patients (38.5%) had alveococcal germination of the caval and/or portal portals of the liver, among which obstructive jaundice was noted in 1 case (7.7%). In 5 cases (38.4%) there were invasions of other organs by the parasitic node. In 4 cases (30.7%) patients were admitted to the hospital due to relapse of the disease.

**Results:** The volumes of radical liver resections during repeated surgical interventions were as follows: extended right hemihepatectomy – 15.4%; extended left hemihepatectomy –7.7%; resection of the central segments of the liver –23.1; non-anatomical resections of affected liver segments – 23.1%. In 11 cases (84.6%), repeated operations were associated with technical difficulties due to the development of a pronounced adhesive process after the initial operations and changes in the topographic-anatomical relationships of the vascular-ductal structures of the liver. Intraoperative blood loss averaged 638.4±40.0 ml per patient.

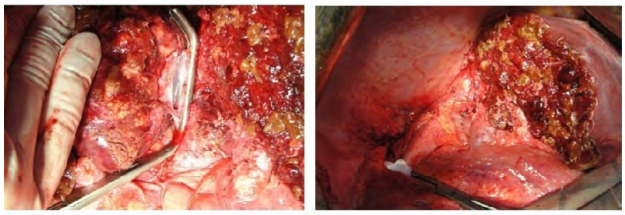
**Conclusions:** Thus, an analysis of our own clinical material revealed the following indications that allow radical resections to be performed for parasitic liver disease:

- the volume of the remaining liver parenchyma must be at least two segments;
- the presence of resectable areas of the parasitic process that have grown into organs adjacent to the liver
- absence of severe concomitant pathology;
- germination of the Glissonian or caval hilum of the liver by a parasitic process is not always an absolute contraindication to radical resection.
- The final decision on resectability must be made intraoperatively!!!

**Keywords:** Liver alveococcosis, Repeated surgery, Liver resections, Echinococcus multilocularis



An adhesive process that developed after initial operations on the liver: in the suprahepatic space; in the subhepatic space



Radical resection of the liver with marginal resection of the inferior vena cava (operation stages): application of a Satinsky vascular clamp; application of continuous vascular sutures; view after applying vascular sutures

## PE-07

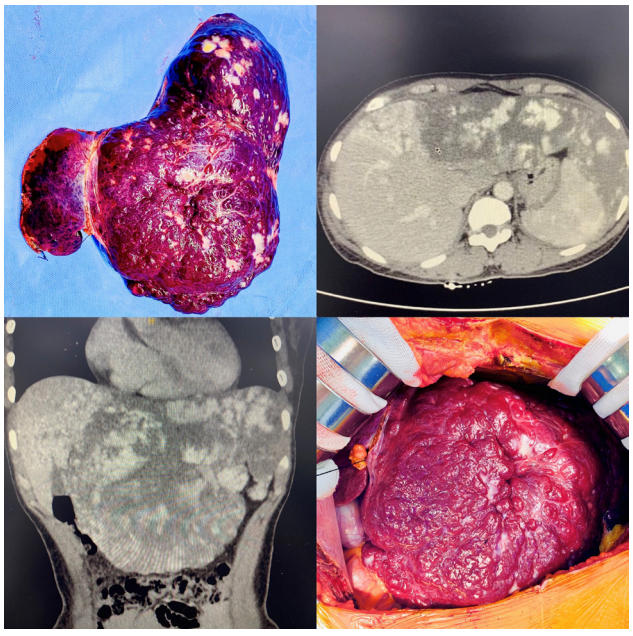
### 9-Year Outcomes after Liver Resection for Giant and Enormous Hepatic Hemangioma: A Single Center Experience in Vietnam

Thi The Trinh Nguyen

Vin University Vietnam

**Aims:** Hemangioma is the most common benign liver tumor. Most patients with hepatic hemangioma were asymptomatic. When their largest diameter is more than 10 cm, they are classified as giants. Known as enormous haemangiomas, these extremely rare presentations measure more than 15 cm. Giant and enormous hepatic cavernous hemangiomas are often symptomatic and require surgical management. This study aimed to describe the clinical findings, diagnostic approach, risk factors, and evaluate the outcome of surgical treatment for giant and enormous hepatic hemangioma.

**Methods:** We performed a retrospective analysis of patients with giant and enormous hepatic hemangioma treated in the Department of Hepato-Biliary-Pancreatic Surgery, Military Central Hospital 108 from September 2015 to December 2023. The medical records of each patient were reviewed to obtain the clinical and surgical data.



**Results:** Among the 23 patients who received elective surgery for giant and enormous hepatic hemangioma, 20 patients underwent open hepatectomies and 3 underwent laparoscopic hepatectomies. The median diameter of giant hepatic hemangioma was 13,5±8,7 cm (10 - 28 cm). Indication of surgery management: abdominal pain (86.9%), rapid growth (13.1%). Enucleation was performed for 10 (43,7%) patients and anatomical liver resection was required in 13 (56,3%) patients. The median blood transfusion was 202.86±211.21 ml, the need of blood transfusion was required in 2 (8,6%) patients, and the median operation time was 143.13±44.23 min. Postoperative complications occurred in 2 (8.6%) patients, including: bile leakage 1 (4.3%) patients, bleeding 01 (4.3%) patient. The average length of hospital stay was 8.53±1.76 days.

**Conclusions:** The main indication for surgery is giant and enormous hepatic cavenous hemangioma, with or without symptoms of tumors. Both enucleation and liver resection by laparoscopic and open procedures are safe and effective surgical treatments for giant and enormous hepatic hemangiomas.

**Keywords:** Giant and enormous hepatic hemangioma

## PE-08

### Early Experience: Simultaneous Ipsilateral Portal Vein And Hepatic Artery Ligation for Rapid Quantitative Liver Hypertrophy

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**Aims:** This study aims to evaluate the effectiveness of simultaneous ipsilateral portal vein and hepatic artery ligation as a method for rapid quantitative liver hypertrophy.

**Methods:** From January 2010 to December 2023, 48 patients who underwent two-stage hepatectomy, including Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS), were enrolled. The patients were divided into three groups: Right Portal Vein Ligation or Embolization (PVO) group, ALPPS group, and Simultaneous Ipsilateral Portal Vein and Hepatic Artery Ligation (SPALQ) group. Perioperative liver volume and outcomes were retrospectively reviewed.

**Results:** PVO was performed in 22 patients, ALPPS in 19 patients, and SPALQ in 7 patients. The median interval between the first and second hepatectomies was 30.9±17.41 days for PVO, 29.5±13.04 days for ALPPS, and 12.3±2.25 days for SPALQ ($P$<0.001). The future liver remnant hypertrophy ratio (FLR/TLV) from the first procedure to the preoperative CT before the second procedure was 37.9±5.85% for PVO, 39.2±6.53% for ALPPS, and 46.1±5.67% for SPALQ ($P$=0.006).

**Conclusions:** The SPALQ procedure is safe and feasible, proving effective in facilitating rapid contralateral liver regeneration.

**Keywords:** Alpps, Two stage hepatectomy

## PE-09

### Extensive Liver Resections for Focal Lesions

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Department of Hospital Surgery, Kyrgyz-Russian Slavic University, Kyrgyzstan

**Aims:** to evaluate the immediate results of surgical treatment of focal liver lesions.

**Methods:** For the period from April 2009 to February 2024. at the clinic named after I.K. Akhunbaeva NH was treated - 691 patients with focal liver lesions. The patients were distributed according to the nature of the focal disease as follows: liver alveococcosis - 573, hemangiomas - 38, colorectal cancer metastases - 36, HCC - 36, cholangiocellular cancer - 4 and FNH - 4. The age of the patients ranged from 16 to 73 years, the average age was 44±2.3

**Results:** Of 691 patients, 630 were operated on, extensive liver resections were performed in 271 patients (45.1%) (the structure is presented in Table No. 1), atypical liver resections were performed in 331 (54.9%). Exploratory laparotomy - 29 cases. Resectability was 87.0%.

The average volume of blood loss was 1145±110 ml, minimum 200 ml. There were the following types of complications in the postoperative period: reactive pleurisy - 22 (9.3%), liver failure - 20 (8.8%), bilateral pneumonia - 4 (1.6%), biloma - 7 (3.1%), bile leakage - 14 (5.7%), gastrointestinal bleeding - 1 (0.5%), portal vein thrombosis (during surgery) - 1 (0.5%), hospital mortality - 4 (1.7%).

| Type of resection | N | With resection of the bile ducts | With portal vein resection | With IVC resection |
|---|---|---|---|---|
| RHHE | 141 (52,0%) | 6 | 15 | 8 |
| LHHE | 52 (19,2%) | 2 | 4 | |
| ERHHE | 56 (20,7%) | 5 | 4 | 3 |
| LHHE | 22 (8,1%) | 1 | 4 | |
| Total | 271 (100%) | 14 (5,2%) | 27 (9,9%) | 11 (4,1%) |

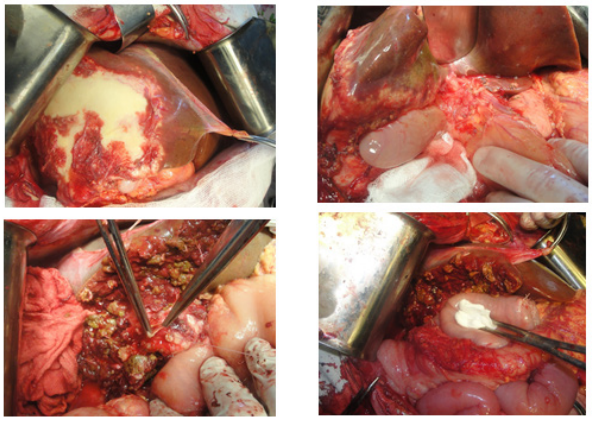
**Conclusions:** Based on a large clinical material (234 extensive liver resections), the experience of treating patients with focal liver lesions is summarized.

The main technical point of reducing operational blood loss is to perform extensive liver resections in an anatomical manner.

Complete vascular isolation of the removed part of the liver: ligation of the portal pedicle and hepatic vein before the stage of separation of the liver parenchyma (portal method), use of the Pringle maneuver during surgery, intraoperative study of hepatic blood flow and clarification of the extent of resection using ultrasound, complete vascular isolation of the liver during extensive resections accompanying resection and reconstruction of the hepatic veins or IVC wall can significantly reduce the risk of massive surgical blood loss.

**Keywords:** Liver focal lesion, Extensive liver resections, Liver alveococcosis, HCC, CCC, MTS

Extensive liver resection with resection of hepaticocholedochus and application of GEA to Roux Y (n=14)



## PE-10

### Prevalence of Variations of the Extra Hepatic Biliary Duct and Vascularization in the Mongolian

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**Aims:** This study was to record the variations in origin of the cystic duct from common bile duct and its cystic artery variations, which descent from different sources and its location in relation to the biliary ducts among Mongolian people and to compare the variations between the sexes and different races

**Methods:** 84 cadavers were examined in the dissection room. The anatomy of the extra biliary ducts and the cystic artery were examined. Variations in the origin and position of the cystic duct and cystic artery from the nearby vessels were noted and the number of cases compared between males and females

**Results:** Mongolians the main length of gallbladder is 10.76±0.24 cm, the main width of gallbladder is 3.97±0.10 cm, the main length of cystic duct is 4.00±0.07 cm, the main diameter of cystic dust is 0.37±0.01cm, the main length of common bile duct is 7.74±0.08 cm, the main diameter of common bile dust is0.87±0.01 cm. Regarding the variation of the cystic duct in Mongolian subjects the following results were obtained: there are 6 types of variation determined. The variation of cystic duct in the 84 Mongolian cases investigated was 1st

type in69%, 2nd type in9.5%, 3rd type in 5.9%, 4th type in 8.3%, 5th type in 5.9% and 6th type in1.1%

**Conclusions:** Mongolians the main length of gallbladder is10.76±0.24 cm, the main width of gallbladder is3.97±0.10cm, the main length of cystic duct is 4.00±0.07 cm, the main diameter of cystic dust is 0.37±0.01cm, the main length of common bile duct is7.74±0.08 cm, the main diameter of common bile dust is 0.87±0.01cm

**Keywords:** Bile duct, Cystic dust variation, Cystic artery variation

## PE-11

### First Case of Pure Laparoscopic Right Hepatectomy (PLRH) at Second State Central Hospital: Samsung Medical Center Approach

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**Aims:** Hemangioma is the most common type of BLT arising in the liver and is frequently detected incidentally during imaging examinations.

**Methods:** The patient was placed in a supine position, with his legs apart, in the reversed French position. The right hepatic artery (RHA) was identified and divided, followed by the right portal vein (RPV). The right liver was then mobilized by dividing the right coronary ligament and triangular ligament, which were actually located on the patient's left side. The ischemic demarcation line on the liver was marked with electrocautery. The liver was transected using a Thunderbeat system (Olympus, Tokyo, Japan). The right Glissonean pedicle was divided with an automatic suturing device. Further parenchyma transection was completed after placing a nelaton tube into the anterior portion of the retrohepatic inferior vena cava (IVC). The right hepatic vein (RHV) was divided with an automatic suturing device. The right liver was placed in an endo-bag and extracted through a Pfannenstiel incision site.

**Results:** We report a case of a giant hepatic hemangioma diagnosed in a 69-year-old man who was hospitalized for intermittent, dull, right upper quadrant abdominal pain. The patient underwent surgery, which was the first case of laparoscopic right hepatectomy (LRH) at the Second State Central Hospital. He underwent a LRH on March 6, 2023, and was discharged on postoperative day 7 without any complications.

**Conclusions:** PLRH is a challenging procedure that requires expertise, and its performance is limited to only a few institutions because of its inherent technical difficulties.

**Keywords:** Pure laparoscopic right hepatectomy, Hemangioma, Laparoscopic right hepatectomy

## PE-12

### Poshepatectomy Liver Failure and Its Predictors: A Single Center Experience in Kazakhstan

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**Aims:** This review aims to share the experience of managing PHLF in a single center.

**Methods:** In the period from 2020 to 2023, 133 liver resections were performed at the National Scientific Oncological Center in Astana. A retrospective analysis of patient data was performed.

**Results:** There were 9 cases of PHLF with the following diseases: 5 PCCC, 2 Angiosarcoma, 1 HCC, 1 CRC LM. With an average age of patients of 51.2 years, only 2 (22.2%) were over 65 years old, 3 (33.3%) were men (Table 1). Complications were observed with any ECOG and MUST status, however, the more severe the patient's initial condition was assessed, the more severe the picture of PHLF was. Cholestasis, which occurred in more than half of the cases, was displayed in cases of PHLF grade B, C. Among surgery-related risk factors was detected a relationship between the extent resection and presence of liver failure, such as left trisecionectomy, left hepatectomy with vascular resection, as well as a blood loss volume of more than 1000 ml. According to the Clavien-Dindo gradation I – 2, II – 4, IIIa – 1, V – 2. Of the 2 lethal cases, one had all the predictors: Klatskin tumor, viral hepatitis B, cholestasis, MUST 4, ASA 3, left hemihepatectomy with resection of the portal vein and common bile duct with blood loss of more than 1000 ml. The second included an extended left hemihepatectomy with caudal lobectomy, also for PCCC. The case was complicated by hyperacute thrombosis of the HA and PV; relaparotomy and thrombectomy were performed. Despite this, MODS developed, from which she died on the 3rd day.

**Conclusions:** Limitations of this study are its retrospective design and small number of patients. However, these results may provide the basis for a future prospective randomized study to determine predictors of PHLF and management options for such patients.

**Keywords:** Posthepatectomy liver failure, Liver resections, Predictors, Single center experience

| Risk factors | Incidence out of total 10 | % | PHLF A | PHLF B | PHLF C |
|---|---|---|---|---|---|
| Patient related | | | | | |
| Age >65 | 2 | 22.2 | | 1 | 1 |
| Male gender | 3 | 33.3 | 1 | 2 | |
| Metabolic disorder | 1 | 11.1 | | | 1 |
| Pre chemo | 3 | 33.3 | | 2 | 1 |
| Cholangitis | 0 | | | | |
| Malnutrition | | | | | |
| 0 | 6 | 66.6 | 2 | 3 | 1 |
| 2 | 1 | 11.1 | | 2 | |
| 4 | 1 | 11.1 | | | 1 |
| 5 | 1 | 11.1 | | 1 | |
| ASA score | | | | | |
| I | 5 | 55.5 | 2 | 2 | 1 |
| II | 2 | 22.2 | | 2 | |
| III | 2 | 22.2 | | 1 | 1 |
| Liver-related | | | | | |
| Hepatitis | | | | | |
| CHB | 1 | 11.1 | | | 1 |
| CHB+HBD | 1 | 11.1 | 1 | | |
| Cirrhosis | 1 | 11.1 | | 1 | |
| Cholestasis | | | | | |
| Parenchymal (intrahepatic) | | | | | |
| Obstructive (extrahepatic) | 5 | 55.5 | | 5 | 5 |
| Surgery-related | | | | | |
| Complex surgery | 0 | | | | |
| Extent of resection | | | | | |
| Major | 5 | 55.5 | | 3 | 2 |
| Minor | 4 | 44.4 | 2 | 2 | |
| Blood loss >1000 ml | 3 | 33.3 | | 1 | 2 |
| Left hepatectomy | 4 | 44.4 | | 2 | 2 |
| Pringle duration (min) | | | | | |
| 10-15 | 2 | 22.2 | | 2 | |
| 15-30 | 3 | 33.3 | 1 | 1 | 1 |
| 30-45 | 1 | 11.1 | | 1 | |
| Complication | | | | | |
| Clavien-Dindo | | | | | |
| Grade I | 2 | 22.2 | 2 | | |
| Grade II | 4 | 44.4 | | 4 | |
| Grade IIIa | 1 | 11.1 | | 1 | |
| Grade V | 2 | 22.2 | | | 2 |

## PE-13

### Posthepatectomy Bile Leakage: A Single-Center Experience in Kazakhstan

**Adina Kulanbayeva**, Zhanat Spatayev, Abylaikhan Sharmenov

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**Aims:** One of the complications after resection, which significantly worsens the postoperative course, is bile leakage (BL). This study shows the experience of one center on this issue.

**Methods:** 133 liver resections were performed based on the National Research Oncology Center in Astana in the period from 2020 to 2023. All data were retrospectively analyzed.

**Table 1.**

| Variables | Number | % | PHBL A | PHBL B | PHBL C |
|---|---|---|---|---|---|
| Etiology | | | | | |
| PCCC | 3 | 21.4 | 1 | 2 | |
| ICCC | 3 | 21.4 | | 1 | 2 |
| HCC+CCC | 1 | 7.1 | | 1 | |
| GBC | 1 | 7.1 | | 1 | |
| CRC LM | 1 | 7.1 | | 1 | |
| Echinococcosis granulosus (EG) | 1 | 7.1 | | 1 | |
| Echinococcosis Multilocularis (EM) | 4 | 28.5 | 1 | 2 | 1 |
| Age >65 | 4 | 28.5 | 1 | 2 | 1 |
| EGOC | | | | | |
| ECOG 0 | 6 | 42.8 | 1 | 4 | 1 |
| ECOG 1 | 5 | 35.7 | | 4 | 1 |
| ECOG 2 | 3 | 21.4 | 1 | 1 | 1 |
| Malnutrition | | | | | |
| MUST 0 | 11 | 78.5 | 2 | 7 | 2 |
| MUST 1 | 1 | 7.1 | | | 1 |
| MUST 2 | 1 | 7.1 | | 1 | |
| MUST 3 | 1 | 7.1 | | 1 | |
| DiabetesMellitus | 3 | 21.4 | | 2 | 1 |
| Cirrhosis | 2 | 14.2 | | 2 | |
| Biliary Hypertension | 5 | 35.7 | 2 | 2 | 1 |
| Extent of operation | | | | | |
| Major resection | 10 | 71.4 | 2 | 6 | 2 |
| Minor resection | 4 | 28.5 | | 3 | 1 |
| Ultrasound device | 12 | 85.7 | 2 | 7 | 3 |
| Ultrasound device (not used) | 2 | | | 2 | |
| Extrahepatic duct resection | | | | | |
| Roux-en-Y | 5 | 35.7 | 2 | 2 | 1 |
| Bile duct stenting | 6 | 42.8 | | 5 | 1 |
| Pringle maneuver | 2 | 14.2 | | | |
| Blood loss >1000 ml | 7 | 50 | 2 | 4 | 1 |
| Duration of surgery | Max – 575<br>Min – 227<br>Av – 375.71 | | | | |
| Complication | | | | | |
| Clavien-Dindo | | | | | |
| Grade I | 3 | 21.4 | 2 | 1 | |
| Grade IIIa | 8 | 57.1 | | 8 | |
| Grade IIIb | 1 | 7.1 | | | 1 |
| Grade V | 2 | 14.2 | | | 2 |

**Results:** During the entire follow–up period, there were 14 cases of bile leakage: ICCC – 3 (21.4%), PCCC – 3 (21.4%); HC-C+CCC – 1 (7.1%); GBC - 1 (7.1%); CRC LM – 1 (7.1%); 1 (7.1%) EG and 4 (28.5%) EM. The largest number of BL was observed in patients with CCC (42.8%), and in none of the cases of HCC. The average age of patients is 56.07 years, due to the senile age of patients with malignant tumors. Gender ratio: women (71.4%) and men (28.5%). In a way to consider possible predictors of postoperative BL main criteria related to the patient, liver and surgery were analyzed and displayed in Table No. 1. As it shown, the more severe the ECOG status of the patient, the higher the probability of any type of complication, even though this is not observed in the assessment of MUST. Intraoperative blood loss of more than 1000 ml, extent liver resection, resection of extrahepatic bile duct with formation of biliodigestive anastomosis is likely to lead to complications.

**Conclusions:** The limitation of this study is the small number of patients. Nevertheless, these results may form the basis for a future prospective randomized trial to determine the predictors of BL and the management options for patients with such a complication.

**Keywords:** Posthepatectomy bile leakage, Liver resection, Single center experience, Predictors of PHBL

## PE-14

### Robotic vs Laparoscopic in Pancreatic Surgery

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**Aims:** Robotic procedures have an important developmental role in pancreatic surgery, almost all types of pancreatic surgery are performed robotically. Robotic methods are developing into more complex methods and can provide the potential benefit of short hospital stays. Laparoscopic pancreatic surgery has evolved over the years and is currently used for diagnostic and therapeutic purposes. This study aims to identify the advantages of robotics compared to laparoscopic in pancreatic surgery.

**Methods:** A literature review using health website data, and journal articles related to robotic and laparoscopic pancreatic surgery, then the author carried out selection and analysis of robotic and laparoscopic surgery.

**Results:** Robotic Surgery has several advantages, including accurate and precise robot movements, making wounds smaller, thereby minimizing post-surgical pain, reducing tissue trauma and the risk of bleeding as well as a smaller risk of infection, and shorter length of stay for patients so that patients can move more quickly. return. In addition, robotic surgery overcomes the intrinsic limitations of laparoscopy (a long straight instrument that does not bend). Compared with the open approach, robotic pancreatectomy has demonstrated reduced morbidity with a significant reduction in the incidence of wound complications and length of postoperative hospital stay while allowing for the implementation of improved recovery protocols and timely adjuvant treatment.

**Conclusions:** Robotic surgery has the advantage of minimizing post-surgical side effects and also improving recovery after surgery.

**Keywords:** Robotic, Laparoscopy, Surgery, Pancreatectomy

# Others

## PE-01

### Decoding the Genomic Landscape of Hepatocellular Carcinoma: Personalized Hepatic Resection for Optimized Surgical Outcomes

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**Aims:** Hepatocellular carcinoma (HCC) poses a formidable challenge in surgical management, necessitating an in-depth understanding of its molecular underpinnings for optimized outcomes. This study employs advanced bioinformatics to decode the intricate genomic landscape of HCC, with a primary focus on tailoring hepatic resection strategies based on individualized genomic profiles.

**Methods:** Over one year, we prospectively enrolled 90 HCC patients scheduled for hepatic resection. Multi-omics data, including whole-exome sequencing, transcriptomics, and DNA methylation profiles, were systematically obtained from tumor and adjacent non-tumor tissues. Employing a robust bioinformatics pipeline integrating pathway analysis, mutation burden assessment, and machine learning algorithms, we identified patient-specific genomic signatures influencing HCC progression and surgical outcomes.

**Results:** Distinct genomic alterations, such as Wnt signaling and TP53 mutations, were unveiled, significantly associated with aggressive HCC phenotypes. Mutation burden exhibited a noteworthy correlation with postoperative recurrence ($P<0.05$, 95% CI), facilitating the identification of high-risk patients. Our personalized surgery planning model, integrating genomic data with clinical variables, demonstrated an 18% improvement in predicting recurrence risk compared to conventional factors. Additionally, actionable genetic targets were identified, suggesting potential avenues for targeted therapies in postoperative adjuvant settings.

**Conclusions:** Our study unveils groundbreaking insights into HCC's genomic landscape, laying the foundation for personalized hepatic resection. Integrating genomic data enhances high-risk patient identification, ushering in a new era in HCC surgical interventions. This genomic-guided approach holds promise for improved outcomes and refined therapies, revolutionizing hepatocellular carcinoma research and treatment.

**Keywords:** Hepatocellular carcinoma, Genomic landscape, Personalized hepatic resection

## PE-02

### The Assessment of Quality of Life in Patients with Chronic Liver Disease

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[1]NB clinic, [2]Mongolian National University Science and Technology, Mongolia

**Aims:** This study aimed to explore the determinants influencing quality of life (QOL) among patients with chronic liver disease (CLD).

**Methods:** QOL was assessed using a validated short-form 36 (SF-36) survey. Socioeconomic factors, etiology, laboratory parameters, disease severity, and self-rated health perceptions on QOL were documented for analysis.

**Results:** Seventy CLD patients participated in the study. QOL scores revealed: physical functioning (PF) (34.4 ±26.7), role limitation due to physical health (RLPH) (7.5 ±17., role limitation due to emotional problems (RLEP) (27.7 ±38.2), energy or fatigue (E/F) (38.5 ±21.5), emotional well-being (EWB) (57.7 ±22., social functioning (SF) (55.2 ±23.5), pain (44.8 ±30.3), and general health (GH) (38.2 ±17). Employment and higher annual family income positively influenced QOL. Ascites and abnormal upper gastrointestinal endoscopic findings correlated with poor health status perceptions. Higher Child-Pugh class was associated with lower QOL scores. A significant negative correlation between the model for end-stage liver disease (MELD) score and QOL domains was noted (*p*: <0.05). Age, gender, religion, education, and duration of CLD diagnosis did not impact QOL.

**Conclusions:** QOL among CLD patients was inferior to that of the general population. Unemployment, low annual family income, ascites, abnormal upper gastrointestinal endoscopic findings, and higher Child-Pugh class and MELD scores were significant factors adversely affecting HRQOL.

**Keywords:** Helth related quality of life, Chronic liver desease

## PE-03

### How to Prevent Hepatitis Early by Giving Hepatitis B (HepB) Vaccine from Infancy in Indonesia?

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**Aims:** Viral hepatitis (HepB) is an infectious disease that can cause liver damage. It is also one of the most dangerous diseases in Indonesia. Hepatitis vaccine is one way to prevent the transmission of hepatitis. This study aims to describe how the level of parental concern for the administration of Hepatitis B vaccine to children in Indonesia.

**Methods:** The data used is the Indonesia Demographic and Health Survey 2017. The indicators used are Percentage of children age 12-23 months and children age 24-35 months who received specific vaccines at any time before the survey by source of information vaccination card or mother's report.

**Results:** Based on the data, it was found that 85.1% of children aged 12-23 months received a dose of hepatitis vaccine at birth where the data from the Vaccination card was 52.7% and the Mother's report was 32.3%. Only 81% participated in the age-appropriate vaccination. While children aged 24-35 months of age-appropriate vaccination is 82.5%. The interesting thing from the data is that from vaccination of children at birth to HepB 1, HepB 2, HepB 3, children aged 12-23 months following age-appropriate vaccination experienced a decrease of 87.2 (HepB 1 ), 80.9 (HepB ) and 73.6 (HepB 3 ). When viewed from the immunization cards of HepB 1 participants it was 55.8%, HepB 2 was 54.1% and HepB 3 was 51.6%. For the acknowledgment from the mother of the child, HepB 1 participants were 31.8%, HepB2 participants were 27.2% and when HepB 3 was vaccinated, it decreased by 22.9%.

**Conclusions:** The low participation of children in hepatitis B vaccination makes the risk of liver disease higher in the future. So that there is a need for government efforts, especially in the health sector to provide education on the importance of giving hepatitis B vaccine to prevent liver disease.

**Keywords:** Hepatitis B, Infancy, Vaccine, Indonesia

## PE-04

### Comparative Performance of Hepatitis E Virus Diagnostic Methods: A Prospective, Nationwide Multicenter Study on Blood Samples from Patients with Acute Hepatitis

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**Aims:** We aimed to analyze and compare the performance of

two anti-HEV enzyme-linked immunosorbent assay (ELISA) testing methods, in addition to HEV reverse transcription polymerase chain reaction (RT-PCR), to inform the future development of diagnostic approaches for HEV.

**Methods:** In a multicenter prospective study of patients with acute hepatitis, we analyzed blood samples from participants who tested positive for HEV IgM and IgG, using the Abia kit (Abia Inc.), which is the only diagnostic test currently approved in Korea. Additionally, we employed the internationally recognized Wantai kit (Wantai Biopharma Co., Ltd.) for further analysis and conducted HEV RT-PCR tests on these samples.

**Results:** In an acute hepatitis cohort, using the Abia kit, 27 out of 315 participants (8.6%) tested positive for anti-HEV IgM, and 33 out of 183 participants (18.0%) tested positive for anti-HEV IgG. These samples were then reanalyzed for HEV Ab IgM and IgG using the Wantai kit to assess concordance between the two methods. The concordance results were as follows: for HEV IgM, 7 cases were positive with both kits, 286 were negative with both, 20 were positive with Abia and negative with Wantai, and 2 were negative with Abia but positive with Wantai, achieving a concordance rate of 93%. For HEV Ab IgG, both kits agreed on 27 positive and 147 negative results, with 6 discordant results being positive with Abia and negative with Wantai, and 3 vice versa, resulting in a concordance rate of 95.1%. Among the participants who tested positive for HEV IgM, the RT-PCR detection rates for HEV were 11.5% (3 out of 26) with the Abia kit and 23.8% (5 out of 21) with the Wantai kit.

**Conclusions:** The two predominant anti-HEV ELISA testing methods exhibit high concordance rates, suggesting their reliability for clinical diagnosis of hepatitis E. On the other hand, the detection rate of HEV RT-PCR in patients positive for HEV Ab IgM was found to be very low.

**Keywords:** Hepatitis E, Acute disease, Hepatitis, Epidemiology

## PE-05

### How Is Shared Decision Making used in the Care of Patients with Liver Disease?: A Scoping Review

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**Aims:** Shared decision making is defined as approach where health care providers and patients shared the best available evidence when they have to make decision and patients are supported to consider options and to achieve informed preferences. However, there are the lack of evidences regarding the roles of health care providers and patients in shared decision making in the care of patients with liver disease. The aim of this scoping review was to analyze what health care situations used shared decision making and who participated in shared decision making in the care for patients with liver disease.

**Methods:** This research focused on what were the medical situations using shared decision making (Concept) for patient with liver disease(population) in all worldwide studies (Context). Following the Arksey & O'Malley scoping review method, structured searches for articles published from January 2014 to April 2024 were conducted in three electronic databases: PubMed, CINAHL, Embase. Twenty one studies were included in the final review.

**Results:** Shared decision making occurred when deciding on liver transplantation (n, %= 4, 19 %), medical and surgical treatment for advanced liver cirrhosis(n, %= 5, 24 %) or hepatocellular carcinoma(n, %= 2, 9.5 %), hepatitis(n, %= 8, 38 %), and end-stage liver disease(n, %= 2, 9.5 %). Participants in shared decision making were patients and physicians (n, %= 3, 14%), the multidisciplinary team participated in 4(19 %). 14 researches were not reported regarding participants. Intervention for shared decision making was only 2(9.5%) of 21.

**Conclusions:** Patients and health care providers face complex decision from dynamic and changing treatment option. Shared decision-making helps make the best choice in complex problems, however it has not been widely applied in the treatment of patients with liver disease. Interventions for multidisciplinary team-based shared decision making should be developed for patients with liver disease.

**Keywords:** Shared decision making, Patients with liver disease, Scoping review

## PE-06

### Comparative Study on the Hepato-Protective Role of Vitamin C and Vitamin E on Mercury Induced Toxicity in Heteropneustes Fossilis Model

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**Aims:** Mercury contamination poses a significant threat to aquatic ecosystems and human health due to its ubiquitous presence and toxic effects. *Heteropneustes fossilis*, a widely studied freshwater catfish, serves as an excellent model organism for assessing the hepatotoxic effects of mercury and evaluating potential hepatoprotective agents. In this comparative study, we investigated the efficacy of two renowned antioxidants, vitamin C and vitamin E, in mitigating mercury-induced hepatotoxicity in *H. fossilis*.

**Methods:** The experimental setup involved four groups of *H. fossilis*: a control group, a group exposed to mercury chloride

($HgCl_2$), a group co-treated with $HgCl_2$ and vitamin C, and a group co-treated with $HgCl_2$ and vitamin E. After a specified exposure period, hepatic function parameters including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin levels were assessed to gauge hepatocellular damage. We also performed antioxidant assay such as Superoxide Dismutase (SOD), Catalase (CAT), Lipid Peroxidation (LPO) and Glutathione (GSH). Additionally, histopathological examinations of liver tissues were performed to evaluate structural alterations

**Results:** Our findings demonstrate that both vitamin C and vitamin E exerted significant hepatoprotective effects against mercury-induced toxicity in *H. fossilis*. Co-administration of either antioxidant with $HgCl_2$ resulted in a notable attenuation of serum ALT, AST, ALP, and total bilirubin levels compared to the $HgCl_2$-exposed group. Antioxidant level also increase such as SOD, GSH and LPO level decreased. Histological analysis revealed that vitamin C and vitamin E supplementation mitigated mercury-induced hepatic damage, characterized by reduced necrosis, inflammation, and fatty degeneration

**Conclusions:** Overall, our study underscores the potential of vitamin C and vitamin E as effective therapeutic agents in ameliorating mercury-induced hepatotoxicity in *H. fossilis*. Further investigations are warranted to elucidate the underlying molecular mechanisms and optimize dosage regimens for clinical and environmental applications

**Keywords:** Hepato-protective, Mercury induced toxicity, Antioxidant

## PE-07

### Peronema Canescens Bioactives: Implications for Parkinsonism in Cirrhosis - Molecular Docking and ADMET Investigation

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**Aims:** Parkinsonism in cirrhosis (acquired hepatolenticular degeneration) is a complex neurological complication associated with liver dysfunction, characterized by motor symptoms resembling Parkinson's disease. Alterations in dopamine signaling and dopamine transporter (DAT) expression have been implicated in its pathogenesis. *Peronema canescens*, a plant known for its bioactive compounds, has shown potential psychostimulant effects. In this study, we investigated the potential of *Peronema canescens* bioactives as psychostimulants targeting dopamine signaling to mitigate parkinsonism in cirrhosis.

**Methods:** This study examined the psychostimulant potential of 7 natural compounds and 1 reference compound against key player Dopamine Transporter (DAT) (PDB ID 4M48) protein employing Autodock Vina 4. Additionally, absorption, distribution, metabolism, excretion, and toxicity (ADMET) were predicted using SwissADME servers. Additionally, ADMET properties of the most promising compounds were evaluated to assess their drug-likeness and pharmacokinetic profiles.

**Results:** The docking revealed that Peronemin A2, A3, and B2 exhibited great binding affinity toward Dopamine Transporter (DAT) protein. Their activity against receptor protein depicted binding affinities of -10.6; -10.5; -10.3 kcal/mol, respectively. The binding affinity as great as nortriptyline as native ligand (antidepressant commonly used in cirrhotic patients). Furthermore, the study elucidated the drug-target interaction profiles of these compounds, highlighting the binding similarity of those compound toward receptor protein at 72.2 – 94.4 %, surpassing all other compounds. Moreover, these compounds demonstrated psychostimulant activity and great ADMET properties.

**Conclusions:** Our findings suggest that *Peronema canescens* bioactives possess potential psychostimulant properties targeting dopamine signaling and DAT expression, which may offer therapeutic benefits in mitigating parkinsonism in cirrhosis. Further *in vitro* and *in vivo* studies are warranted to validate the efficacy and safety of these bioactives as potential therapeutic agents for neurological complications associated with liver disease.

**Keywords:** *Peronema canescens*, Dopamine transporter, Cirrhosis, Parkinsonism

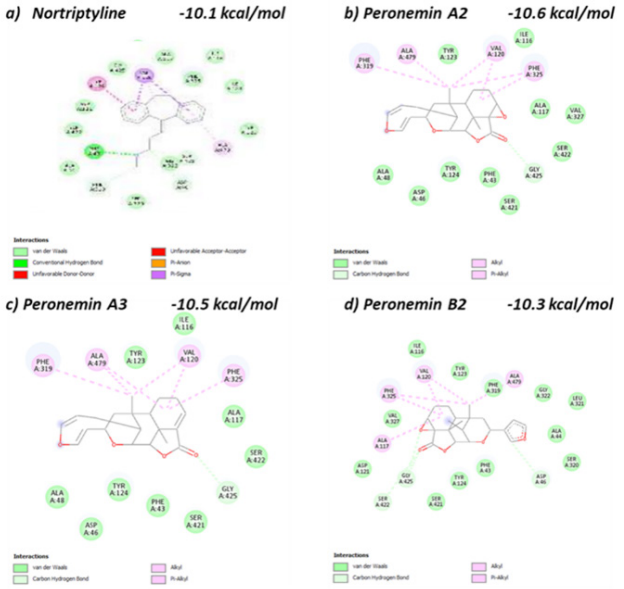


**Figure 1.** 2D Visualization of Binding Interaction Between Ligand and 4M48-Dopamine Transporter Protein.

## PE-08

### TGF-β1 Receptor Inhibition by Resveratrol Derivatives: Promising Therapeutic Approach for Liver Fibrosis

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**Aims:** Liver fibrosis is a progressive condition marked by excessive deposition of extracellular matrix (ECM), culminating in liver dysfunction and cirrhosis. The signaling pathway of transforming growth factor-beta 1 (TGF-β1) plays a pivotal role in initiating and advancing liver fibrosis by stimulating activation of hepatic stellate cells (HSCs) and ECM synthesis. Current therapeutic options for liver fibrosis are limited, emphasizing the critical need for innovative treatments. Natural product compounds have emerged as promising sources for identifying potential lead compounds in drug research. This study aimed to explore natural bioactive compounds targeting the TGF-β1 receptor for the treatment of liver fibrosis.

**Methods:** Using virtual screening, we searched for potential inhibitors of the TGF-β1 receptor among bioactive compounds derived from resveratrol and analyzed their molecular mechanisms. AutoDockTools were employed to screen and dock nine natural bioactive compounds of resveratrol derivatives known for their antioxidant, anti-inflammatory, and antifibrotic properties. Additionally, we assessed their absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics using online pkCSM prediction.

**Results:** All resveratrol derivatives exhibited better binding energies ranging from -8.7 to -11.3 kcal/mol compared to galunisertib, a known TGF-β1 receptor inhibitor, which showed a binding energy of -7.5 kcal/mol. Their interaction with the TGF-β1 receptor binding site primarily involved hydrophobic interactions with the aromatic ring and hydrogen bonding with the oxygen moiety. Furthermore, resveratrol derivatives displayed drug-like properties based on ADMET predictions.

**Conclusions:** In conclusion, resveratrol derivatives show promise as potential inhibitors of the TGF-β1 receptor. Further research is needed to explore the pharmacophore model and identify novel lead compounds. These findings hold significance for utilizing resveratrol derivatives as potential candidates in TGF-β1 inhibition and may aid in the development of additional natural bioactive compounds found in everyday foods as anti-fibrotic agents.

**Keywords:** Liver fibrosis, TGF-β1 receptor, Resveratrol derivatives, Natural products

## PE-09

### Cost Analysis of Chronic Liver Related Disease: What Should we Do Next?

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**Aims:** The cost of chronic liver disease (CLD) and its associated complications (cirrhosis and liver cancer) is becoming one of the biggest challenges for families and patients with chronic liver disease. The cost of actual medicine as healthcare expenditure, psychosocial and mental financial burden consequences are cornering the families and patients. This study aims to analyze the cost related to chronic liver disease, and the supporting factors.

**Methods:** The method used is a descriptive analysis through Medline, Embase, Web of Science, and Scopus online database, which serves to describe or give an overview of the object under study by identifying 33 published papers from 2015-2024. Longitudinal and cross-sectional studies were used to break down the analysis.

**Results:** The studies observe several factors that need to be considered related to CLD. First, the psychosocial program requires patients and families for long treatment and professional support resulting in loss of savings, or even medical debt. Then, professional caregivers are expensive too, in the long run, not only time costing but also mental costing needs to be highlighted. As depression and anxiety rise through the families and patients, improving health-related quality of life is the first place for concern. For all the costs, it is challenging for the family, especially from the low-middle income family. To reduce the burden, support-seeking financial coping, such as crowdfunding is one of the best solutions to obtain donations from mass people, especially in Indonesia using kitabisa.com. This financial support scheme has been effectively helping families and patients to get financial support for treatment.

**Conclusions:** Several elements of CLD treatment require financial allocations. However, a solution such as crowdfunding can be a solution due to mass donation.

**Keywords:** Cost analysis, Chronic liver disease, Financial distress, Crowdfunding

## PE-10

### Lavandula Angustifolia Oil Extract: A Potential Therapeutic Agent for Hepatic and Renal Protection in Cholesterol Diet-Induced Hyperlipidemia in Female Rats

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**Aims:** Lavandula angustifolia, known for its aromatic properties, was chosen for its reported effects on intracellular calcium levels, hypolipidemic activity, and insulin secretion in mouse and human $\beta$ cells with type 2 diabetes

The objective of this study was to investigate the hypolipidemic effects of Lavandula angustifolia essential oil (LAEO) in a diet-induced hypercholesterolemic model in female rats, focusing on its impact on the kidney, heart, and liver.

**Methods:** Essential oil samples were obtained from Lavandula angustifolia plants collected in the Uttarakhand region of the Western Himalayas and analyzed using GC-MS. Sixty-eight Wistar albino rats were divided into six groups, including a normal control group, a group fed a high-cholesterol (HC) diet, a group fed the HC diet with different doses of LAEO, and a group treated with Atorvastatin as the standard drug. Over the 30-day study period, the effects of LAEO on various parameters such as serum lipid profile, glomerular filtration rate (GFR), atherogenic index, cardiac markers, hepatic glucose homeostasis, and hepatic enzymes were evaluated.

**Results:** The results revealed that LAEO significantly reduced serum lipid levels, improved hepatic glucose homeostasis, decreased GFR, and lowered lipogenic enzyme activity in a dose-dependent manner. Furthermore, LAEO demonstrated significant downregulation of the atherogenic index and cardiac marker enzymes, such as aspartate transaminase, while increasing high-density lipoprotein (HDL) levels.

**Conclusions:** These findings suggest that LAEO extract could serve as a potential intervention for the treatment of cardiometabolic diseases and type 2 diabetes mellitus.

**Keywords:** DIET- Induced Hypercholesterolemic, Lavandula Augustifolia Oil, Serum aspartate aminotransferase

## PE-11

### From Teacup to Treatment: Molecular Mechanisms of Green Tea Epigallocatechin-3-Gallate in the Treatment of Hepatic Tuberculosis

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**Aims:** Hepatic tuberculosis poses a significant global health challenge, prompting the exploration of innovative therapeutic approaches that can be integrated into daily consumption habits. Green tea's epigallocatechin-3-gallate (EGCG) has emerged as a potential candidate for treating various diseases. This research aimed to elucidate the molecular mechanisms involved in EGCG's therapeutic effects against hepatic tuberculosis.

**Methods:** Through the utilization of bioinformatics tools and molecular modeling techniques, we investigated the interaction between EGCG and key molecular targets associated with *Mycobacterium tuberculosis* infection in the liver. Bioinformatics tools such as STITCH v.5.0 and VICMPred were employed to identify protein targets and ascertain their functional roles. Additionally, BepiPred v.2 software predicted peptide epitopes of *M. tuberculosis* proteins, while PSORTb v.3 was used to analyze subcellular localization.

**Results:** The bioinformatics approach revealed ten protein targets of *M. tuberculosis* affected by EGCG, including integral membrane proteins like ABC transporter (MT1726), daunorubicin-DIM-transport integral membrane proteins (drrb and drrC), transmembrane ABC transporter ATP-binding proteins (MT1789), antibiotic-transport integral membrane ABC transporter (MT1504), methylated-DNA-[protein]-cysteine S-methyltransferase (ogt), 3-oxoacyl-ACP reductase (fabG), enoyl-ACP reductase (inhA), short-chain dehydrogenase (Rv1928c), and 3-ketoacyl-ACP reductase (fabG2). These proteins play crucial roles in bacterial cell survival and metabolism.

**Conclusions:** The antipathogenic mechanism of EGCG against *M. tuberculosis* in hepatic tuberculosis appears to involve inhibiting several virulence factors associated with bacterial cell survival and metabolism. However, further validation through *in vitro* and *in vivo* experiments is necessary to corroborate the findings of this computational study.

**Keywords:** *M. tuberculosis*, Hepatic tuberculosis, Epigallocatechin-3-gallate, Green tea

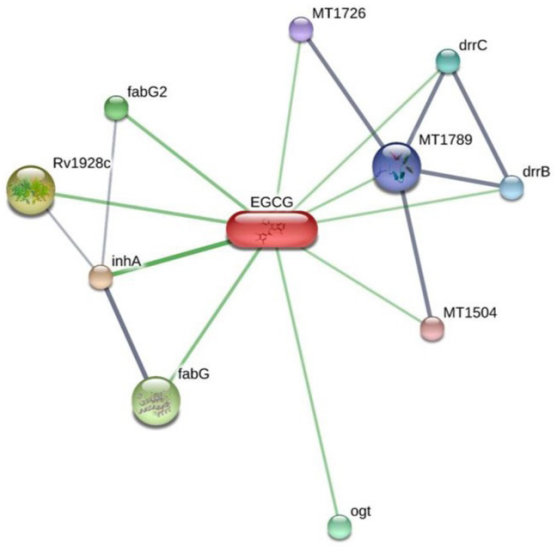


**Figure 1.** Molecular actions of green tea EGCG in the treatment of hepatic tuberculosis.

## PE-12

# Immunohistochemical Subtypes of Hepatocellular Adenomas in Iranian Patients, A Cross Sectional Study in a Single Center

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**Aims:** Hepatocellular adenomas (HCAs) are rare and benign liver tumors, often found following abdominal pain or incidentally on imaging. These tumors are rarely manifested by bleeding or malignant changes, particularly in inflammatory and Beta-catenin activated subtypes. Because of the importance of identifying HCA subtypes in predicting the risk of their progression to malignancy, it seems necessary to classify them. We assessed morphologic findings of HCAs and their correlation with immunohistochemistry analysis and radiologic data in this study.

**Methods:** Twenty cases of HCAs were classified by morphology; then they were stained by immunohistochemistry method for glutamine synthetase (GS), liver fatty acid-binding protein (LFABP), Beta-catenin, Serum amyloid A (SAA) and C-reactive protein (CRP) markers. Also, MRI findings and clinical characteristics were recorded.

**Results:** Based on immunohistochemistry, 11 HCAs (55%) were categorized as inflammatory type, four HCAs (20%) as steatotic type, two HCAs (10%) as the beta-catenin type and three HCAs (15%) as unclassified type. In 13 out of 20 cases (65%), HCAs were correctly subclassified by morphology alone. Multiple masses and oral contraceptive (OCP) usage were seen more commonly in inflammatory HCAs.

**Conclusions:** Definite subtyping of HCAs, especially on needle biopsies, is critical; because it is one of the most important factors for selecting the best choice of treatment. Our findings showed that morphologic diagnosis alone cannot determine HCA subtypes correctly in all cases and using ancillary tests such as immunohistochemistry seems to be necessary for classifying of HCAs.

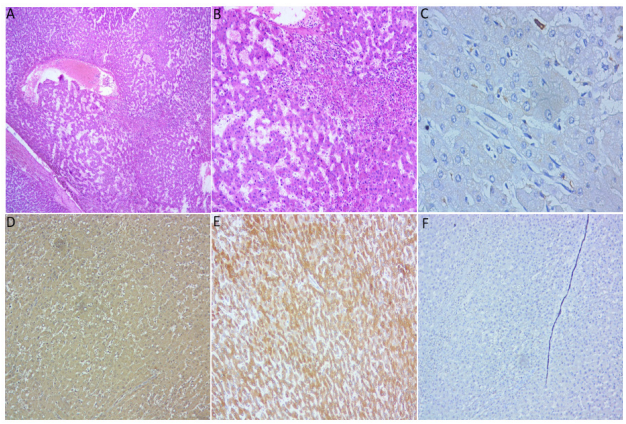


Figure 1.

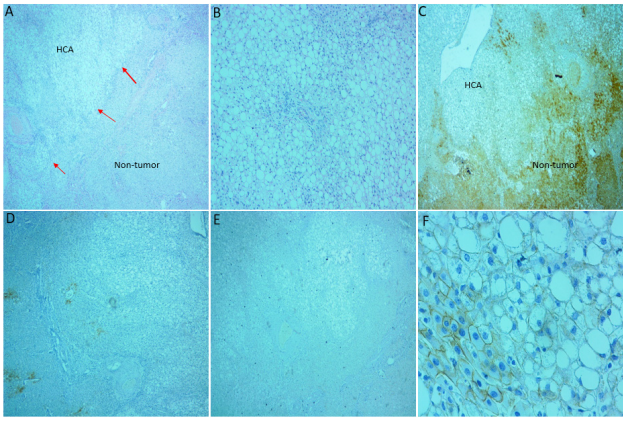


Figure 2.

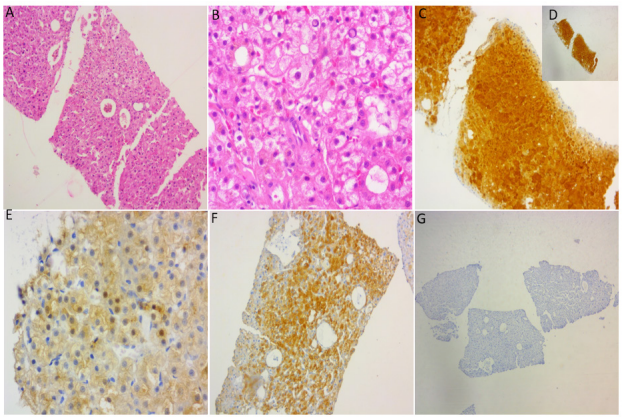


Figure 3.

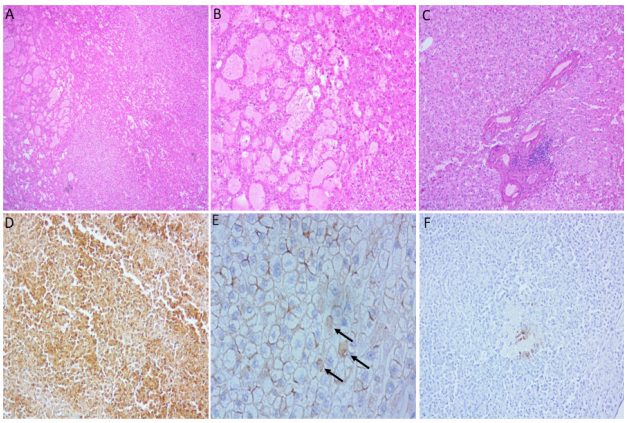


Figure 4.

**Keywords:** Hepatocellular adenoma, Immunohistochemistry, Needle biopsy, Subtypes

## PE-13

### Long-Term Effect of Alcohol Consumption to the Incidence of Pancreatic Cancer: Country Level Anayses

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Economics, Universitas Islam Indonesia, Indonesia

**Aims:** Excessive amount of alcohol consumption has been long recognized as a source of many diseases. Beside the fact that the effects might be different for each individuals, effect of alcohol to health issues are generally not experienced directly. This substance might need time to destroy certain part on human body. This study aims to analyse the relationship of alcohol consumption and the incidence of pancreatic cancer using country-level data.

**Methods:** Data of cancer are utilized from the world health organization while data of alcohol consumption per capita are gained from the world bank data. Descriptive analyses and ordinary least square (OLS) regression are conducted involving sample of 57 countries. This study uses data that were collected in 2020 except variable of alcohol consumption. Confounding factor might arise on longitudinal analyses. To anticipate this issue, this study uses data of alcohol consumption in multiple years and is used alternately: 2000, 2005, and 2010.

**Results:** Results show that countries with high level of alcohol consumption tend to have higher level of pancreatic cancer incidence. Finding provides insight that, statistically, alcohol consumption has positive impact to the incidence of this cancer. Result is stable when variable of alcohol consumption in the year 2000, 2005, and 2010 are uses alternately.

**Conclusions:** In conclusion, it is found that past alcohol consumption in one until two decades has association with the current incidence of pancreatic cancer. Further research are needed to clinically find out the mechanism on how past alcohol consumption associates with pancreatic cancer.

**Keywords:** Alcohol, Pancreas, Cancer

## PE-14

### Predictive Identification Activity of Curcumin Analogs as Hepatitis Antivirals by Molecular Docking Method

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**Aims:** Antivirals are generally derived from synthetic materials that work to stop the replication of the virus in some way. However, the use of synthetic antivirals has cytotoxic effects, and more frequent use of antibiotics can lead to greater resistance of the virus to antibiotics, which reduces antiviral activity. Since ancient times, herbal extracts have been used for treatment. They are known for their antiviral properties and more tolerable side effects than commonly used antivirals. Therefore, remedies based on natural ingredients may be a better option for treating viral diseases. Curcumin is one such plant that has antiviral potential. This study aims to quantify the sensitivities of kurkumin modifications through in silico molecular docking pendekatan, utilizing the structure and physical properties of protein virus target to determine the active protein virus sisi that can trigger biological activity.

**Methods:** By using the molecular docking method, this study conducted the activity of curcumin analog compounds as antiviral. The materials used in this study include 5 (five) kinds of antivirals with each comparator compound, namely maraviroc, docosanol, ribavirin, and zanamivir. The validated target proteins amounted to 5 (five) receptors with PDB codes 1V2I, 4WEG, 2HWI, 2QAD, and 3ALP.

**Results:** Based on the results shown by the comparison of docking scores between curcumin compounds and synthesized curcumin analog compounds, the synthesized curcumin compound has a higher ChemPLP score at the 1V2I receptor than the natural curcumin analog compound, with a score of -79.94233. So at the 1V2I receptor, the compound 2,5-bis(3,5-di-tert-butyl-4-hydroxybenzyl)cyclopentanone can be predicted to have better activity compared to the parent compound. Based on the statistical test data, the *P*-value of the best test compound shows a value of less than 0.05, meaning there is a significant difference between the test compound and the comparator compound.

**Conclusions:** The recommended antiviral properties of synthetic kurkumin include 2,5-bis(3,5-ditertbutil-4-hidroksibenzil)siklopentanon; 1,7-difenil-1,6-heptadien-3,5-dion; 1,7-bis(3,4-dibenziloksifenil)-1,6-heptadien-3,5-dion; and 2,5-bis(3,5-ditertbutil-4-hidroksibenzil)siklopentanon. This substance has the potential to be developed as an antiviral during the *in vitro* and *in vivo* synthesis and uji processes.

**Keywords:** Curcumin analogs, Hepatitis antivirals, Molecular docking

## PE-15

### Rapid and Sensitive Method for the Detection Selective Androgen Receptor Modulators by Liquid Chromatography Mass Spectrometry (LC-MS/MS): A Severe Drug Induced Liver Injury (DILI) Causing Drugs

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National Dope Testing Laboratory (NDTL), New Delhi, India

**Aims:** Drug-induced liver injury (DILI) is one of the leading causes of death from acute liver failure (ALF) in the United States, accounting for approximately 12-14% of ALF cases in

the United States. Selective androgen receptor modulators (SARMs) were first developed to increase muscle mass while avoiding the side effects of conventional androgenic steroids. Although their use is not approved by the US Food and Drug Administration (FDA) and by the World Anti-Doping Agency, they are widely available online and are consumed to enhance athletic performance. FDA issued a warning against using SARM because of potential liver injury. Therefore, a sensitive & rapid analytical method was developed & validated for detecting SARMs using sophisticated LC-MS/MS techniques in human urine matrix.

**Methods:** The SARMs detection method was developed and validated as per ISO17025 & WADA ISL guidelines for LOI (Limit of Identification), specificity, robustness, selectivity, carryover, and matrix effect. The reference standards of the targeted SARMs & internal standards were purchased from authentic and traceable sources (TRC Canada). An analytical method involving liquid-liquid extraction and detection by Liquid Chromatography Mass spectrometric analysis (LC-MS/MS) using Scheduled MRM.

**Results:** A rapid analytical method was developed to detect five SARMs (LGD-4033, Dihydroxy-LGD-4033, Andarine (S4), O-de-Phenyl-Andarine, Enobosarm (Osterine), O-de-Phenyl-Ostarine) in a run time of 10 minutes. The developed method achieved the limit of detection (LOD) ranging from 50 picograms to 300 picogram/ml levels for the targeted SARMs. The detection limit of up to 50 picograms is a very low detection of SARMs in human urine matrix to the best of our knowledge. The validation results were found within acceptable limits. The method has been successfully applied for the confirmatory analysis of SARMs in routine analysis.

**Conclusions:** A rapid & sensitive method was developed for the detection and confirmation of SARMs. This method could be a useful tool for the detection of these prohibited SARMs in sports doping control and in clinical, hepatological studies & medical fields. This method has facilitated the detection of SARMs at very low levels in human urine (at the picogram level). The applicability of the method was also verified by analyzing the real excretion study urine samples from human oral intake.

| S. No | SARMs | Limit if identification (LOI) | % Matrix Effect |
|---|---|---|---|
| 1 | Andarine | 0.05 ng/ml | 90.5% |
| 2 | O-De-Phenyl-Andarine | 0.16 ng/ml | 71.6% |
| 3 | Ostarine | 0.05 ng/ml | 70.0% |
| 4 | O-De-Phenyl-Ostarine | 0.05 ng/ml | 139.9% |
| 5 | LGD-4033 | 0.3 ng/ml | 98.1% |
| 6 | Dihydroxy-LGD-4033* | – | — |

**Keywords:** Sarms, Drug induced liver injury, LC-MS/MS

## PE-16

### Assessment of Knowledge about Risk Factors for Chronic Liver Disease among Patients Admitted to Dornod Medical Center

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[1]Dornod Medical Center, Choibalsan, Mongolia

**Aims:** Chronic liver disease (CLD) encompasses various insults to the liver, including hepatitis, alcohol abuse, and non-alcoholic liver disease, posing a significant global public health concern. Liver disease is highly prevalent but, studies on public awareness of its risk factors, particularly in Mongolia, are limited. This study aims to evaluate the understanding of CLD risk factors among patients admitted to Dornod Medical Center.

**Methods:** A quantitative cross-sectional study was conducted, involving 467 patients admitted to Dornod Medical Center from March 2023 to September 2023. Frequencies and percentages were analyzed using SPSS version 22. Chi-square tests determined significant associations between variables ($P$<0.05).

**Results:** Only 36% of participants demonstrated good knowledge of CLD risk factors, with 64% having poor knowledge. While over 68% were aware of obesity, high fat intake, drug use, alcohol, hepatitis B, and C as risk factors, many did not recognize diabetes as a risk factor. Additionally, 49.1% believed hepatitis B and C could not be transmitted sexually or from mother to child. Education level showed a positive association with awareness of CLD risk factors ($P$=0.007).

**Conclusions:** Efforts to enhance public awareness of CLD are imperative. Lack of knowledge contributes to its prevalence, particularly in the Eastern province of Mongolia. Comprehensive awareness campaigns and further research are crucial in controlling its spread.

**Keywords:** Chronic liver disease, Knowledge

## PE-17

### A Higher Blood Ferritin Level Can Accurately Distinguish between the Severity of the Coronavirus Disease 2019 Pneumonia and Liver Damage

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[1]Department of Medical Laboratory Technology, Aarogyam Institute of Paramedical & Allied Sciences, Roorkee, Uttarakhand-247661, India (Affiliated by H.N.B. Uttarakhand Medical Education University); [2]Department of Molecular Pathology, OncoBiomedical Research and Services, Gurgaon, HR India; [3]Department of Physiotherapy, Aarogyam Institute of Paramedical & Allied Sciences, Roorkee, Uttarakhand-247661, India (Affiliated by H.N.B.

Uttarakhand Medical Education University)

**Aims:** Ferritin is a liver protein that is essential for disease diagnosis and prognosis, yet it is questionable how ferritin may help with COVID-19.

**Methods:** From 158 COVID-19 patients at Ivory Hospital in Greater Noida, India, we gathered their clinical records. The receiver operating characteristic (ROC) curve, Kaplan-Meier survival curves, and Spearman's correlation analysis were used.

**Results:** When compared to individuals with normal ferritin levels, patients with elevated levels experienced a greater frequency of severe illness (50.0 vs 2.9%) and liver injury (52.3 vs 20.0%) ($P$<0.001).

**Conclusions:** It signifies that ferritin may serve as a simple diagnostic tool for liver damage, severity of sickness, and prognosis prediction in COVID-19 patients. Patients whose ferritin levels are abnormal require close observation.

**Keywords:** Ferritin, Liver damage, Coronavirus, COVID-19

## PE-18

### Knowledge, Attitude and Practice of Hepatitis B and Hepatitis C among University Students of Pokhara Valley, Nepal

**Bishnu Raj Tiwari**[1], Bimala Sharma[2]

[1]School of Health and Allied Science, Pokhara University, Kaski, Nepal; [2]Community Medicine Department, Gandaki Medical College, Pokhara, Kaski, Nepal

**Aims:** Adolescents are at high risk of behavioral exposure to Hepatitis B and other blood-borne diseases. Lack of education about the knowledge of Hepatitis B virus contributes to an increase in cases. This study aims to determine the knowledge of the Hepatitis B and C virus among the adolescent in Gandaki province, Nepal.

**Methods:** This purposive cross-sectional study was conducted in Gandaki province, Nepal, among adolescents from October 2023 to December 2023 and a total of 400 adolescents were included in the study. A face-to-face interview was done for data collection by paper and pen method. The data was exported into IBM SPSS from Microsoft Excel for statistical analysis.

**Results:** A total of 400 responses were collected from adolescents. The age of respondent was range from 17 to 26 years. The Majority 23.5% respondent were belonging to 21 & 22 age group. Regarding the mode of transmission through un -sterilized syringe and contaminated blood 100% of respondent were found aware followed by blade of barbers and tattooing 91.0% and 73.5% respectively.

The knowledge on vaccine availability was 69.5 % and 42.0% respectively regarding Hepatitis B and Hepatitis C. Similarly, 72.0% adolescent were found knowledgeable regarding treatment availability of Hepatitis B and least 41.0% for Hepatitis C treatment availability among the adolescents.

Majority 100% adolescents use sterilized syringe when required and blood screened for hepatitis B and C before transfusion. Likewise, 87% and 74% adolescents use new blades for shaving or hair cutting and share personal belongings (Glass, razor and towel) respectively.

Regarding the adolescent's attitude majority 77.5% like to get screened for hepatitis B and C and like to get vaccinated for hepatitis B free of cost. Only 66% adolescents like to get further investigation and treatment if found positive for hepatitis B or C without any symptoms.

**Conclusions:** This study shows the better knowledge, attitude, and practice toward the HBV and HCV among the adolescents. However, the study findings recommend the implementation of a awareness program among the adolescents.

**Keywords:** Hepatitis B, Hepatitis C, Knowledge, Attitude, Practice

## PE-19

### The Laboratory Findings of Liver Disease Suspected People Residing at Gandaki Province, Nepal

**Ganga Sagar Bhattarai**[1], Bishnu Raj Tiwari[2]

Prithvi Narayan Campus, Tribhuvan University, Department of Microbiology, Nepal

**Aims:** Liver illnesses, with their diverse etiologies and symptoms, constitute a substantial worldwide health burden. Comprehending the laboratory results linked to hepatic disorders is essential for prompt diagnosis and treatment. This study focuses on evaluating the laboratory findings of individuals suspected of liver disease residing in Gandaki Province, Nepal.

**Methods:** Cross-sectional retrospective study.

**Results:** A retrospective analysis was done on laboratory data obtained from individuals presenting with suspected liver disease. The study included 399 participants, and their laboratory test results were categorized into three groups: high percentage, low percentage, and normal percentage. The laboratory parameters assessed included Serum Glutamic Oxaloacetic Transaminase (SGOT or AST), Serum Glutamic Pyruvic Transaminase (SGPT or ALT), total bilirubin, albumin, and total protein.

The findings among individuals suspected of liver disease in Gandaki Province, Nepal, highlights significant insights into the prevalence and nature of liver problem within this population.

Serum Glutamic Oxaloacetic Transaminase (SGOT or AST): Among the 399 participants, 58 individuals (14.54%) exhibited elevated SGOT levels, indicating hepatocellular injury. Interestingly, no participants displayed low SGOT levels, suggesting a

lack of cases with reduced AST activity. The majority (85.46%) had normal SGOT levels, indicating a relatively lower prevalence of AST elevation compared to the normal range.

Serum Glutamic Pyruvic Transaminase (SGPT or ALT): Elevated SGPT levels were observed in 89 individuals (22.31%), reflecting hepatocellular damage or inflammation. Similar to SGOT, no participants had low SGPT levels. The majority (77.69%) exhibited normal SGPT levels, although with a higher percentage of elevation compared to SGOT.

Total Bilirubin: A total of 33 individuals (8.27%) had elevated total bilirubin levels, suggestive of impaired bilirubin metabolism or excretion. As with SGOT and SGPT, finding did not showed low bilirubin levels. The majority (91.73%) had normal total bilirubin levels.

Albumin: Only one individual (0.25%) presented with decreased albumin levels, indicating compromised hepatic synthetic function. Conversely, 44 individuals (11.03%) had elevated albumin levels, which may be attributed to factors such as dehydration or chronic inflammation. The majority (88.72%) exhibited normal albumin levels.

Total Protein: Eleven individuals (2.76%) had decreased total protein levels, possibly reflecting impaired protein synthesis by the liver. Conversely, 38 individuals (9.52%) had elevated total protein levels, which may result from various physiological or pathological conditions. The majority (87.72%) had normal total protein levels.

All things considered, the research reveals a noteworthy prevalence of liver dysfunction among people in Gandaki Province, Nepal, who may have liver illness. While the changes in albumin and total protein levels may indicate impaired hepatic synthesis activity, the observed elevations in SGOT, SGPT, and total bilirubin levels point to possible underlying hepatocellular damage or malfunction.

**Conclusions:** The significance of thorough laboratory assessment for the prompt detection and treatment of liver disorders in this population is highlighted by these findings. To clarify the precise etiologies causing liver failure and to create focused therapies meant to enhance clinical outcomes, more research is necessary.

Table 1: Analysis of laboratory findings

| Test | Test Result | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | High | Percentage | Low | percentage | Normal | percentage | Total | |
| SGOT(AST) | 58 | 14.53634 | 0 | 0 | 341 | 85.46366 | 399 | |
| SGPT(ALT) | 89 | 22.30576 | 0 | 0 | 310 | 77.69424 | 399 | |
| Bilirubin (Total) | 33 | 8.270677 | 0 | 0 | 366 | 91.72932 | 399 | |
| Albumin | 1 | 0.250627 | 44 | 11.02757 | 354 | 88.7218 | 399 | |
| Total protein | 11 | 2.756892 | 38 | 9.52381 | 350 | 87.7193 | 399 | |

**Keywords:** SGPT or alt, SGOT or ast, Total bilirubin, Albumin, Total protein, Nepal

## PE-20

### Cardiological Features of TACE Patients in Hepatocellular Carcinoma: Study on the Kazakhstan Population

Saule Kubekova[1],Natalya Zagorulya[1], Niyaz Malayev[2], Dinara Bayanova[1]

[1]Department of Internal Disease with Geriatric Course, Astana Medical University; [2]Department of Interventional Oncoradiology, Kazakhstan

**Aims:** To conduct a retrospective analysis of patient data following TACE of the hepatic artery in Astana, Kazakhstan.

**Methods:** 113 patients with liver cancer from 2018 to 2022 on TACE of which 71 were male participated in this retrospective study. The mean age of patients in the sample was 64.6±7.82 years.out. The analysis was carried out within the framework of the grant project of the Ministry of Education and Science of the Republic of Kazakhstan IRN AR 19176025 (2023-2025).

**Results:** The duration of the disease varied in different years (10.0±2.4 in 2021 and 36.7±21.6 in 2019). The average duration of the disease was 19.2±5.2 months, with a median of 17.6 months. The structure of cardiovascular diseases also varied by year. The most common diseases were arterial hypertension (45 cases) and chronic heart failure (33 cases). Targeted therapy was received by 22 patients, multicomponent chemotherapy by 33 patients, TACE by 113 patients, and 12 patients underwent surgical treatment. The number of TACE procedures ranged from 1.5±1.0 to 2.1±0.8, with doxorubicin and irinotecan being the most commonly used drugs. Among the sampled patients, 54 deaths were registered within 5 years.

**Conclusions:** According to a retrospective analysis of patient data after transarterial hepatic artery chemoembolization, the most common comorbidities were arterial hypertension and chronic heart failure, most patients were more likely to receive doxorubicin and irinotecan, and 54 deaths within 5 years were recorded.

**Keywords:** Cardiovascular disease, Liver cancer, Tace

## PE-21

### The Impact of Intermittent Fasting on Liver Health: A Comprehensive Review

Sheffali Verma

Dr. Bhimrao Ambedkar Medical College, India

**Aims:** 1. To provide a comprehensive overview of existing literature regarding the effects of intermittent fasting on liver health.

2. To analyze the mechanisms through which intermittent fasting may influence liver function, including metabolic pathways, cellular signaling, and gene expression.

3. To evaluate the impact of different intermittent fasting protocols (e.g., time-restricted feeding, alternate-day fasting) on various aspects of liver physiology, such as hepatic lipid metabolism, inflammation, and oxidative stress.
4. To assess the potential benefits of intermittent fasting for preventing or managing liver diseases, including non-alcoholic fatty liver disease (NAFLD), hepatic steatosis, and liver fibrosis.
5. To identify gaps in current research and propose future directions for investigating the role of intermittent fasting in promoting liver health and preventing liver-related disorders.
6. To provide evidence-based recommendations for healthcare professionals and individuals considering intermittent fasting as a dietary intervention for improving liver function and overall metabolic health.

**Methods:** The methods section of "The Impact of Intermittent Fasting on Liver Health: A Comprehensive Review" would involve several key steps:

1. Literature Search: Conduct a systematic review of relevant scientific literature using databases such as PubMed, Google Scholar, and Web of Science. Search terms may include "intermittent fasting," "time-restricted feeding," "liver health," "hepatic function," and related keywords.
2. Inclusion Criteria: Define specific criteria for selecting studies, such as publication date range, study design (e.g., human clinical trials, animal studies), and relevance to intermittent fasting and liver health.
3. Data Extraction: Extract relevant data from selected studies, including study design, participant characteristics (e.g., age, sex), intermittent fasting protocol (e.g., fasting duration, frequency), liver-related outcomes (e.g., liver enzymes, histological changes), and key findings.
4. Quality Assessment: Evaluate the quality and reliability of included studies using appropriate tools or criteria, such as the Cochrane Collaboration's tool for assessing risk of bias or the Newcastle-Ottawa Scale for assessing non-randomized studies.
5. Data Synthesis: Summarize and synthesize findings from the selected studies, categorizing them based on intermittent fasting protocol, study population, and liver-related outcomes. Identify patterns, trends, and inconsistencies across studies.
6. Analysis of Mechanisms: Analyze the proposed mechanisms through which intermittent fasting may affect liver health, including changes in hepatic lipid metabolism, insulin sensitivity, inflammation, autophagy, and oxidative stress.
7. Limitations: Discuss potential limitations of the included studies, such as sample size, study duration, heterogeneity of intermittent fasting protocols, and variations in outcome measures.
8. Ethical Considerations: Address any ethical considerations related to the conduct of the review, such as potential conflicts of interest or biases.
9. Statistical Analysis (if applicable): Conduct statistical analysis if appropriate, such as meta-analysis or subgroup analysis, to quantify the effects of intermittent fasting on liver health outcomes.
10. Reporting: Present the findings of the review in a clear, structured manner, following the guidelines of relevant reporting frameworks (e.g., PRISMA for systematic reviews).

By following these methods, the review aims to provide a comprehensive and rigorous assessment of the impact of intermittent fasting on liver health.

**Results:** Based on the information provided, as of April 12th, 2023:

- There were a total of 1304 clinical trials related to NAFLD identified in the ClinicalTrial.gov registry.
- Among these trials, only five studies included intermittent fasting (IF) as an intervention.
- These five clinical trials focused primarily on NAFLD along with comorbidities such as obesity, diabetes mellitus, insulin resistance, and gut microbiota.
- The total number of participants across the five trials was 325.
- The interventions varied, including time-restricted feeding, intermittent calorie restriction, and calorie restriction.
- The status of the trials varied, with some recruiting, completed, and others having an unknown status.

Overall, the findings suggest that there is limited research specifically examining the effects of intermittent fasting on NAFLD, despite the prevalence of clinical trials focused on NAFLD in general.

The discussion of the research findings regarding the influence of intermittent fasting (IF) on NAFLD encompasses various aspects:

1. **Background on NAFLD**: NAFLD is characterized by excessive fat accumulation in the liver without excessive alcohol intake. It is closely associated with obesity, insulin resistance, dyslipidemia, and metabolic syndrome components, making it a subject of extensive clinical trial investigation.
2. **Interest in IF for NAFLD**: There is a growing interest in exploring the potential impact of IF on NAFLD due to its diverse patterns and methodologies. IF involves alternating periods of fasting and feeding, including time-restricted feeding, alternate-day fasting, and periodic fasting observed during Ramadan.
3. **Mechanisms of IF on NAFLD**: Several potential mechanisms have been proposed for how IF may affect NAFLD. These include improved glucose homeostasis and insulin sensitivity, modulation of lipid metabolism, alterations in gut

microbiota, induction of autophagy, and modulation of oxidative stress and inflammation.

4. **Improved Glucose Homeostasis**: IF can lead to changes in insulin signaling pathways, resulting in improved insulin sensitivity, reduced hepatic gluconeogenesis, and increased glucose uptake in peripheral tissues, which may reduce hepatic fat accumulation.
5. **Modulation of Lipid Metabolism**: IF can induce changes in lipid metabolism, such as increased lipolysis, reduced lipogenesis, and increased $\beta$-oxidation of fatty acids, potentially leading to a decrease in hepatic fat content.
6. **Impact on Gut Microbiota**: IF can influence gut microbiota composition, affecting bile acid metabolism and subsequently impacting lipid metabolism and hepatic steatosis.
7. **Induction of Autophagy**: IF has been shown to induce autophagy, which may reduce hepatic triglyceride levels and improve liver function, offering a potential therapeutic approach for NAFLD treatment.
8. **Modulation of Oxidative Stress and Inflammation**: IF may modulate oxidative stress and inflammation, key contributors to NAFLD pathogenesis. Studies suggest that IF may decrease indicators of oxidative stress while reducing pro-inflammatory cytokine levels and increasing anti-inflammatory cytokine levels in the liver.

Overall, the discussion highlights the complex mechanisms through which IF may influence NAFLD and suggests its potential as a dietary intervention for managing the condition through various metabolic and cellular pathways.

**Conclusions:** In conclusion, the findings from the studies reviewed highlight the potential benefits of intermittent fasting (IF) in positively affecting non-alcoholic fatty liver disease (NAFLD) through various physiological pathways. These include improvements in insulin sensitivity, modulation of lipid metabolism, induction of autophagy, modulation of oxidative stress and inflammation, and alterations in gut microbiota composition.

However, it's important to acknowledge the limitations of the current clinical evidence. Many studies are small-scale and lack long-term follow-up, which makes it challenging to establish conclusive evidence regarding the safety and efficacy of IF for NAFLD management. Moreover, the diversity of fasting regimens employed across studies complicates the establishment of standardized guidelines.

Therefore, while IF shows promise as a potential therapeutic approach for NAFLD, further research is warranted to elucidate its mechanisms and determine optimal fasting protocols. Patients should seek guidance from healthcare professionals before initiating IF or making significant dietary changes.

**Keywords:** Intermittent fastng, Liver health, Metabolism

## PE-22

### How the Scientist Minimises Mortalities with the Technology Artificial Intelligence in Hepato-Pancreato-Biliary Surgery: Is That Effective?

Zulfa Saumia, Fikri Gemilang

Universitas Jambi, Alumnus, Upn Veteran Jogjakarta, Indonesia

**Aims:** Hepato-pancreato-biliary (HPB) surgery is a general surgery for benign and malignant diseases of the liver, pancreas and gall bladder. HPB is one of the most challenging and complicated surgical procedures performed by general surgeons with high expertise and skills. How do scientists use artificial intelligence to reduce mortality rates and is it effective?

**Methods:** This abstract uses the literature study from BJS Open, Journal of surgery, HPB journal, etc.

**Results:** One of the best outcomes after surgery is achieving textbook results (TO). The success rate of TO is defined as no long-term hospitalization, no complications and no death surgical outcomes are usually best in specialized centers. They use TO as a useful measure of quality.

Second, failure and non-technical complications of emergency surgery predict 90-day mortality. Acute kidney injury, non-technical complications and surgery predict in-hospital mortality. Third, minimally invasive surgical technique (MIS) is often used in HPB with full laparoscopic technique without blood transfusion. Post-operative recovery is going well. Fourth, to minimize postoperative complications, postoperative rehabilitation can be done. Fifth, machine learning to evaluate predictive performance in hepatopancreatic biliary surgery.

**Conclusions:** Regarding prehabilitation in HPB operation, future trials with standardized measures are needed. The application of AI in HPB surgery will also produce new scientific insights.

**Keywords:** HPB, AI, Surgery

## PE-23

### Determining the Nutritional Status and Life Quality of Critically Ill Patients and Identifying the Results of Enteral Nutrition Treatment

Bayarmaa Nyamaa[1], Nandintsetseg Tumendemberel[2], Dagiisuren Bavuu[3]

[1]Mongolian National University of Medical Science, Mongolia

**Aims:** Malnutrition is prevalent among critically ill patients. Due to lack of nutrition, the mass of muscles and tissues decreases, the muscle becomes weak, and the movement capacity decreases and the decreased immune response increases the risk of infection, and respiratory failure, prolongs recovery time,

and even can lead to death.

**Methods:** A total of 60 patients were included in the study who were hospitalized in the Intensive Care Unit and Inpatient clinic of the Mongolia Japan Hospital of MNUMS. The study was conducted using a cross-sectional and hospital-based clinical trial design.

**Results:** In the current study, 43.3% of the respondents were male and 56.7% were female. 26 (43.3%) of them were malnourished, 32 (53.3%) were at risk of malnutrition, and 2 (3.3%) had normal nutritional status. In terms of quality of life, the average of the respondents was 59.32 points. After treatment, nutritional status in the trial group was changed from 17.48±3.60 points to 19.19±3.42 points ($P$<0.0066), BMI decreased from 26.10±6.29 kg/m$^2$ to 25.81±6.22 kg/m$^2$ ($P$<0.0045) and waist circumference decreased from 89.38±13.48 cm to 88.71±13.46 cm ($P$<0.0004). Quality of life in the trial group was 55.65±7.07 points before treatment and it improved to 62.59±7.83 points after treatment ($P$<0.01); in the control group, it was 62.90±6.42 points before treatment and it changed to 60.92±7.45 points after treatment ($P$<0.01).

**Conclusions:** Enteral feeding treatment in malnourished and at-risk patients has improved nutritional status, anthropometric parameters, clinical symptoms, laboratory parameters, and quality of life.

**Keywords:** Malnutrition, Critically illnes, Enteral nutrition therapy

## PE-24

### Biological Test of Biliary Stent Which Has Advanced Features Applied to Biliary System Related to Mammal

Hyung Tae Kim

Strategic Planning, R&D, Marketing, S&G Bio*tech Inc, Republic of Korea*

**Aims:** One of the most important factors when we develop the biliary stent is the biocompatibility and hemocompatibility. Because stent is the medical device which has the feature about implantable medical device to patient. If stent does not qualify these characteristics, it cannot be called as a stent. In this biological test, mammal types of animals are used.

**Methods:** This is the explanation of *in vitro* mammalian chromosomal aberration test. Cells were cultured and remove the MEM medium. MEM medium added to the culture flask. Cells were treated for 6 hours in the short-term treatment method and 24 hours in the continuous treatment method. Genotoxicity test is proceeded by the pre-incubation method.

**Results:** Following contents are the result from *in vitro* mammalian chromosomal aberration test. No precipitation or pH changes of the test substance were observed at the initiation of the test substance treatment. No inhibitory effects on bacterial growth due to the toxicity of the test substance were observed in both the metabolic activation system non-applied and metabolic activation system applied conditions. In sterility test, no contamination by bacteria or fungi was observed in the test substance.

**Conclusions:** The results indicated that, irrespective of metabolic activation, the frequencies of cells with chromosomal structural abnormalities and numerical abnormalities were both less than 5% in both short-term and continuous treatment methods. And results of the test, irrespective of the presence of metabolic activation, showed no significant increase in the number of colonies in the test substance treatment groups compared to negative control.

**Keywords:** Biliary, Biliary stent, Mammal


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# Enhanced Liver Fibrosis (ELF) Test

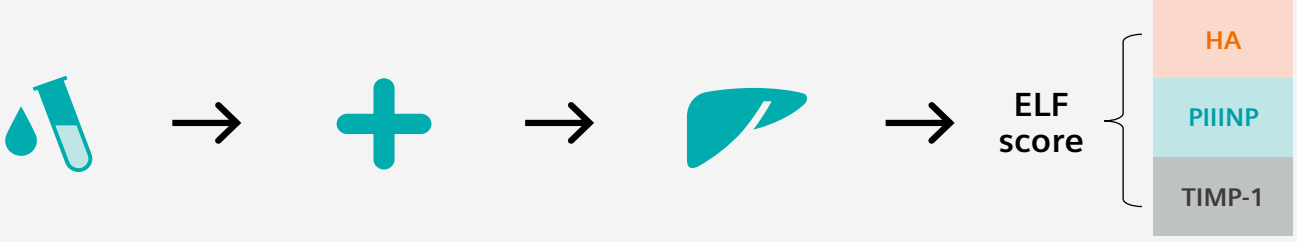
**Asses the risk of NAFLD/NASH progression with a simple blood test**

↗ siemens-healthineers.com/elf

## Enhanced Liver Fibrosis (ELF) Test

- Access non-invasive testing with a simple blood test available to all healthcare practitioners and patients, including those with type 2 diabetes mellitus and obesity.[2,3]
- Improve patient care by identifying NAFLD patients and stratifying those at risk of progressing to cirrhosis and LREs.[1]
- Enhance prognostic patient management with a test that has been shown to outperform biopsy for the risk assessment of progression to cirrhosis and LREs.[1]

## How does the ELF Test work?




The ELF Test measures three serum biomarkers, which directly contribute to liver fibrosis, in a sample of patient's blood

The three direct markers are combined into an ELF score

This ELF score indicates the risk of a patient's progression to cirrhosis, and their likelihood of having a liver-related event in the future

HA : Hyaluronic Acid
PIIINP : N-terminal Propeptide of Type III Procollagen
TIMP-1 : Tissue Inhibitor of Matrix Metalloproteinase 1

The ELF Test enables accessible, effortless, prognostic risk assessment in NAFLD/NASH and helps support the transformation of healthcare in "at-risk" patients.

**References:**
1. Sanyal AJ, et al. Hepatology. 2019;70(6): 1913–1927.
2. Patel P, et al. Hepatol Commun. 2018;2:893–905.
3. Karlas T, et al. PLoS ONE. 2015;10(11):e0141649.

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**IMBrave150 :** 501patients with unresectable hepatocellular carcinoma who had not previously received systemic treatment were randomly assigned in a 2:1 ratio to receive either atezolizumab plus bevacizumab or sorafenib. The coprimary endpoints were OS and IRF assessed PFS. **HR :** Hazard ratio **CI :** Confidence interval **OS :** Overall survival **IRF :** Independent review facility **PFS :** Progression free survival **References 1.** Finn et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905. May 14, 2020.
**2.** AL Cheng, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2021 Dec 10;S0168-8278(21)02241-8. *descriptive purpose only

*보다 자세한 제품정보 문의 및 제품 관련 부작용 보고는 (주)한국로슈 (02-3451-3600) 로 연락 주시기 바랍니다 *티쎈트릭과 아바스틴의 최신 제품정보는 QR code 를 스캔하여 확인하실 수 있습니다.

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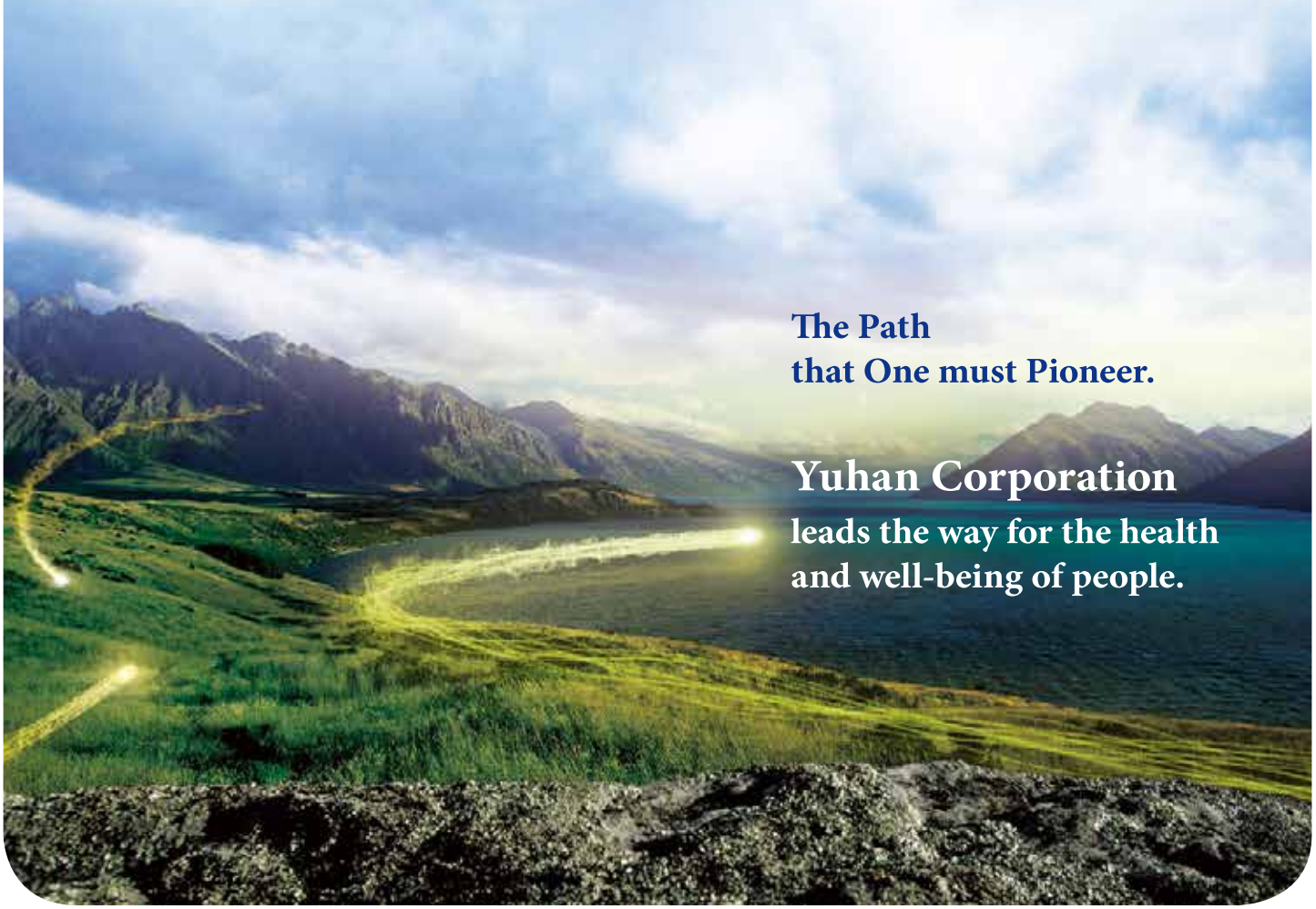
# Elecsys® PIVKA-II[1]

## A sensitive and accurate tool for use as an aid in the diagnosis of hepatocellular carcinoma (HCC)[2]

References
1. Elecsys PIVKA-II (체외 수허 20-8호) *"Sensitivity 86.9%, Specificity 83.7%"*
2. Roche studies No. RD002542 and RD002543

MC-KR-00711

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* Diabetes Ther. 2020 Apr;11(4):859-871(rosuvastatin 10mg monotherapy 대비 로수바이브 10/5mg의 유효성과 안전성을 확인). § 2022년 유비스트 '로수바이브정' 처방건 수 기준

전문의약품

**로수바이브정(에제티미브/로수바스타틴칼슘) 10/5mg, 10/10mg, 10/20mg [원료약품 및 분량]** • 로수바이브 10/5mg : 에제티미브(USP) 10.0mg, 로수바스타틴칼슘(별규) 5.2mg(로수바스타틴으로서 5mg) • 로수바이브 10/10mg : 에제티미브(USP) 10.0mg, 로수바스타틴칼슘(별규) 10.4mg(로수바스타틴으로서 10mg) • 로수바이브 10/20mg : 에제티미브(USP) 10.0mg, 로수바스타틴칼슘(별규) 20.8mg(로수바스타틴으로서 20mg) **[성상]** • 로수바이브 10/5mg : 분홍색의 장방형 필름코팅정 • 로수바이브 10/10mg : 노란색의 장방형 필름코팅정 • 로수바이브 10/20mg : 분홍색의 달걀형 필름코팅정 **[효능 · 효과]** 원발성 고콜레스테롤혈증; 원발성 고콜레스테롤혈증(이형접합 가족형 및 비가족형) 또는 혼합형 이상지질혈증 환자의 상승된 총 콜레스테롤(totalC), LDL-콜레스테롤(LDL-C), 아포 B 단백(Apo B), 트리글리세라이드(TG) 및 non-HDL-콜레스테롤을 감소시키고, HDL-콜레스테롤(HDL-C)을 증가시키기 위한 식이요법의 보조제로서 이 약을 투여합니다. 고콜레스테롤혈증에 기인한 동맥경화성 혈관 질환의 위험성이 증가한 환자에게 지질조절약물을 투여할 때에는 많은 위험 인자를 고려해야 합니다. 지질조절약물은 적절한 식이요법(포화지방 및 콜레스테롤 제한을 포함)과 함께 사용하고, 식이요법 및 다른 비약물학적 조치에 대한 반응이 불충분한 경우에 사용해야 합니다. 이 약 투여에 앞서 이상지질혈증의 다른 이차적 원인(예를 들면, 당뇨, 갑상선기능저하증, 폐쇄성 간질환, 만성 신부전, LDL-콜레스테롤을 증가시키는 약물 및 HDL-콜레스테롤을 감소시키는 약물[progestin, anabolic steroid, 및 corticosteroid])을 확인하여야 하며, 필요한 경우 이차적 원인을 치료해야 합니다. 지질 검사시에는 총콜레스테롤, LDL-콜레스테롤, HDL-콜레스테롤 및 트리글리세라이드를 포함해야 합니다. 트리글리세라이드 수치가 400mg/dL 이상(4.5mmol/L 이상)인 경우에는 초원심분리로 LDL-콜레스테롤 농도를 측정해야 합니다. 급성 관상동맥 사고로 입원할 경우에는 입원 시 혹은 입원 후 24시간 이내에 지질을 측정해야 합니다. 환자의 퇴원 전 혹은 퇴원 시에 LDL 저하치료를 시작하는데 있어 이 측정치가 참고가 될 수 있습니다. **[용법·용량]** 이 약은 식사와 관계없이 1일 1회 투여합니다. 이 약을 투여하기 전 또는 투여 중인 환자는 반드시 표준 콜레스테롤 저하식을 지속적으로 해야 합니다. 이 약의 투여량은 환자의 LDL-콜레스테롤의 기저치, 권장되는 치료목표치 및 환자의 반응에 따라 조절되어야 합니다. 원발성 고콜레스테롤혈증: 이 약의 용량범위는 1일 10/5mg~10/20mg입니다. 초회용량으로 1일 10/5mg이 권장됩니다. LDL-콜레스테롤 감소가 더 많이 요구되는 환자의 경우 용량을 조절하여 투여할 수 있습니다. 이 약의 투여를 시작한 후 또는 용량을 적정한 후에는 4주 이상의 간격을 두고 혈중 지질 수치를 확인한 후 그에 따라 용량을 조절하며, 1일 최대 10/20mg까지 증량할 수 있습니다. 에제티미브와 로수바스타틴을 병용으로 복용하고 있는 환자인 경우, 복용의 편리함을 위하여 이 약(개개의 주성분 함량이 동일한 복합제)으로 전환할 수 있습니다. **[사용상의 주의사항]** 1. 다음 환자에는 투여하지 마십시오. 1) 이 약의 주성분 또는 구성성분에 과민반응이 있는 환자 2) 활동성 간질환 환자 또는 혈청 아미노전달효소 수치가 원인불명으로 지속적으로 높은 증상을 수반한 환자('5. 일반적 주의' 참조) 3) 근질환 환자 4) 사이클로스포린 병용투여 환자 5) 중증의 신부전의 신장애 환자(creatinine clearance (CLcr)<30mL/min) 6) 임부 또는 임신하고 있을 가능성이 있는 여성 및 수유부 ('7. 임부 및 수유부에 대한 투여' 참조) 7) 근병증/횡문근융해증에 걸리기 쉬운 환자들에게 로수바스타틴 40밀리그램 용량 투여는 금기입니다. 이러한 인자들은 아래와 같습니다. (1) 중등도의 신장애 (크레아티닌 청소율 < 60ml/min) (2) 갑상선기능저하증 (3) 유전적인 근질환 병력 또는 가족력이 있는 경우 (4) 다른 스타틴계 약물(HMG-CoA 전환효소 저해제) 또는 피브레이트 계열 약물에 대한 근육 독성의 병력이 있는 경우 (5) 알코올 중독 (6) 혈장 농도가 증가할 수 있는 상황 (7) 아시아계 환자 (8) 피브레이트 계열 약물 병용투여 8) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 됩니다.자세한 내용은 제품설명서 참조) **[저장방법]** 기밀용기, 실온(1~30℃) 보관 **[포장단위]** 30정(PTP), 100정(병) **[개정연월일]** 22.10.21 ※ 제품에 대한 자세한 내용은 최신의 제품설명서 또는 식약처 의약품통합정보시스템 홈페이지(https://nedrug.mfds.go.kr/)를 참조하여 주시기 바랍니다.

제조판매자
유한양행
• 본사 : 서울 동작구 노량진로 74 • 공장 : 충청북도 청주시 청원구 오창읍 연구단지로 219
• 홈페이지 : www.yuhan.co.kr • 소비자상담실 : 080-024-1188 (수신자 요금부담)

로수바스타틴과 에제티미브의 복합제
로수바이브®정

KR-RSM-2300002

DAEWOONG

# The new wave of GERD Treatment, P-CAB

# FEXUCLUE

Fexuprazan hydrochloride

- Full and fast onset of effect with the first dose
- Rapid and superior heartburn symptom relief
- Excellent nocturnal symptom control: Longest half-life
- Significantly improved chronic cough of EE
- Take once a day regardless of meal
- Less affected by CYP2C19: Low potential of DDI · individual variations


**【Product name】** Fexuclue Tab. 40mg **【Formulation】** Active Pharmaceutical Ingredient: Fexuprazan HCl 40 mg Additives: lactose hydrate (bovine, milk), Yellow No.4, Microcrystalline Cellulose, Magnesium stearate, Opadry Green AMB2 88A610038, Opadry White 03B28796, Croscarmellose Sodium, Yellow Iron Oxide. **【Appearance】** Pale-green, Oblong film-coated tablet with the breaking line on the tablet **【Indication】** Treatment of erosive esophagitis (EE) **【Dosage and Administration】** The Product is administered to adults as follows. • Treatment of erosive esophagitis (EE) - 40 mg is administered orally once a day for 4 weeks. - In the case of patients with untreated esophagitis or symptoms persisting, the administration given for another 4 weeks. The Product can be administered with or without meals. **【Contraindications】** 1) Patients who have a history of hypersensitivity to the Product or its components 2) Patients taking a drug containing atazanavir, nelfinavir, or rilpivirine (refer to '5. Interactions') 3) Pregnant and lactating women (refer to '6. Administration to Pregnant and Lactating Women') 4) Patients who have congenital conditions for lactose such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, as this medicine contains lactose **【The following patients should be administered with care.】** 1) Patients with hepatic impairment (no experience of use) 2) Patients with renal impairment (no experience of use) 3) Elderly (refer to '8. Geriatric Use') 4) Patients who have a history of hypersensitivity or allergy to Yellow 4 Tartrazine **【Storage】** Store at temperatures not exceeding 30°C in an airtight container **【Shelf-life】** 36 Months **【Availability】** 28T/Box (7T/PTP*4), 56T/Box (7T/PTP*8), 28T/Btl, 100T/Btl, 300T/Btl **【Manufactured by】** Daewoong Pharmaceutical Co., Ltd./ 1, Osongsaengmyeong 2-ro, Osong-eup, Heungdeok-gu, Cheongju-si, Chungcheongbuk-do, Republic of Korea ※ This medicine has passed strict quality control. If the use-by date or expiration date has passed at the time of purchase, or it the drug is spoiled, contaminated, or damaged, it can be exchanged or refunded through the pharmacy or drug distributor where it was purchased in accordance with the Fair Trade Commission Notice (Consumer Dispute Resolution Standard) ※ Report side effects and apply for damage relief: Korea Pharmaceutical Safety Management Agency (14-3330, 1644-6223)
※ For detailed and up-to-date approval information, please refer to the Ministry of Food and Drug Safety's integrated drug information system (https://nedrug.mfds.go.kr) or the product label.

For healthcare professionals only

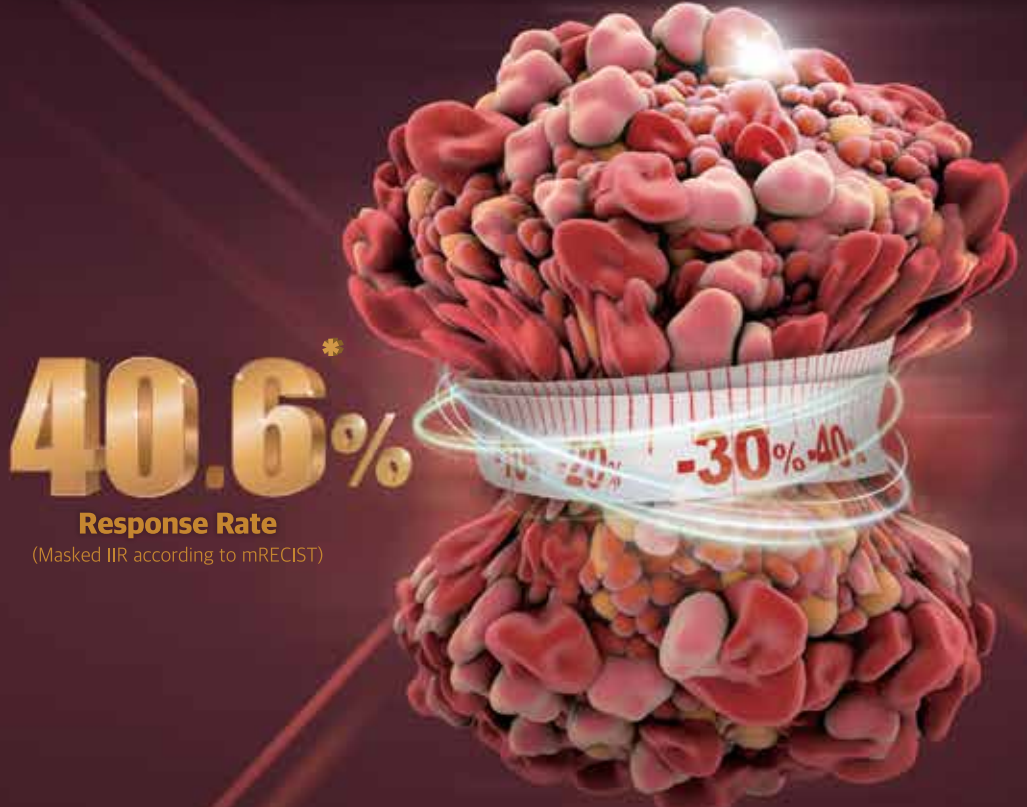
LENVIMA® (lenvatinib) capsules
RESPONSE THAT MATTERS

# Remarkable Response

**The ORR was more than three times higher** with lenvatinib versus control group.[1]

Based on the masked IIR according to mRECIST,

**about 41% of patients* showed ≥ 30% decrease in tumor size.**[1,2]




* ORR is one of the secondary endpoints and this is the result of the post-hoc exploratory tumour assessments using mRECIST by masked central independent imaging review. For more information, please refer to the full text of the article. (Kudo M, et al. 2018)

**[Study design]** This was an open-label, phase 3, multicentre, non-inferiority trial that recruited patients with unresectable hepatocellular carcinoma, who had not received treatment for advanced disease, at 154 sites in 20 countries throughout the Asia-Pacific, European, and North American regions. Patients were randomly assigned (1:1) via an interactive voice-web response system-with region; macroscopic portal vein invasion, extrahepatic spread, or both; Eastern Cooperative Oncology Group performance status; and bodyweight as stratification factors-to receive oral lenvatinib (12 mg/day for bodyweight ≥60 kg or 8 mg/day for bodyweight <60 kg) or sorafenib 400 mg twice-daily in 28-day cycles. The primary endpoint was overall survival, measured from the date of randomisation until the date of death from any cause. The efficacy analysis followed the intention-to-treat principle, and only patients who received treatment were included in the safety analysis. Lenvatinib(median OS 13.6 months, 95% CI 12.1-14.9) was non-inferior to sorafenib(median OS 12.3 motnhs, 95% CI 10.4-13.9) in overall survival in untreated advanced hepatocellular carcinoma(HR 0.92, 95% CI 0.79-1.06).[1]

| | Lenvatinib (n=478) | Sorafetinib (n=476) | Effect size (95% CI) | *P* value |
|---|---|---|---|---|
| **Investigator review according to mRECIST** | | | | |
| Objective response (%, 95% CI) | 115 (24.1%, 20.2-27.9) | 44 (9.2%, 6.6-11.8) | OR 3.13 (2.15-4.56) | <0.0001 |
| **Masked Independent Imaging review according to mRECIST** | | | | |
| Objective response (%, 95% CI) | 194 (40.6%, 36.2-45.0) | 59 (12.4%, 9.4-15.4) | OR 5.01 (3.59-7.01) | <0.0001 |
| **Masked Independent Imaging review according to RECIST 1.1** | | | | |
| Objective response (%, 95% CI) | 90 (18.8%, 15.3-22.3) | 31 (6.5%, 4.3-8.7) | OR 3.34 (2.17-5.14) | <0.0001 |

mRECIST, modified Response Evaluation Criteria in Solid Tumors; IIR, Independent imaging review; ORR, Objective Response Rate; CI, Confidence Interval; uHCC, unresectable hepatocellular carcinoma; OR, Odds ratio; OS, Overall Survival

**[References]** 1. Kudo M et al. Lancet. 2018 Mar 24;391(10126):1163-1173 2. Lencioni R, Llovet JM. Semin Liver Dis. 2010 Feb;30(1):52-60

**Lenvim 4mg, 10mg Capsules (Lenvatinib mesilate) [Composition]** 4mg capsule: Active ingredient: lenvatinib mesilate (in house specification) -4.90mg (4.0mg equivalent to lenvatinib free base) 10mg capsule: Active ingredicent: lenvatinib mesilate (in house specification) -12.25mg (10.0mg equivalent to lenvatinib free base) **[Therapeutic indication]** 1. Lenvima is indicated for the treatment of patients with progressive, locally recurrent or metastatic, differentiated thyroid carcinoma (DTC), refractory to radioactive iodine (RAI). 2. LENVIMA is indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma. 3. LENVIMA, in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. **[Dosage and administration]** 1) Posology **DTC** In Adults the recommended daily dose of Lenvima is 24 mg taken once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan (See 2) Dose Adjustment section below). **HCC** The recommended dosage of LENVIMA is based on actual body weight: • For patients greater than or equal to 60 kg: 12 mg • For patients less than 60 kg: 8 mg Take LENVIMA orally once daily until disease progression or until unacceptable toxicity. There is no clinical evidence to support the use of 10 mg dose in HCC. **Endometrial Carcinoma** The recommended dosage of LENVIMA is 20 mg orally once daily, in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks, until unacceptable toxicity or disease progression. Refer to the pembrolizumab prescribing information for recommended pembrolizumab dosing information. **[Precautions for Use]** 1. Contraindications 1) Hypersensitivity to the active substance or to any of the excipients 2) Breast-feeding 2. Careful Administration 1) Patients with hypertension 2) Patients with thromboembolism or a history of the condition 3) Patients with brain metastasis 4) Patients in whom the wound from a surgical procedure has not yet healed 5) Patients with tumor invasion to the cervical artery/vein, etc. **[Importer]** Eisai Korea Inc. 10F Revessant, 6, Bongeunsa-ro 86-gil, Gannam-gu, Seoul, 135-878, Korea (tel 02-3451-5500) - Date of written manual: Jul 1st, 2021 - For details, please refer to the full prescribing information.

Eisai Korea Inc.

**EISAI KOREA** 10F Revessant, 6, Bongeunsa-ro 86-gil, Gangnam-gu, Seoul, 06163, Korea TEL: 02-3451-5500

KR-LVM-2106-01

Vemlidy®
tenofovir alafenamide 25mg tablets

# VEMLIDY-for the flow of life with chronic hepatitis B

## 평생 관리해야 하는 만성 B형 간염[1],
## 환자의 생애주기를 고려한다면[2], Vemlidy® 로 시작해 주세요.[1,3,4]

**References** 1. 2018 대한간학회 만성 B형 간염 진료 가이드라인 2. Oh H, et al. Aliment Pharmacol Ther 2020;52:371-81. 3. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection 4. Terrault NA, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560-1599.

**베믈리디®정 (테노포비르알라페나미드헤미푸마르산염)**

**[수입자]** 길리어드 사이언스 코리아(유), 서울특별시 중구 을지로5길 26 센터원빌딩 서관 15층 (대표전화: 02-6030-3300, 제품관련문의: 0079-814-800-9172 (수신자 부담))

* 처방하시기 전에 반드시 허가사항 전문을 확인하여 주시기바랍니다. 최신 허가사항은 아래 QR 코드를 통해 확인하실수 있으며, 길리어드사이언스코리아 홈페이지(www.gilead.co.kr) 또는 식품의약품안전처 의약품통합정보 시스템 (http://nedrug.mfds.go.kr) 에서도 보실 수 있습니다.)

GILEAD YUHAN

KR-VEM-0185_v1.0(29/August/2023)

QR 코드를 스캔하여
Vemlidy® PI를 확인하십시오.

IMFINZI®
durvalumab
Injection for Intravenous Use 50 mg/mL

IMJUDO™
tremelimumab
Injection for Intravenous Use 20 mg/mL

For HCPs only

# The only* IO-IO combination in first-line advanced or unresectable HCC[1,2]

*2023-06-30 기준

**IMFINZI + IMJUDO :**
**The First-line treatment of advanced or unresectable HCC with extension of overall survival vs. sorafenib[1]**

# REACH BEYOND

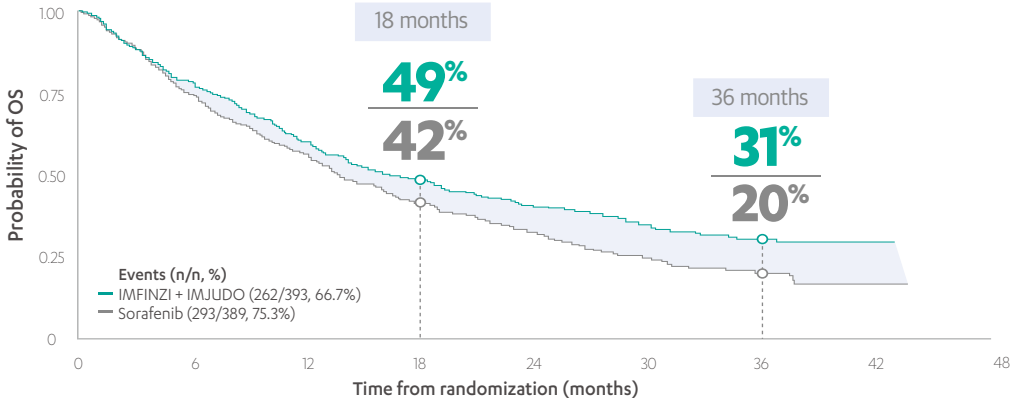
**with IMFINZI + IMJUDO**

## IMJUDO in combination with IMFINZI is indicated for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma[2]

## STATISTICALLY SUPERIOR OVERALL SURVIVAL (primary endpoint)

IMFINZI + IMJUDO achieved a statistically significant 22% reduction in risk of death vs sorafenib (HR, 0.78; 96.02% CI, 0.65-0.93; *P*=0.0035; Median OS: 16.4 months (95% CI,14.2-19.6) with IMFINZI + IMJUDO vs 13.8 months (95% CI, 12.3-16.1) with sorafenib[1]

### OVERALL SURVIVAL IN THE INTENT-TO-TREAT POPULATION (primary endpoint)[1]




| Number of patients at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| IMFINZI + IMJUDO | 393 | 308 | 235 | 190 | 158 | 98 | 32 | 1 | 0 |
| Sorafenib | 389 | 283 | 211 | 155 | 121 | 62 | 21 | 1 | 0 |

Adapted from Abou-Alfa GK, et al. *NEJM Evidence. 2022.*

**HCC**=Hepatocellular carcinoma; **OS**=Overall survival; **CI**=Confidence interval; **HR**=Hazard ratio

**Study design[1] :** this is a double-blind, placebo-controlled, phase 3 study, patients with previously untreated unresectable or metastatic biliary tract cancer or with recurrent disease were randomly assigned in a 1:1 ratio to receive durvalumab or placebo in combination with gemcitabine plus cisplatin for up to eight cycles, followed by durvalumab or placebo monotherapy until disease progression or unacceptable toxicity. The primary objective was to assess overall survival. Secondary end points included progression-free survival, objective response rate, and safety.

## References


**1.** Abou-Alfa GK, et al. Tremelimumab Plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evidence;1(8):1-12.
**2.** 이뮤도주 제품설명서 (https://nedrug.mfds.go.kr/pbp/CCBBB01/getItemDetailCache?cacheSeq=202301925aupdateTs2023-06-27%2013:59:15.70742b) (Accessed on June 30, 2023).


※ 보다 자세한 사항은 임핀지주(더발루맙) 제품설명서 전문을 참고하시기 바랍니다.

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KR-13941 | Exp.2025-07(Pre 2023-07)


Samil


# For QoL of Patients with Liver Disease – LIVACT®

# Original Branched Chain Amino Acids(BCAA) – LIVACT®

- Detoxification of Ammonia – Improvement of Hepatic Encephalopathy[1]
- Improvement of hypoalbuminemia by liver regeneration[2]
- Improvement of Sarcopenia[3]
- Improvement of Nutrition status for patients with Liver cirrhosis[4]

**References** **1.** Nutr Clin Pract. 2013 Oct;28(5):580-8 **2.** Muto Y et al. Clinical Gastorenterology and Hepatology 2005;3:705-713 **3.** Hanai T, Shiraki M, Shimizu M, Moriwaki H et al. Nutrition. 2015;31:193-9, Koya et al.,Hepatol Res 2017;47;E22-34 **4.** J Gastroenterol (2016) 51:629-650

**Product name:** LIVACT granules **Composition:** L-isoleucine 925mg, L-leucine 1904mg, L-Valine 1144mg **Indication:** decompensated Liver cirrhosis patients with hypoalbuminemia even though diet intake is sufficient **Dosage:** three times a day after meals **Unit:** 4.15g X 42

오리지널 BCAA
LIVACT®
Granules

# Vemlia

tenofovir alafenamide 25mg tabletes

## Our heartfelt wish for curing HBV, we present Vemlia.

- Comparable antiviral efficacy vs. TDF[1]
- Improved safety profile in renal and bone parameters[2]
- Increased affordability with lower price, 2,474/tablet[3]*
- Improved patients' compliance with daily pill bottle[4]


1. Agarwal K, et al. J Hepatol. 2018, 68, 672–681
2. Lampertico P, et al. Lancet Gastroenterol Hepatol. 2020 May;5(5):441-453.
※ The data above are clinical data conducted with Tenofovir alafenamide hemi-fumarate.
3. https://www.health.kr/searchDrug/result_drug.asp?drug_cd=2022122100010 약학정보원, 베믈리아 의약품 상세정보, accessed on April 2023
4. Vervloet M, et al. J Am Med Inform Assoc 2012;19(5):696-704.
*896 won lower price than Original drug (June 2023)

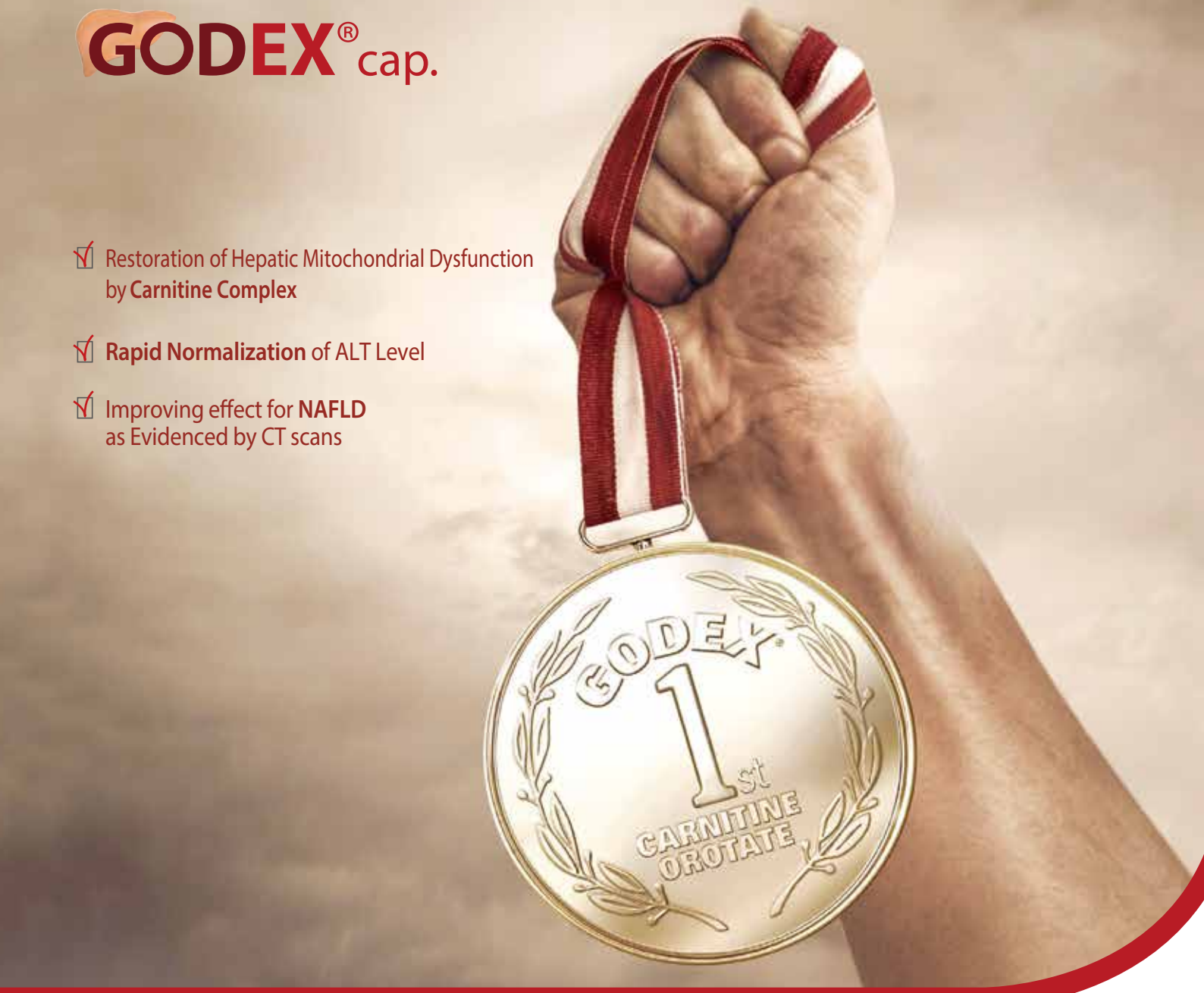

동아ST

VMA-23F011

# Confidence for NAFLD treatment

## Evidenced by numerous clinical results

**GODEX® cap.**




- Restoration of Hepatic Mitochondrial Dysfunction by **Carnitine Complex**
- **Rapid Normalization** of ALT Level
- Improving effect for **NAFLD** as Evidenced by CT scans

### Product Information

**| Description |** Reddish brown colored hard gelatin capsule containing yellowish brown colored powder **| Composition |** Each capsule contains Carnitine Orotate 150mg (73.8mg as orotic acid, 76.2mg as carnitine), Liver Extract Antitoxic fraction 12.5mg, Adenine HCl 2.5mg, Pyridoxine HCl 25mg, Riboflavin 0.5mg, Cyanocobalamin 0.125mg, Biphenyl dimethyl dicarboxylate 25mg **| Indication |** 1) General therapeutics for the following hepatic disease - Acute, Subacute and Chronic Hepatitis, Hepatic cirrhosis, Fatty liver, Drug or chemical induced hepatitis 2) Acute, chronic hepatitis involving high transaminase value **| Dosage & Administration |** Usually, each time 2 capsules, 2~3 times a day as adult dosage. Dosage unit can be changeable depending on symptom or age of patient. **| Special caution |** 1) Severe state of chronic hepatitis 2) Severe state of hapatic cirrhosis **| General caution |** 1) Rarely skin rash can be represented, in this case general antihistamin therapy will be required. 2) In severe case, sometimes intermittent jaundice can be occur in this case, discontinue administration for awhile and other adjuvant therapy for jaundice shall be required. 3) Rarely nausea, gastric discomfortness can be represented. 4) Rarely itching or reddness can be occur, in this case, discontinue administration and follow physician's instruction. **| Insurance Code |** 693900080 **| Packing Unit |** 100, 300 caps. (bottle)/ 100 caps. (PTP) **| Storage |** Tight closed container, room temperature (1~30℃) in dry place. Expiry - 60 months from Manufacturing date.

### Diagnostic Codes

**B15-19** Viral hepatitis **K70.0** Alcoholic fatty liver **K71.0** Toxic liver disease **K73.0** Chronic persistent hepatitis, NEC **K74.0** Hepatic fibrosis **K75.8** Other specified inflammatory liver disease, Nonalcoholic steatohepatitis **K77.0** Liver disorders in disease classified elsewhere

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GODEX® cap.

**MAVIRET**®
glecaprevir/pibrentasvir


# Quickly† deliver cure‡ with 8-week MAVIRET so your patients§ can move forward free from HCV.

*Free from HCV with cure. †For GT 1–6 treatment-naïve, non-cirrhotic and compensated-cirrhotic patients, 8-week MAVIRET versus 12-week MAVIRET.
‡Cure=sustained virologic response (SVR12), defined as HCV RNA less than the lower limit of quantification at 12 weeks after the end of treatment.
§GT 1–6 treatment-naïve, non-cirrhotic and compensated-cirrhotic patients. MAVIRET is not indicated in decompensated cirrhosis.

**MAVIRET** is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C).[1]
**MAVIRET** is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adult and adolescent patients over 12 years of age.[1]

**References 1.** MAVIRET® Product information(Revised from 16th Feb 2023).

**[Product name]** Maviret® Tab. **[Ingredients and quantity]** Glecaprevir 100.0mg, pibrentasvir 40.0mg
**[Importer/Distributor]** AbbVie Korea, 6th floor, Samtan Building, 421, Yeongdong-daero, Gangnam-gu, Seoul, Korea, Tel: 02) 3429-9300, www.abbvie.co.kr
※ For the latest and full product information, please refer to the QR code or product information.
※ To report adverse events and apply for damage relief: Korea Institute of Drug Safety & Risk Management (1644-6223 or 14-3330, www.drugsafe.or.kr)
KR-MAVI-240023 / Mar 2024

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oral suspension Megace® (megestrol acetate, USP)

Oral Suspension Megace® F (megestrol acetate, USP)

# 메게이스®가 항상 선생님을 응원합니다.

**식욕 개선, 체중 증가, QOL개선을 통해 암환자의 생존률 증가에 도움이 될 수 있습니다.**

**Megestrol Acetate Original Product**입니다.

**국내에서 가장 많이 처방**되어지고 있습니다.

**FDA승인**을 받은 유일한 **Megestrol Acetate 제제**입니다.


**No Food Effect ✓**
식전, 식후 상관없이 편리하게

**더 낮아진 점도 ✓**
목넘김 개선을 통해복용순응도향상

**더 적어진 용량 ✓**
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**더 빠르고 강해진 효과 ✓**
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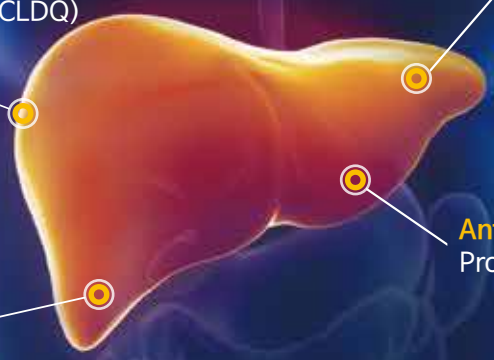
# Damaged Livers Can Be Recovered

**The Only Korean Medicine Proven to Reduce the Level of MDA, a Biomarker of Oxidative Stress, Through Phase IV Clinical Trials**
Significantly Reduced the Level of MDA in Alcoholic Hepatitis, Nonalcoholic Steatohepatitis and Viral Hepatitis Patients

**Safe Medicine Proven to Improve Quality of Life for Patients**
Patients' Improved Quality of Life Verified Through Chronic Liver Disease Questionnaire (CLDQ)



**Antioxidative Effect Reduces Fat in the Liver**
Proven to Reduce MDA Level

**Proven Efficacy**
Quickly Reduces and Helps You Maintain Optimal Level of Alanine Transaminase (ALT)
Contains Garlic Oil Which is Known to Have Strong Antioxidative and Anti-Inflammatory Effects

PENNEL®


**[Ingredients]** Chronics hepatitis with continuously elevated ALT level
**[Directions]** Take 1 or 2 capsules each time, 3 times a day, after meals

Diagnostic Code
B15-19 Viral hepatitis K70.0 Alcoholic fatty liver K71.0 Toxic liver disease K73.0 Chronic persistent hepatitis, NEC
K74.0 Hepatic fibrosis K75.8 Other specified inflammatory liver disease,
Nonalcoholic steatohepatitis K77.0 Liver disorders in disease classified elsewhere

Baraclude® (entecavir) 0.5mg/1mg tablets

15년간의 입증된 증거와 임상 경험을 보유한 CHB 치료제[1]

# 바라크루드®

VIEW
Values In Evidence and real-World-data

# 바라 보다. 바로 보다.

• 간경변을 동반한 경우에도[2,3] • HBV DNA 레벨에 관계 없이[4] • 신질환, 골질환의 위험이 있거나 동반한 경우에도[2,5,6]

**Reference 1.** 바라크루드정 국내허가사항. 식품의약안전처. 의약품통합정보시스템. Available at https://nedrug.mfds.go.kr/searchDrug. Accessed Feb 01, 2021 **2.** 대한간학회. 만성 B형간염 진료 가이드라인 2018. **3.** Chang TT, et al. Hepatology 2010;52:886-93. **4.** Wu IT, et al. Clin Microbiol Infect 2017;23:464-469. **5.** AASLD. Practice Guidance. 2018. **6.** EASL. Clinical Practice Guidelines on the management of hepatitis B virus infection. 2017.

**[원료약품의 분량]** [0.5mg] 1정(206mg) 중 엔테카비르(별규) 0.53mg(엔테카비르무수물로서 0.5mg) [1.0mg] 1정(412mg) 중 엔테카비르(별규) 1.06mg(엔테카비르무수물로서 1.0mg) [시럽 0.05mg/mL] 100mL 중 엔테카비르(별규) 5.3mg(엔테카비르무수물로서 5.0mg) **[주의]** 제품설명서의 사용상의 주의사항 참조 **[효능·효과]** 활동성 바이러스의 복제가 확인되고, 혈청 아미노전이효소(ALT 또는 AST)의 지속적 상승 또는 조직학적으로 활동성 질환이 확인된 성인(16세 이상)과 2세 이상의 소아 환자의 만성 B형간염 바이러스 감염의 치료 **[용법·용량]** 1. 성인(16세 이상)의 권고 용량: 1일 1회 엔테카비르로서 0.5mg(시럽제의 경우 10mL) 경구투여. 라미부딘 저항성 환자, 즉, 라미부딘 치료에도 불구하고 B형간염 바이러스의 지속적 증식을 경험하였거나, 라미부딘 저항성 변이가 있는 16세 이상의 환자: 1일 1회 공복시 엔테카비르로서 1mg(시럽제의 경우 20mL) 2. 소아의 권고 용량: 제품설명서 참조 **[사용상 주의사항]** 1. 경고 1) 유산증 및 지방증이 있는 중증 간종대 : 간질환에 대한 알려진 위 험인자 들을 가진 환자 2) 항B형간염 요법을 중단한 환자 3) HIV와 HBV에 함께 감염된 환자 2. 다음 환자에게 투여하지 말 것 1) 과민반응이 있는 환자 2) 갈락토오스 불내성, 유당분해효소 결핍증, 포도당-갈락토오스 흡수장애 등의 유전적 문제가 있는 환자
***신부전 환자의 용량 조절 및 자세한 내용은 제품설명서를 참조하십시오.**

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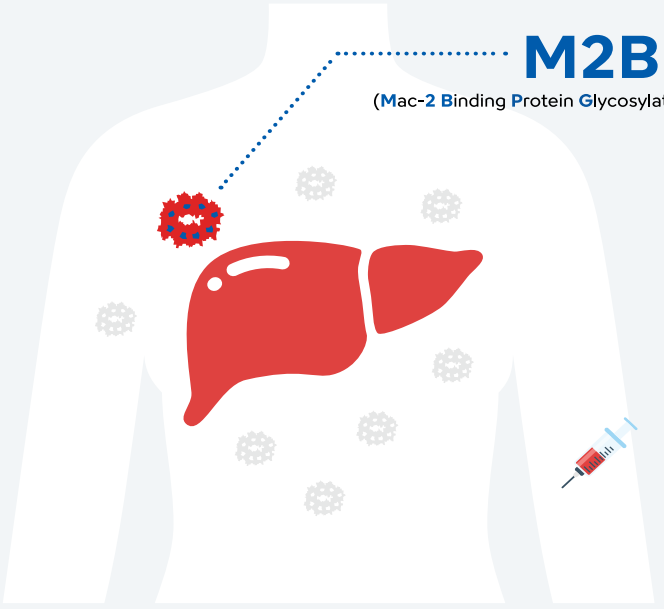
686-KR-2200095 Aug.2022/Jul.2024

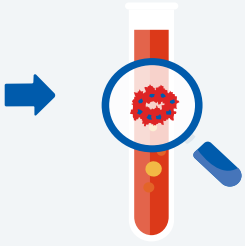
# Liver Fibrosis Single Biomarker



**M2BPGi**
(Mac-2 Binding Protein Glycosylation isomer)

[ **M2BPGi** forms in blood when hepatic fibrosis occurs ]

**Collect blood** for M2BPGi test



Measure with full **automated system**

Sysmex "HISCL-800"

**The only single biomarker** that is approved reimbursement (Code: D1980)

**Pick up only 10μl** of serum

Test time **17min**

**Included in the KASL clinical practical guidelines** for managing NAFLD and CHB

## Subject & Utility of M2BPGi Test

**Diabetes:** There is a high possibility of advanced hepatic fibrosis with an abnormal M2BPGi level (>1.0).[1]

**NAFLD patients:** Serum M2BPGi could serve as a reliable biomarker for diagnosing advanced fibrosis and cirrhosis.[2]

**Liver fibrosis risk population:** Serum M2BPGi has proven to be a dependable, non-invasive surrogate marker for predicting advanced fibrosis.[3]

**CHB patients receiving long-term antiviral treatment:** The serum M2BPGi level functions as an independent predictor of HCC and complements the stratification of HCC risks.[4]

**CHB with oral antiviral therapy:** A baseline M2BPGi level above 1.73 consistently demonstrated predictive value for higher HCC risk.[4]

**TACE treatment for HCC:** The combination of M2BPGi and up-to-seven criteria could serve as a surrogate marker for predicting CP grade deterioration.[5]

**CHB:** The M2BPGi level can predict HCC development independently.


References
**1.** Park H, *et al. Ann Transl Med.* 2020;8(23):1583 **2.** Jang SY, *et al. Ann Lab Med.* 2021;41(3):302-309. **3.** Kim M, *et al. J Clin Med.* 2020;9(4):1119. **4.** Tseng TC, *et al. Liver Cancer.* 2020;9(2):207-220. **5.** Eso Y, *et al. Cancers (Basel).* 2019;11(3):405.
**6.** Kim SU. *et al. Liver Int.* 2016; 1-9.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GODEX® cap.

# Carnitine Complex의
# NAFLD 치료 효과

## Beyond ALT/AST normalization effect

- ✔ Carnitine 성분의 **미토콘드리아 회복** 효과
- ✔ 영상학적으로 입증된 **지방간 개선**효과
- ✔ **인슐린 저항성 개선**효과


### 고덱스®캡슐

**성상** | 황갈색의 분말이 들어있는 상 · 하 적갈색 불투명의 경질캡슐제 | **성분 · 함량** | 1캡슐 중 Carnitine orotate 150mg Liver extract antitoxic fraction 12.5mg Pyridoxine HCl 25mg Riboflavin 0.5mg Cyanocobalamin 0.125mg Biphenyl Dimethyl Dicarboxylate 25mg Adenine HCl 2.5mg | **효능 · 효과** | 트란스아미나제(SGPT)가 상승된 간질환 | **용법 · 용량** | 통상 성인 1회 2캡슐, 1일 2~3회 복용, 연령, 증상에 따라 적의 증감. | **사용상의 주의사항** | 1. 다음 환자는 투여 하지 말 것. 1) 이 약 및 이 약에 포함된 성분에 과민반응이 있는 환자 2) 레보도파를 투여 받고 있는 환자 2. 다음 환자는 신중히 투여할 것. 1) 만성 활동성 간염 환자 2) 간경화 환자 3. 이상반응 1) 간혹 입안마름, 메스꺼움, 발진, 가려움증, 발적 등이 생길 수 있으며, 이러한 이상반응은 투약을 중지하거나 항과민약을 병용투여하면 소실된다. 2) 일과성 황달이 나타날 수 있으나 투약을 중지하거나 황달치료제를 병용투여하면 소실된다. 3) 드물게 구역, 복부팽만, 변비, 메스꺼움, 상복부 불쾌감이 나타날 수 있다. | **보험코드** | 693900080 | **포장단위** | 100캡슐, 300캡슐(병) / 100캡슐(PTP) | **저장방법** | 기밀용기, 실온보관(1~30℃)

### 고덱스®캡슐 상병코드

B15-19 바이러스성 간염(Viral hepatitis) K70.0 알코올성 지방간(Alcoholic fatty liver) K71.0 독성 간질환(Toxic liver disease) K73.0 달리 분류되지 않은 만성 지속성 간염(Chronic persistent hepatitis, NEC) K74.0 간섬유증(Hepatic fibrosis) K75.8 기타 명시된 염증성 간질환, 비알코올성 지방간염(Other specified inflammatory liver disease, Nonalcoholic steatohepatitis) K77.0 달리 분류된 질환에서의 간장애(Liver disorders in disease classified elsewhere)

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BG2024-01

BUKWANG PHARM

# Protect from Various Liver Disease with Legalon® Cap

As the original brand of silymarin, Legalon® always be with doctors for the treatment of various liver disease.


**Originality & Worldwide**

- The original silymarin for treatment of liver disease by numerous Clinical trials since 1960's.[1-2]

**Treatment of Liver disease**

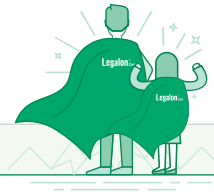
- Proven efficacy in improvement of liver function [5-11]
  * NAFLD, NASH, ALD, cirrhosis

**Various MoA & All stages**

- Multi-therapeutic targets in all-stage of liver disease by various MoA.[3-4]
  * Improvement of insulin resistance
  * Anti-oxidative stress, Anti-inflammation, Anti-fibrosis

**Safety & Good tolerance**

- Good tolerance and safety with lower side effects [5-9]

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**[제품정보]** 레가론 캡슐 70mg / 140mg **[성분,함량]** 밀크시슬건조엑스산 169.7mg / 339.4mg(실리마린으로서 70mg / 140mg) **[효능,효과]** 다음 질환의 보조 치료 : 독성 간질환 , 만성 간염, 간경변 **[용법,용량]** 성인 : 실리마린으로서 초기용량 1회 140mg(또는 실리빈으로서 1회60mg), 1일 3회, 유지용량 1회 70mg(또는 실리빈으로서 1회 30mg), 1일 3회(또는 1회 140mg(또는 실리빈으로서 60mg), 1일 2회)복용한다. **[금기]** 1) 심한 담도 폐쇄 환자 2) 이 약의 과민증 환자 3) 12세 이하의 소아 **[신중투여]** 다음과 같은 사람은 이 약을 복용하기 전에 의사, 치과의사, 약사와 상의할 것 : 임부, 수유부 [이상반응] 다음과 같은 경우 이 약의 사용을 즉각 중지하고 의사, 치과의사, 약사와 상의할 것. 상담시 가능한 한 이 첨부문서를 소지할 것. 1) 드물게 위통 또는 설사 2) 알레르기 반응 **[일반적주의]** 1) 정해진 용법 · 용량을 지킬 것. 2) 황달의 경우에는 의사 또는 약사와 상의할 것. 3) 1개월 정도 복용하여도 증상의 개선이 없을 경우나 장기복용시에는 의사 또는 약사와 상의할 것.

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