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CMH Clinical and Molecular Hepatology

The Liver Week 2020

VIRTUAL CONFERENCE

August 13-14, 2020

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

DAY 1. Thursday, August 13, 2020

The Liver Week 2020 Virtual Conference

08:40-09:00	The Liver Week 2020 Opening Ceremony	
09:00-09:05	ISALPDC Opening Ceremony	

09:00-11:00

09:00-10:10	**KASL Symposium 1. Up-to-Date Treatment for Liver Diseases**	Real Time Discussion *Dong Joon Kim (Hallym Univ.), Joo Hyun Sohn (Hanyang Univ.)*
09:00-09:20	Pharmacological Treatment of Alcoholic Hepatitis	*Gyongyi Szabo (Harvard Univ., USA)*
09:20-09:40	Pharmacological Treatment of Nonalcoholic Steatohepatitis	*Manal Abdelmalek (Duke Univ., USA)*
09:40-10:00	New Horizon of Immuno-Oncologic Therapy	*Amit Singal (UT Southwestern Medical Center, USA)*
10:00-10:10	Discussion	
09:00-10:10	**PG1. Current Issues in Chronic Hepatitis B** (*K)	
09:00-09:10	Case Presentation and Key Questions	*Hyun Woong Lee (Yonsei Univ.)*
09:10-09:30	Immune Tolerant Chronic Hepatitis B: To Treat or Not?	*Jonggi Choi (Univ. of Ulsan)*
09:30-09:50	Risks and Benefits of Antiviral Therapy During Pregnancy	*Young-Sun Lee (Korea Univ.)*
09:50-10:10	Prophylactic Antiviral Therapy for Hepatitis B During Immunosuppressive Therapy	*In Hee Kim (Chonbuk National Univ.)*
09:05-11:00	**ISALPDC 1. Obesity-Alcohol Synergism**	Real Time Discussion *Won-IL Jeong (KAIST), Kenichi Ikejima (Juntendo Univ., Japan)*
09:05-09:25	Obesity and Alcohol Are Deadly Combination to Induce Steatohepatitis	*Bin Gao (National Institutes of Health, USA)*
09:25-09:45	Alcohol-NAFLD Interactions	*Kenichi Ikejima (Juntendo Univ., Japan)*
09:45-10:05	Autophagy Regulation in Alcoholic and Non-Alcoholic Liver Steatosis	*Sang Geon Kim (Seoul National Univ.)*
10:05-10:25	Alcohol-NAFLD Interactions in a Large Korean Cohort Study	*Yong Kyun Cho (Sungkyunkwan Univ.)*
10:25-10:35	Interaction between CD40L and CD40 Mediates Hepatic Exosomal Delivery to Kupffer Cells in Alcoholic Liver Disease	*Kyurae Kim (KAIST)*
10:35-10:45	The Effect of Intestinal Flora Modification on Alcoholic Liver Injury in Obese KK-Ay Mice	*Kazuyoshi Kon (Juntendo Univ., Japan)*
10:45-11:00	Round Table Discussions	

10:20-11:20

10:20-11:20	**Plenary Presentation 1**	Real Time Discussion *Kwan Sik Lee (Yonsei Univ.), Kwan Soo Byun (Korea Univ.), Ho Seong Han (Seoul National Univ.)*
10:20-10:35	ROS-Induced Activation of YAP-1 through a c-Myc Pathway Is a Therapeutic Target in Hepatocellular Carcinoma	*Yuri Cho (CHA Univ.)*
10:35-10:50	Oral L-Carnitine on Quality of Life and Cognition in Covert Hepatic Encephalopathy: A Randomized, Double-Blind, Placebo-Controlled (HELIOS) Study	*Eileen L. Yoon (Inje Univ.)*
10:50-11:05	Impact of Existing Liver Disease on Clinical Outcomes of COVID-19: A Multicenter Study	*Yu Rim Lee (Kyungpook National Univ.)*
11:05-11:20	Adverse Effect of Sarcopenic Obesity on Postoperative Complications after Major Hepatectomy in Patients with Hilar Cholangiocarcinoma	*Youngju Ryu (Sungkyunkwan Univ.)*

DAY 1. Thursday, August 13, 2020

11:00-13:00

11:00-13:00	**ISALPDC 2. Novel Cellular and Organ Crosstalk in Alcoholic Liver Disease**	Real Time Discussion *Bin Gao (National Institutes of Health, USA), Yasuko Iwakiri (Yale Univ., USA)*
11:00-11:20	Neuroendocrine-Fat-Liver Axis	*Laura E. Nagy (Cleveland Clinic, USA)*
11:20-11:40	Lymphatic System and Organ Crosstalk	*Yasuko Iwakiri (Yale Univ., USA)*
11:40-12:00	Liver-Lung Crosstalk	*Gavin E. Arteel (Univ. of Pittsburgh, USA)*
12:00-12:20	Glutamate/mGluR5-mediated Endocannabinoid in Alcoholic Fatty Liver	*Won-IL Jeong (KAIST)*
12:20-12:30	CYP2E1 Regulation of Ethanol-Induced Intestinal miRNAs in Liver Injury	*Je-Hyun Yoon (Medical Univ. of South Carolina, USA)*
12:30-12:40	Chronic Alcohol Consumption Alters the Phenotype of F4/80+CD11b+ Bone Marrow Cells by Neuro-Metabolic Signaling Pathway	*Young-Ri Shim (KAIST)*
12:40-13:00	Round Table Discussions	
11:30-12:00	**State-of-the-Art Lecture**	Real Time Discussion *Seung Woon Paik (Sungkyunkwan Univ.)*
	Past, Present, and Future of Precision Hepatology: Where Do We Need to Go?	*W. Ray Kim (Stanford Univ., USA)*
11:30-12:40	**PG2. Current Issues in Chronic Hepatitis C** (*K)	
11:30-11:40	Case Presentation and Key Questions	*Hyun Woong Lee (Yonsei Univ.)*
11:40-12:00	Retreatment Options for Chronic Hepatitis C after Oral Direct-Acting Antiviral Agent Failure	*Jung Hyun Kwon (The Catholic Univ. of Korea)*
12:00-12:20	Risks and Benefits of Oral Direct-Acting Antiviral Agent Therapy in Patients with Hepatitis C Virus-Related Hepatocellular Carcinoma	*Nae-Yun Heo (Inje Univ.)*
12:20-12:40	Hepatocellular Carcinoma Surveillance in Chronic Hepatitis C Patients Who Achieved Sustained Virological Response	*Yun Bin Lee (Seoul National Univ.)*

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12:10-12:55	**Satellite Symposium 1 [Bayer]**
12:40-13:25	**Satellite Symposium 2 [Gilead]**
13:00-13:45	**Satellite Symposium 3 [AbbVie]**

DAY 1. Thursday, August 13, 2020

13:00-14:40

13:00-14:30	**KLCA Symposium 1.** **The Changing Landscape and New Evidences in Treatment Strategies for Hepatocellular Carcinoma (HCC)**	Real Time Discussion *Joong-Won Park (National Cancer Center Korea), Jung-Hwan Yoon (Seoul National Univ.)*
13:00-13:20	Current Evidences and Future Perspectives for the Treatment of Advanced HCC	*Jeong Won Jang (The Catholic Univ. of Korea)*
13:20-13:40	When Should We Consider Systemic Therapy in BCLC Stage B HCC?	*Hyung Joon Yim (Korea Univ.)*
13:40-14:00	Therapeutic Efficacy of Transarterial-Based Treatment vs. Targeted Therapy in Advanced HCC	*Sadahisa Ogasawara (Chiba Univ., Japan)*
14:00-14:20	Optimizing Therapeutic Efficacy with Systemic Therapy and Radiotherapy in HCC	*Jinsil Seong (Yonsei Univ.)*
14:20-14:30	Discussion	
13:30-14:40	**PG3. Consensus on the Management of Nonalcoholic Fatty Liver Disease** (*K)	
13:30-13:40	Case Presentation and Key Questions	*Young-Joo Jin (Inha Univ.)*
13:40-14:00	Assessment of Co-Morbidities in Patients with Nonalcoholic Fatty Liver Disease	*Jung Il Lee (Yonsei Univ.)*
14:00-14:20	Pathogenesis and Management of Non-Obese Nonalcoholic Fatty Liver Disease	*Hwi Young Kim (Ewha Womans Univ.)*
14:20-14:40	Currently Available Treatment Strategy in Patients with Nonalcoholic Steatohepatitis and Metabolic Syndrome	*Won Sohn (Sungkyunkwan Univ.)*

DAY 1. Thursday, August 13, 2020

14:00-16:00

14:00-15:10	**General Oral Presentation 1**	Real Time Discussion *Myung Seok Lee (Hallym Univ.), Byung Ik Kim (Sungkyunkwan Univ.)*
14:00-14:10	Kahweol Activates the NRF2/HO-1 Pathway by Decreasing Keap1 Expression Independently of p62 and Autophagy Pathways	*Hye-Young Seo (Keimyung Univ.)*
14:10-14:20	TIP-47-Accelerates Fatty Change of Liver During Alcohol Ingestion in HBx Transgenic Mice	*Hoon Gil Jo (Wonkwang Univ.)*
14:20-14:30	Hepatitis B Core-Related Antigen Is a Satisfactory Marker in Differentiating Hepatitis B e Antigen-Positive Chronic Infection and Hepatitis B e Antigen-Positive Chronic Hepatitis	*Han Ah Lee (Korea Univ.)*
14:30-14:40	All Cause of Mortality and Incidence of Hepatocellular Carcinoma Among Chronic Hepatitis C Patients in South Korea: A Prospective, Multicenter Cohort Study	*Gwang Hyeon Choi (Seoul National Univ.)*
14:40-14:50	Weight Gain during Early Adulthood, Trajectory of Body Shape and the Risk of Nonalcoholic Fatty Liver Disease Among Women: A Prospective Cohort Study	*Mi Na Kim (CHA Univ.)*
14:50-15:00	Bedside Risk-Scoring Model for Prediction of 30 Days' Mortality in Patients with Cirrhosis Underwent Endoscopic Band Ligation for Acute Variceal Bleeding	*Jung Hee Kim (Hallym Univ.)*
15:00-15:10	Population-Based Epidemiology of Primary Biliary Cholangitis in South Korea	*Kyung-Ah Kim (Inje Univ.)*
14:40-15:50	**LCGSJ-KLCA Joint Symposium. Similarities and Differences in HCC Management**	Real Time Discussion *Shoji Kubo (Osaka City Univ., Japan), Jin Wook Chung (Seoul National Univ.)*
14:40-14:55	Current Approaches to the Treatment of Early HCC in Japan	*Shuichiro Shiina (Juntendo Univ., Japan)*
14:55-15:10	Current Approaches to the Treatment of Early HCC in Korea	*Myeong Jun Song (The Catholic Univ. of Korea)*
15:10-15:25	Selection of Particle Beam vs. Photon Beam Radiation Therapy for HCC: Japanese Experience	*Hideyuki Sakurai (Univ. of Tsukuba, Japan)*
15:25-15:40	Selection of Particle Beam vs. Photon Beam Radiation Therapy for HCC: Korean Experience	*Hee Chul Park (Sungkyunkwan Univ.)*
15:40-15:50	Discussion	
14:50-16:00	**PG4. Assessment and Management of Liver Cirrhosis Complications** (*K)	
14:50-15:00	Case Presentation and Key Questions	*Young-Joo Jin (Inha Univ.)*
15:00-15:20	How to Assess Minimal Hepatic Encephalopathy in Patients with Liver Cirrhosis?	*Eileen L. Yoon (Inje Univ.)*
15:20-15:40	When and How to Use Anticoagulants for Benign Portal Vein Thrombosis in Patients with Liver Cirrhosis	*Young Kul Jung (Korea Univ.)*
15:40-16:00	Update of Beta Blocker and Albumin Use for Patients with Decompensated Liver Cirrhosis	*Ki Tae Yoon (Pusan National Univ.)*

DAY 1. Thursday, August 13, 2020

15:10-18:10

15:10-18:10	**Abdominal Ultrasonography Training Course for Certified Trainer** (*K)	
15:10-15:30	Introduction to Ultrasonography Training Program for Trainer and Trainee of KASL	*Moon-Young Kim (Yonsei Univ. Wonju)*
15:30-15:50	Useful Tips for Setting-up of Ultrasound Rooms	*Soo Young Park (Kyungpook National Univ.)*
15:50-16:10	Experience of Ultrasonography Education Programs for Residents and Fellows in Korea	*Jun Yong Park (Yonsei Univ.)*
16:10-16:30	Tips for Ultrasonography Examination in Patients with Poor Sonographic Window	*Jaeyoun Cheong (Ajou Univ.)*
16:30-16:50	Contrast-enhanced Ultrasonography in the Diagnosis of Focal Liver Lesions	*Sae Hwan Lee (Soonchunhyang Univ.)*
16:50-17:10	Ultrasonography-guided Procedures: Percutaneous Drainage Insertion and Liver Biopsy	*Seung Whan Cha (Yonsei Univ. Wonju)*
17:10-17:30	Clinical Application of Liver Stiffness and Viscosity Measurement Using Shear Wave Elastography	*Sang Gyune Kim (Soonchunhyang Univ.)*
17:30-17:50	Technological advancement in Ultrasonography: Real-Time Fusion Imaging of Liver Ultrasonography with CT or MRI	*Ji Young Kwon (Canon Medical Systems)*
17:50-18:10	Comparison Between Transabdominal Ultrasonography and Endoscopic Ultrasonography for the Diagnosis of Pancratobiliary Disease	*Young Koog Cheon (Konkuk Univ.)*

16:00-17:30

16:00-17:30	**KASL Symposium 2. New Insights to Unanswered Issues in Treatment for Chronic Hepatitis B**	Real Time Discussion *Seung Kew Yoon (The Catholic Univ. of Korea), Kyun-Hwan Kim (Sungkyunkwan Univ.)*
16:00-16:20	Exploring Unrecognized Risks in Immune Tolerant Phase of Chronic Hepatitis B	*Young-Suk Lim (Univ. of Ulsan)*
16:20-16:40	Clonal Hepatocyte Expansion and Hepatitis B Virus Integration	*Patrick Kennedy (Queen Mary Univ. of London, UK)*
16:40-17:00	Effect of Current and Novel Antivirals on the Prevention of Hepatocellular Carcinoma: Beyond Viral Suppression	*George Papatheodoridis (National and Kapodistrian Univ. of Athens, Greece)*
17:00-17:20	Functional Cure of Chronic Hepatitis B and Beyond	*Man-Fung Yuen (The Univ. of Hong Kong, China)*
17:20-17:30	Discussion	
16:10-17:30	**PG for Basic Research** (*K)	
16:10-16:30	Assessment of Mitochondrial Function in Liver Research	*Hyon-Seung Yi (Chungnam National Univ.)*
16:30-16:50	Adipocyte Death Preferentially Induces Liver Injury and Inflammation Through the Activation of Chemokine (C-C Motif) Receptor 2-Positive Macrophages and Lipolysis	*Seung-Jin Kim (Kangwon National Univ.)*
16:50-17:10	Understanding Genomics and Proteomics for Studying Liver Cancer	*Ju-Seog Lee (UT MD Anderson Cancer Center, USA)*
17:10-17:30	A Noble and Powerful Tool: Single Cell RNA Sequencing	*Young Seok Ju (KAIST)*

DAY 2. Friday, August 14, 2020

08:30-10:50

08:30-10:20	**ISALPDC 3. Alcohol Promotion of Cancer**	Real Time Discussion *Wen-Xing Ding (Univ. of Kensas, USA), Yingzi Yang (Harvard Univ., USA)*
08:30-08:50	Hippo Pathway Regulation of Liver Inflammation and Cancer	*Yingzi Yang (Harvard Univ., USA)*
08:50-09:10	Complement C3, tRNA-derived Fragments Gly-tRFs, and ALD	*Songqing He (Guangxi Medical Univ., China)*
09:10-09:30	Autophagy and Cancer	*Wen-Xing Ding (Univ. of Kensas, USA)*
09:30-09:50	Risk Factors for Alcohol-related HCC	*Makiko Taniai (Tokyo Women's Medical Univ., Japan)*
09:50-10:00	Catecholamine Signaling Pathway Protects Alcoholic Fatty Liver by Inducing Growth Differentiation Factor 15	*Hee-Hoon Kim (KAIST)*
10:00-10:20	Round Table Discussions	
08:30-10:50	**Policy Symposium. Nationwide Policies to Eliminate Hepatitis C**	Real Time Discussion *Dong Jin Suh (Korean Liver Foundation), W. Ray Kim (Stanford Univ., USA), Han Chu Lee (Univ. of Ulsan)*
08:30-09:00	Hepatitis C Elimination Program in Taiwan: "The Taiwan Hepatitis C Policy Guideline 2018 - 2025"	*Chien-Jen Chen (Former Vice President of Taiwan, Academia Sinica, Taiwan)*
09:00-09:20	Elimination of HCV in Taiwan: What and How We Have Achieved from the Beginning till Today	*Jia-Horng Kao (National Taiwan Univ., Taiwan)*
09:20-09:40	HCV Elimination in Japan: The Japanese Policy and Outcome	*Tatsuya Kanto (National Center for Global Health and Medicine, Japan)*
09:40-10:00	National Policies on Hepatitis C in Korea	*Hyungmin Lee (Korea Centers for Disease Control & Prevention)*
10:00-10:20	Current Status and Suggestions for Hepatitis C Control in Korea	*Do Young Kim (Yonsei Univ.)*
10:20-10:50	Panel Discussion	*Panel: Do Young Kim (Yonsei Univ.), Hyungmin Lee (Korea Centers for Disease Control & Prevention), Chul Joong Kim (Chosun Media), Goo Hyun Yoon (Liver Korea), Young-Suk Lim (Univ. of Ulsan), Jae Young Jang (Soonchunhyang Univ.)*
08:50-09:50	**Basic Science Workshop**	
08:30-08:50	Transcriptomic Signature of Nonalcoholic Fatty Liver Disease	*Murim Choi (Seoul National Univ.)*
08:50-09:10	Immunologic Circuits of Hepatocellular Carcinoma	*Su Jong Yu (Seoul National Univ.)*
09:10-09:30	Interactive Interface between Gut Microbiome and Immunome in Alcohol-Related Liver Disease	*Bernd Schnabl (Univ. of California San Diego, USA)*
09:30-09:50	Microbiome Meets Cancer and Immunology	*Hansoo Park (Gwangju Institute of Science and Technology)*

09:50-10:50

09:50-10:50	**Special Interest Group Forum. Clinical Issues in Autoimmune Liver Disease**	
09:50-10:10	Pathology of Autoimmune Liver Diseases	*Masayoshi Kage (Kurume Univ., Japan)*
10:10-10:30	Autoimmune Hepatitis: From Bench to Clinic	*Xiong Ma (Shanghai Jiao Tong Univ., China)*
10:30-10:50	Primary Biliary Cholangitis: Unsolved Issues and New Treatment	*Gideon M. Hirschfield (Toronto Centre for Liver Disease, Canada)*

DAY 2. Friday, August 14, 2020

10:30-12:45

10:30-12:45	**ISALPDC 4. Translational Studies and Public Health on Alcoholic Liver Disease**	Real Time Discussion *Shiv Kumar Sarin (Institute of Liver and Biliary Science, India), Suthat Liangpunsakul (Indiana Univ., USA)*
10:30-10:50	Prognostic Potential of LncRNAs for Alcoholic Liver Disease Patients	*Suthat Liangpunsakul (Indiana Univ., USA)*
10:50-11:10	Predictors of Steroid Non-Response and New Approaches in Severe Alcoholic Hepatitis	*Shiv Kumar Sarin (Institute of Liver and Biliary Science, India)*
11:10-11:30	Global and Regional Impacts of Alcohol Use on Public Health	*Dong Joon Kim (Hallym Univ.)*
11:30-11:50	Impact of Genetic Traits and Drinking Mode on Alcoholic Liver Disease in China	*Jia Xiao (Fujian Normal Univ., China)*
11:50-12:10	TAPPY: Multi-Professional Care of Alcoholic Patients	*Masahiro Kikuchi (Tokyo Medical Center, Japan)*
12:10-12:20	The Evolution of Liver Donor Liver Transplantation for Alcoholic Liver Cirrhosis in a High-Volume Center: The Eastern Perspective	*Jeffrey Samuel Co (Kaohsiung Chang Memorial Hospital, Taiwan)*
12:20-12:40	Round Table Discussions	
12:40-12:45	Closing Remarks	

11:00-12:00

11:00-12:00	**Plenary Presentation 2**	Real Time Discussion *Jin Mo Yang (The Catholic Univ. of Korea), Chul Ju Han (Korea Cancer Center Hospital), Yang Won Nah (Univ. of Ulsan)*
11:00-11:15	Serum miRNA as a Useful Diagnostic Biomarker for Diagnosis of NASH and a Clue for Disease Progression Pathway in NAFLD Patients	*Young-Sun Lee (Korea Univ.)*
11:15-11:30	Association of Metabolic Risk Factors with Risks of Cancer and All-Cause Mortality in Patients with Chronic Hepatitis B Virus Infection: A Korean Nationwide Cohort Study	*Yun Bin Lee (Seoul National Univ.)*
11:30-11:45	Regorafenib versus Nivolumab after Sorafenib Failure: Real-World Data in Patients with Hepatocellular Carcinoma	*Won-Mook Choi (Univ. of Ulsan)*
11:45-12:00	Circulating Cancer Stem Cells in Hepatocellular Carcinoma: A Pilot Study of Prediction for Tumor Recurrence after Living Donor Liver Transplantation	*Hyeo Seong Hwang (Yonsei Univ.)*

12:10-13:30

12:10-12:55	**Satellite Symposium 4 [Yuhan]**
12:10-12:55	**Satellite Symposium 5 [Eisai]**
12:40-13:30	**Satellite Symposium 6 [BMS]**

DAY 2. Friday, August 14, 2020

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13:00-14:00	**KLCA Symposium 2. Updates in Diagnosis and Biomarkers of Hepatocellular Carcinoma**	
13:00-13:20	Biomarkers of Hepatocellular Carcinoma with Focus on Recent Clinical Trials	*Joong-Won Park (National Cancer Center Korea)*
13:20-13:40	Imaging Biomarkers in the Era of Precision Medicine	*Sun Young Lee (Yonsei Univ.)*
13:40-14:00	Pathologic Biomarkers that Indicate the Aggressiveness and Prognosis of HCC	*Young Nyun Park (Yonsei Univ.)*
13:00-14:10	**KLCA-KAHBPS-KLTS Joint Symposium. Treatment Options for HCC beyond the Milan Criteria in Patients with Marginal Liver Function**	Real Time Discussion *Jong Young Choi (The Catholic Univ. of Korea), Shin Hwang (Univ. of Ulsan)*
13:00-13:20	Locoregional Therapy	*Yoon Jun Kim (Seoul National Univ.)*
13:20-13:40	Down-Staging Living Donor Liver Transplantation	*Jae Geun Lee (Yonsei Univ.)*
13:40-14:00	Is There a Role for TKIs and Immune Checkpoint Inhibitors?	*Thomas Yau (The Univ. of Hong Kong, China)*
14:00-14:10	Discussion	
13:30-14:30	**General Oral Presentation 2**	Real Time Discussion *Young Oh Kweon (Kyungpook National Univ.), Sang-Jae Park (National Cancer Center Korea)*
13:30-13:40	Serum Small Extracellular Vesicle-Derived LINC00853 as a Novel Diagnostic Marker for Early Hepatocellular Carcinoma	*Suna Sung (Ajou Univ.)*
13:40-13:50	Current Status of Ultrasonography Examination Operated by National Cancer Surveillance Program for HCC: Multi-center Large-Scale Research	*Jeong-Ju Yoo (Soonchunhyang Univ.)*
13:50-14:00	Development of Machine Learning-Based Clinical Decision Support System for Hepatocellular Carcinoma	*Gwang Hyeon Choi (Seoul National Univ.)*
14:00-14:10	Proton Beam Radiotherapy versus Radiofrequency Ablation Treatment in Patients with Recurrent Hepatocellular Carcinoma: A Randomized Controlled Phase 3 Non-Inferiority APROH Trial	*Joong-Won Park (National Cancer Center Korea)*
14:10-14:20	Clinical Significance of Intraoperative Bile Culture in Surgery Including Bile Duct Resection	*Youngju Ryu (Sungkyunkwan Univ.)*
14:20-14:30	Development of Novel Multivariable Logistic Regression Model for Predicting Graft Failure within 2 Weeks and 4 Weeks after Liver Transplantation	*Jinsoo Rhu (Sungkyunkwan Univ.)*

DAY 2. Friday, August 14, 2020

14:10-15:20

14:10-15:10	**KAHBPS-KLTS Joint Symposium. Optimal Use of ICG Fluorescence Technology in Daily Practice**	
14:10-14:30	Tumor Localization in Oncologic Surgery	*Masaki Ueno (Wakayama Medical Univ., Japan)*
14:30-14:50	Anatomical Liver Resection	*Dai Hoon Han (Yonsei Univ.)*
14:50-15:10	Donor Hepatectomy	*Young Rock Choi (Seoul National Univ.)*
14:20-15:20	**KASL Plenary Presentation**	Real Time Discussion *Seong Gyu Hwang (CHA Univ.), Kwon Yoo (Ewha Womans Univ.)*
14:20-14:35	Therapeutic Effects of Function-Enhanced PRL-1 in Placenta-Derived Mesenchymal Stem Cells on Accelerating Hepatic Functions via Mitochondrial Dynamics in Liver Diseases	*Jae Yeon Kim (CHA Univ.)*
14:35-14:50	The Role of Urinary Biomarkers in Cirrhotic Patients with Acute Kidney Injury: Multicenter, Prospective Cohort Study	*Jeong-Ju Yoo (Soonchunhyang Univ.)*
14:50-15:05	Lean Non Alcoholic Fatty Liver Disease Increases Cardiovascular Risk more than Obese Non Alcoholic Fatty Liver Disease	*Yuna Kim (Yonsei Univ.)*
15:05-15:20	Multicenter Analysis of Clinical Features and Treatment Outcomes of COVID-19 Patients with Hepatic Impairment	*Jeong Eun Song (Daegu Catholic Univ.)*
14:40-15:25	**Satellite Symposium 7 [ILDONG]**	

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15:20-16:40	**KASL Symposium 3. Exploration of Biomarkers in Liver Diseases**	
15:20-15:40	New and Old Biomarkers for Diagnosis and Management of Chronic Hepatitis B Infection	*Il Han Song (Dankook Univ.)*
15:40-16:00	Non-Invasive Diagnosis and Biomarkers in Alcohol-Related Liver Disease	*Suthat Liangpunsakul (Indiana Univ., USA)*
16:00-16:20	Quantitative Imaging Biomarkers: Assessment of Hepatic Fibrosis and Steatosis	*Woo Kyoung Jeong (Sungkyunkwan Univ.)*
16:20-16:40	Clinical Application of Liquid Biopsy as a Prognostic Biomarker in Hepatocellular Carcinoma	*Soo Young Park (Kyungpook National Univ.)*
15:30-17:00	**KASL-KAHBPS-KLTS Joint Symposium. How to Improve Outcome in Critically Ill Patients Awaiting Liver Transplantation**	Real Time Discussion *Soon Ho Um (Korea Univ.), Hee Chul Yu (Chonbuk National Univ.)*
15:30-15:50	Liver Transplantation for Alcoholic Hepatitis	*Philippe Mathurin (Chu De Lille, France)*
15:50-16:10	Risk Stratification and Optimal Management for Liver Transplantation in Acute-on-Chronic Liver Failure	*Dong Hyun Sinn (Sungkyunkwan Univ.)*
16:10-16:30	Risk Stratification and Optimal Management for Liver Transplantation in Acute Liver Failure	*Young-dong Yu (Korea Univ.)*
16:30-16:50	How to Improve Post-Transplant Outcomes in Patients with High MELD Scores	*Dong-Hwan Jung (Univ. of Ulsan)*
16:50-17:00	Discussion	
17:00-17:30	**Closing and Award Ceremony**	

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State-of-the-Art Lecture

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LCGSJ-KLCA Joint Symposium. Similarities and Differences in HCC Management

KASL Symposium 2. New Insights to Unanswered Issues in Treatment for Chronic Hepatitis B

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Liver Cancer, Basic

Liver Cirrhosis, Portal Hypertension with Cx. Clinical

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Liver Cirrhosis, Portal Hypertension with Cx. Basic

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DAY 1: Thursday, August 13, 2020 (09:00-10:10)

KASL Symposium 1

Up-to-Date Treatment for Liver Diseases

Chairs:

Dong Joon Kim (Hallym Univ.)

Joo Hyun Sohn (Hanyang Univ.)

Pharmacological Treatment of Alcoholic Hepatitis

Gyongyi Szabo

Harvard Univ., USA

Severe alcoholic hepatitis (AH) is an acute and often devastating form of alcohol-associated liver disease. Clinically, AH is characterized by elevated bilirubin, MELD >20, and nonspecific symptoms that are caused by underlying inflammation, hepatocyte injury, and impaired intestinal barrier function. Compromised immune defense in AH contributes to infections, sepsis and organ failure. To date, corticosteroids are the only recommended treatment for severe AH, however it does not provide survival benefits beyond one month. Recent preclinical and early clinical studies in AH aided understanding of the disease and presented opportunities for new therapeutic options targeting inflammation, oxidative stress, liver regeneration and modification of intestinal microbiota. In this comprehensive review, we discuss promising preclinical results and ongoing clinical trials evaluating novel therapeutic agents for the treatment of severe AH.

Pharmacologic Therapy for the Treatment of NASH

Manal Abdelmalek

Duke University, USA

Nonalcoholic steatohepatitis is a leading cause of chronic liver disease worldwide. Although lifestyle modification remains the primary recommendation NAFLD/NASH, sustaining lifestyle changes is challenging for the majority of patients. There are currently no FDA approved drugs for the treatment of NASH, many pharmacologic approaches are being evaluated to prevent the developed of progressive hepatic fibrosis, cirrhosis and its associated complications. While there are a vast number of targets in preclinical and early clinical development, few have progressed to late phase clinical trials. Focus in this presentation will be paid only on the primary mechanisms of action of specific drugs entering or currently in phase 3 clinical studies. Of note, NASH is likely a heterogeneous disease, with patients arriving at a common phenotype by different mechanisms. In the future, there may be an era of personalized medicine and/or use of combination therapy by which clinicians can select specific therapies based on a patient's genetic, histologic or clinical phenotype.

Currently available pharmacotherapy for treatment of NASH include pioglitazone and vitamin E. Both pioglitazone can improve NASH. Based on these data, the AASLD and the EASL guidelines on NASH state that pioglitazone can be considered in patients with biopsy-proven NASH, taking into account the risks of weight gain, loss of bone density, and bladder cancer. Two placebo-controlled studies, one in children and one in adults, did show a benefit of vitamin E, although only in some patients in both groups. However, using therapeutic doses of vitamin E may not be completely benign, as studies have suggested an increased risk of cardiovascular disease. The society guidelines recommend that vitamin E be considered in noncirrhotic, nondiabetic patients with biopsy-proven NASH at a dose of 800 IU of the natural form (i.e, rrr-α-tocopherol).

Emerging Pharmacotherapies in Phase 3 Clinical Trials

Antimetabolic compounds may serve as a bone of treatment NASH. Antimetabolic compounds currently in phase 3 clinical studies include PPARs, GLP-1 receptor agonists, thyroid hormone receptor β agonists, and stearoyl coenzyme A desaturase inhibitors (SCD-1) A trial of the GLP1 receptor agonist liraglutide resulted in the resolution of NASH in 39% of patients compared to 9% treated with placebo18; however, the trial was relatively small (n=45 with end-of-treatment biopsies), and these results need to be validated in larger studies. A study of a more potent GLP1 receptor agonist, semaglutide, as well as dual and triple agonists are underway.

Thyroid hormone regulates diverse metabolic processes throughout the body with increased oxidative disposal of -metabolic substrates; however, augmenting thyroid hormone responses with the native hormone can lead to adverse effects attributable to the activation of thyroid hormone receptor (THR) α. In animal models, activation of the liver-specific THR β increases oxidative metabolism in the liver without the systemic side effects, and a human study demonstrated beneficial effects on serum lipids. A trial of a small molecule activator of this receptor in patients with NASH has been undertaken, and the preliminary results are promising.

PPARS are nuclear receptor family with isoforms found in muscle (where it increases fatty acid oxidation), in macrophages (where it mediates polarization away from the proinflammatory M1 phenotype to the anti-inflammatory M2 phenotype), and in stellate cells (where it may modulate fibrogenesis). The nuclear receptor PPAR α regulates mitochondrial biogenesis, and PPAR α activators such as fibrates are often used to treat dyslipidemia. Whether these agents have an adjunctive role in the treatment of NASH is now being explored with a number of drugs that target PPAR α, among other PPARs. PPAR δ ligands are being evaluated as therapeutic agents in a number of disorders; one agent is currently in trials for NASH. While elafibranor (PPAR α/δ), drugs with pan-PPAR activity, lanfibranor, is being evaluated and hold promise in treatment of NASH and improvement in hepatic fibrosis.

The primary function of the bile acid–sensing nuclear FXR is to sense the presence of excess bile acids and decrease their uptake, inhibit their synthesis, and increase their secretion from hepatocytes into the bile. FXR signaling increases the expression of the inhibitory nuclear receptor small heterodimer protein (SHP) 1, which effectively downregulates the nuclear receptor sterol regulatory element-binding protein (SREBP) 1c. SREBP1c is the master regulator of the expression of genes responsible for DNL: acetyl coenzyme A carboxylase (ACC), fatty acid synthetase, and stearoyl coenzyme A desaturases. Treatment with FXR ligands increases SHP1, which decreases SREBP1c and leads to decreased fatty acid synthesis in the liver. Multiple FXR ligands are in various stages of evaluation, and obeticholic acid now in a large phase 3 trial.

Aramchol is a bile acid–fatty acid conjugate that was developed to dissolve gallstones but in preliminary animal studies was found to improve fatty liver. Further evaluation demonstrated that the agent inhibits the stearoyl coenzyme A desaturases, the phase in DNL that introduces double bonds into fatty acids, thereby inhibiting DNL. A phase 2 clinical trial demonstrated that the agent improved liver fat but did not lower serum ALT levels. This agent is now being evaluated in a phase 3 clinical trial with histologic endpoints.

Inhibitors of the C-C motif chemokine receptors 2 and 5 (CCR2/5) were developed as potential treatments for HIV infection, and studies in this patient population demonstrated potential benefits on liver markers. CCR2 and 5 mediate key aspects of the inflammatory signaling in the liver, and receptor inhibition revealed benefits in mouse models of NASH. A clinical trial of the CCR2/5 inhibitor cenicriviroc demonstrated no significant improvement in NASH, but it did appear to improve fibrosis in some patients.45 Based on these results, the drug is now being evaluated in a large phase 3 trial.

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New Horizon of Immuno-Oncologic Therapy

Amit Singal

Univ. of Texas Southwestern, USA

Hepatocellular carcinoma (HCC) is the 4th leading cause of cancer-related death worldwide. The high mortality observed in patients with HCC is related to a high proportion of patients being diagnosed at an advanced stage when curative options are not available. There has been a tremendous amount of advances in the treatment landscape for advanced HCC, with evolution from sorafenib as the only proven therapy to now having multiple options as both first-line and second-line options. During this time, there has been increased interest in immunotherapy (i.e. checkpoint inhibitors). Although there are many potential targets for immunotherapy, most early efforts have targeted primarily PD-1 and CTLA-4 cell receptors.

Phase II trials, such as Checkmate 040 and Keynote224, showed that single-agent checkpoint inhibitors (i.e. Nivolumab and Pembrolizumab) could induce durable objective responses in 15-20% of patients; however subsequent phase III trials, i.e. Checkmate 459 and Keynote 240, failed to demonstrate significant improvements in overall survival compared to standard of care in either the first or second-line. There are many reasons for immunotherapy "resistance" including lack of antigen presentation, production of factors that reduce T cell recruitment, and tumor extrinsic mechanisms including myeloid-derived suppressor cells and tumor associated macrophages. Several of these pathways could be overcome with the use of combination therapies – either in combination with VEG-F inhibitors, tyrosine kinase inhibitors (TKIs), or dual checkpoint inhibitors (e.g. PD1 and CTLA4).

Recently, the combination of atezolizumab, a PD-L1 inhibitor, and bevacizumab, a VEGF inhibitor, was approved for first line treatment of HCC. In the the IMbrave150 study, a multicenter phase III study atezolizumab/bevacizumab was associated with a 42% reduction in mortality (HR 0.58, 95%CI 0.42-0.79) after a median follow-up of 8.6 months and improved progression-free survival (HR 0.59, 95%CI 0.47-0.76) compared to sorafenib. At the interim analysis, median OS has not yet been reached for atezolizumab/bevacizumab but was 13.2 months for the sorafenib arm. Atezolizumab/bevacizumab was associated with increased response rate (33% vs 13%, $p<0.0001$) and was well tolerated with minimal adverse events. Of specific note, incident GI bleeding was low in the arm, likely due to patient selection (Child-Pugh A cirrhosis without significant portal hypertension) and patients being required to have an upper endoscopy with control of varices prior to entering the trial.

There are other ongoing trials evaluating immunotherapy in combination with TKI therapy. The combination of pembrolizumab and lenvatinib was evaluated in the single-arm KEYNOTE 524 study including 104 patients. The combination demonstrated an objective response rate of 36%, median duration of response of 12.6 months, and median survival of 22.0 months. The therapy resulted in grade 3 AEs in 63% of patients and grade 4-5 AEs

in 4% of patients. The combination is now undergoing phase III evaluation in a large RCT comparing the combination to lenvatinib monotherapy (LEAP 002). In parallel, COSMIC 312 is a large phase III trial evaluating the combination of atezolizumab and cabozantinib with sorafenib monotherapy.

As above, there has also been interest in dual checkpoint inhibitor therapy, such as PD-1/PD-L1 and CTLA4 inhibitors. Nivolumab and ipilimumab, a combination regimen targeting PD-1 and CTLA-4, was approved in the second line setting based on phase II single-arm data showing durable responses in 32% of patients and a median OS of 22.8 months. Checkmate 9DW comparing this combination to sorafenib or lenvatinib in the front-line setting is ongoing. Similarly, the combination of durvalumab and tremelimumab has been evaluated in Study 22, demonstrating an ORR of 24% and median overall survival of 18.7 months. The combination had an acceptable AE profile, resulting in grade 3-4 AEs and TRAEs in 58.1% and 35.1% of patients, respectively. This combination is currently being evaluated in the ongoing phase III HIMALAYA trial.

Given the objective responses and now improved survival seen with immunotherapy in the advanced stage setting, there is increased interest in combination trials in earlier stages of disease. In the intermediate stage, TACE is the standard of care and is associated with median survival of 2-3 years, although it continues to have a 5-year survival of only ~30%, highlighting the potential for improvement. Prior trials evaluating combinations with TKI therapy largely failed to produce any benefit in progression-free survival or overall survival. There is strong rationale for revisiting this concept with immunotherapy including locoregional therapy increasing antigen load and inducing tumor-specific T cell responses as well as augmenting the abscopal effect that can be sometimes observed. Accordingly, there are several ongoing trials evaluating combinations of checkpoint inhibitors, with or without TKI/anti-VEG-F, in combination with locoregional therapies.

In the early stage setting, surgical resection is considered curative with a 5-year survival >60% but is associated with a 50-70% risk of tumor recurrence within 5 years. The risk of recurrence increases with tumor size, number of lesions, and presence of microvascular invasion. The STORM Trial failed to find any benefit of adjuvant sorafenib in improving time to recurrence or survival. There are several ongoing studies evaluating the role of neoadjuvant and adjuvant checkpoint inhibitors to reduce the risk of recurrence. Neoadjuvant nivolumab and ipilimumab were recently reported at ASCO to induce complete pathologic responses in 5 of 21 patients who underwent resection and major pathologic responses (50-99% necrosis) in another 3 patients. Of note, there were 6 patients who underwent neoadjuvant therapy in whom surgery had to be aborted, including 3 with progressive HCC. Further data are needed to see if these objective responses will translate into reduced recurrence and/or improved survival, particularly when evaluated on an intention-to-treat basis. While checkpoint inhibitors may be helpful when combined with surgical resection, it should be noted that they should not be used in post-transplant patients given the high risk of graft loss, observed in over one-third of patients.

Overall, there is a lot of enthusiasm for how checkpoint inhibitors can transform the entire landscape of HCC. This increased interest in combination therapies across tumor stages will increase the importance of multidisciplinary care in the future.

The Liver Week 2020

August 13-14, 2020 | VIRTUAL CONFERENCE

DAY 1: Thursday, August 13, 2020 (11:30-12:00)

State-of-the-Art Lecture

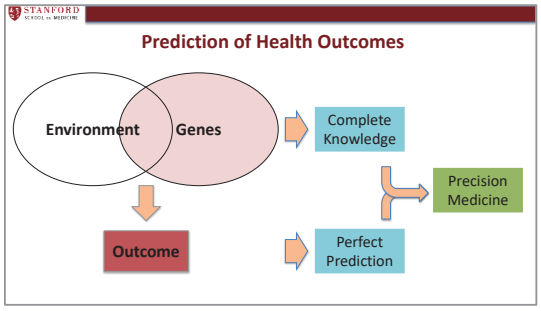
Chair:

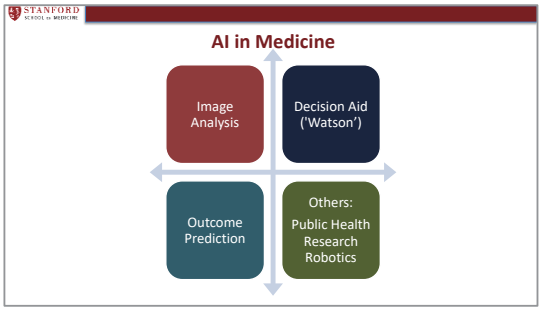
Seung Woon Paik (Sungkyunkwan Univ.)

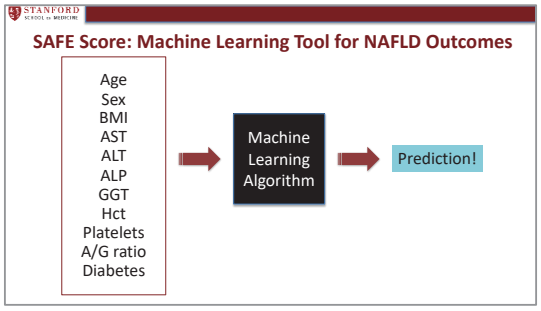
Past, Present, and Future of Precision Hepatology: Where Do We Need to Go?

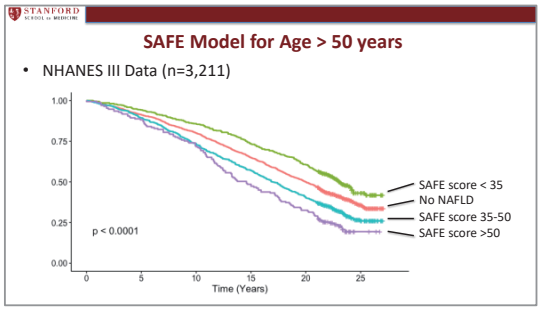
W. Ray Kim

Stanford University, USA









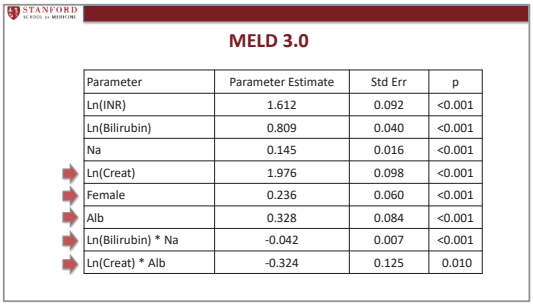
Precision Medicine commonly refers to methods by which to tailor medical treatment by classifying individuals according to their susceptibility to a particular disease, prognosis in case the disease does develop and likelihood of response to a specific treatment for the condition. Predicting health outcomes is a key ingredient of precision medicine.

It is long held that health outcomes are a result of interaction between the genes of the individual and their environment. It follows then by acquiring complete information about the genes and the environment and developing tools to integrate the information, precise prediction of health outcomes would be possible.

Artificial intelligence has received much attention as a new tool to revolutionalize precision medicine. AI has been used in image analysis, modeling decision making and outcome prediction as well as a number of other applications. Machine learning represents a group of new tools that recognize patterns in data that may be used for medical decision making.

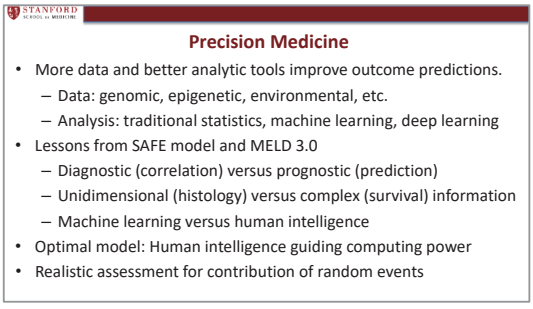
We have recently completed a study in which we developed a machine learning model to predict clinically significant liver fibrosis (>F2) among patients with NAFLD. Out of a number of algorithms tested, random forest performed the best compared, for example, to the conventional multivariable logistic regression analysis and existing markers of fibrosis such as FIB-4 and NFS. The model now termed Steatosis Associated Fibrosis Estimator (SAFE) score has a high negative predictive value – patients with a good SAFE score may be considered 'safe' from the risk of long term complications of NAFLD.

When the SAFE score is applied to a population-based followup data, a low SAFE score (<35) portended no in-



MELD 3.0

Parameter	Parameter Estimate	Std Err	p
Ln(INR)	1.612	0.092	<0.001
Ln(Bilirubin)	0.809	0.040	<0.001
Na	0.145	0.016	<0.001
Ln(Creat)	1.976	0.098	<0.001
Female	0.236	0.060	<0.001
Alb	0.328	0.084	<0.001
Ln(Bilirubin) * Na	-0.042	0.007	<0.001
Ln(Creat) * Alb	-0.324	0.125	0.010



Precision Medicine

- More data and better analytic tools improve outcome predictions.
  - Data: genomic, epigenetic, environmental, etc.
  - Analysis: traditional statistics, machine learning, deep learning
- Lessons from SAFE model and MELD 3.0
  - Diagnostic (correlation) versus prognostic (prediction)
  - Unidimensional (histology) versus complex (survival) information
  - Machine learning versus human intelligence
- Optimal model: Human intelligence guiding computing power
- Realistic assessment for contribution of random events

crease in mortality compared to individuals without NAFLD. Increasing SAFE score was associated with progressively higher risk of mortality. This is a diagnostic study which is an example where AI/ML methods my enhance medical decision making compared to traditional statistical analysis.

MELD 3.0 may be a counter-example where human intelligence guiding conventional tools may be more helpful than machine learning. MELD 3.0 is the latest innovation in MELD which incorporates additional variables (female sex and albumin) as well as a number of further refinements. While the model fits the latest waitlist data better than the original MELD or MELDNa, it also addresses gender inequality in waitlist outcomes. In light of the nuances that exist in organ allocation decisions and the need for transparency, the traditional Cox regression was considered the tool of choice. In addition, the superiority of AI/ML algorithsm in predicting future events (e.g.,, waitlist death) compared to existing statistical models remains to be proven.

In summary, increasing availability of more data and better analytic tools holds promises to precision medicine for the future. The SAFE and MELD3.0 examples highlight that as of today, artificial intelligence may be well-suited for correlational diagnostic analysis, whereas human intellignce guiding computing power remains an important tool for precision medicine today, especially for prediction of future events.

The Liver Week 2020

August 13-14, 2020 | VIRTUAL CONFERENCE

DAY 1: Thursday, August 13, 2020 (13:00-14:30)

KLCA Symposium 1

The Changing Landscape and New Evidences in Treatment Strategies for Hepatocellular Carcinoma

Chairs:

Joong-Won Park (National Cancer Center Korea)

Jung-Hwan Yoon (Seoul National Univ.)

Current Evidences and Future Perspectives for the Treatment of Advanced Hepatocellular Carcinoma

Jeong Won Jang

The Catholic University of Korea, Seoul, Korea

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer deaths worldwide. For most patients with HCC, the diagnosis is delayed and the prognosis is poor, especially in patients with advanced HCC. Until recently, few therapies have shown to effectively improve the prognosis of advanced HCC.

Since it was first approved as a treatment option in 2007, sorafenib has remained the only therapy with proven efficacy in advanced HCC over the past decade. In 2018, the phase III trial of lenvatinib showed non-inferior survival versus sorafenib and remains another first-line option for advanced HCC. Other tyrosine kinase inhibitors (TKI), regorafenib and cabozantinib, also provided significantly improved survival in the second-line setting in patients who were refractory to sorafenib. Ramucirumab, a VEGF inhibitor, was also shown to offer survival benefits as a second-line option specifically for sorafenib-refractory patients with AFP $\geq$ 400 ng/dL.

More recently, another type of therapeutics, immune check point inhibitors (ICI), has presented a major breakthrough in treatment of advanced HCC. Nivolumab and pembrolizamab, an anti-PD-1 inhibitor, showed promising results and durable responses in Phase II trials, and thus achieved conditional FDA-approval as the second-line option. However, recent phase III tirlas of these agents have failed to meet their prespecified endpoints on treatment outcomes. Other immuno-targets, such as PD-L1 (durvalumab, atezolimumab, avelumab) or CTLA-4 (tremelimumab, Ipilimumab) are currently being studied in clinical trials of advanced HCC.

The favorable treatment outcomes and acceptable toxicity profiles of ICI brought a treatment paradigm shift from a single therapy to combination strategies: ongoing trials are evaluating combination of anti-PD-1/anti-PD-L1/anti-CTLA4 as a backbone with TKIs, VEGF inhibitors, locoregional therapies, or even other ICI agents in hopes of further increasing objective responses and overall survival in this patient population. The IMbrave150 trial investigating the combination of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF antibody) in patients with advanced HCC with no history of prior systemic therapy demonstrated a significant improvement in both OS and PFS over sorafenib. Based on the promising results, atezolizumab plus bevacizumab regimen was granted FDA approval for patients with unresectable HCC who have not received prior systemic therapy. This regimen not only gives insights into a new standard of first-line therapy for advanced HCC but also changing landscape of systemic therapy.

Currently, several combinations of anti-PD-1/anti-PD-L1 plus TKIs are being tested in different stages of HCC, including lenvatinib + pembrolizumab, camrelizumab + apatinib, atezolizumab + cabozantinib. These TKIs have reportedly immune modulatory effects as well as anti-angiogenic effects in tumor microenvironment, and thus are expected to enhance the antitumor property of ICI. Another promising combination strategy includes anti-PD-1/anti-PD-L1 plus anti-CTLA4 combination agents to achieve antitumor synergy. Trials of nivolumab

plus ipilimumab, durvalumab plus tremelimumab, and triplet combination of cabozantinib, nivolumab, and ipilimumab for patients with sorafenib failure or advanced HCC are underway. Preliminary results of some studies are promising with more than twice objective response rates than a single agent as well as acceptable toxicity profiles, highlighting the increased antitumor effects of ICI combination therapy.

With the recent introduction of effective TKIs and ICIs, therapeutic options for advanced HCCs are rapidly expanding. While this progress is likely to offer improved outcomes for patients with advanced HCC, it has raised important issues regarding the optimal selection and sequencing of individual treatments. Based on a better knowledge of HCC therapeutics and differences in trial design, future efforts should be directed toward the development of biomarker-based therapy and new combination or sequential therapies with synergistic antitumor effects that can target multiple oncogenic pathways, which will provide the best therapeutic option for individual patients.

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When Should We Consider Systemic Therapy in BCLC Stage B Hepatocellular Carcinoma?

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Korea University, Seoul, Korea

The Barcelona Clinic Liver Cancer (BCLC) classification includes 5 disease stages (0, A-D).[1] The BCLC stage B consists of patients with cirrhosis with 1) underlying liver function of Child-Pugh class A or B, 2) multiple tumors beyond Milan criteria, but no vascular invasion, no extrahepatic lesions, and 3) tolerable performance status for anti-cancer therapy. As the definition of BCLC stage B is broad, it includes a heterogeneous population. Hence, response to transarterial chemoembolization (TACE) which is the standard treatment for BCLC B may not be uniform. In some instances, patients who are not suitable for TACE can exist in this stage. If the tumor is not controlled by an initial TACE, the same therapy can be repeated. However, if repeated TACEs do not achieve complete necrosis of tumors, it should be considered as TACE failure or refractoriness, which requires alternative therapies for HCC.[1] If the tumor is localized and the underlying liver function is good, surgical resection may be an option.1 If there is no vascular invasion and no extrahepatic lesions, extended criteria for liver transplantation could be applied.[1] However, most of the patients experiencing TACE failure are not the candidate for such surgical therapies, mainly due to its nature of the BCLC B stage. Currently, there are new pharmacologic therapeutic agents for unresectable or advanced HCCs (BCLC C stage); sorafenib, lenvatinib, regorafenib, cabozantinib, ramucirumab, nivolumab, and atezolizumab plus bevacizumab.[2,3] Hence, timely adjustment of treatment strategy should be undertaken for the best outcomes. Previously, Raoul et al. suggested that patients who show progression after two cycles of TACE need switching therapy to sorafenib.[4] Likewise, Japan Society of Hepatology defined the TACE failure as follows and recommended modifying therapies to molecular targeting agents (MTTs);[5] 1) Intrahepatic lesion with two or more consecutive insufficient responses (viable lesion >50%) or those with two or more consecutive progressions in the liver (tumor number increases as compared with tumor number before the previous TACE procedure) even after having changed the chemotherapeutic agents and/or reanalysis of the feeding artery seen on response evaluation CT/MRI at 1–3 months after having adequately performed selective TACE, 2) Continuous elevation of tumor makers immediately after TACE even though a slight transient decrease in observed, 3) Appearance of vascular invasion, and 4) Appearance of extrahepatic spread. A recent survey conducted in Korea indicated that nearly half of Korean clinicians prefer to consider TACE failure after more than three times of repeated TACEs, and sorafenib and radiotherapy were subsequent choices in that situation. So far, there is no concrete definition of TACE failures, but 2 or 3 times of TACE session would be the reasonable limit for deciding the next treatment.[6] A single-center study also suggested no objective response after two consecutive TACEs is related to poorer survival.[7] Well-designed clinical trials and further discussions should be warranted to improve the patients' survival in patients with TACE failures.

Recently, a proof of concept study compared lenvatinib and TACE in BCLC stage B patients with Child A liver function and multiple tumors exceeding up-to-7 criteria.[8] The lenvatinib group showed a significantly better ob-

jective response rate and significantly longer progression-free survival as well as overall survival than the TACE group. Hence, the early application of an MTT agent could be a better choice for patients with BCLC stage B patients. Combination of immunotherapeutics and MTT is a promising strategy in patients with TACE failure considering results of atezolizumab plus bevacizumab clinical trial which included treatment-experienced patients up to 52%.[3]

In the future, choosing an appropriate time point of treatment modification and the best next option will lead to the improvement of clinical outcomes.

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Therapeutic Efficacy of Transarterial-Based Treatment vs. Targeted Therapy in Advanced Hepatocellular Carcinoma

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For the past several decades, transarterial chemoembolization (TACE) has been one of the most common treatments used for hepatocellular carcinoma (HCC). At the moment, TACE is the recommended therapy in patients with intermediate-stage HCC in both Eastern and Western guidelines. In 2007, the first oral molecular target agent, sorafenib was demonstrated to prolong overall survival (OS) in a phase III clinical trial in advanced HCC in a Western population. This result was replicable in other phase III trials, including advanced HCC patients from Asia-Pacific regions. After sorafenib approval, several studies have demonstrated the effectiveness of the conversion from TACE to sorafenib at the time of TACE refractoriness in patients with intermediate-stage HCC. Nowadays, several anticancer agents have become systemic therapies in HCC patients, and conversion from TACE to systemic therapies has become a more common treatment choice.

In 2019, atezolizumab combined with bevacizumab for the first-line treatment of patients with advanced HCC prolonged OS and progression-free survival compared with sorafenib, according to the results of a global phase III trial (IMbrave150). The result of IMbrave150, the first phase III study of combination setting with ICIs or ICI-based therapies in patients with advanced HCC that released outcomes, showed a large magnitude of impacts that resulted from the combination of atezolizumab and bevacizumab as the first regimen to prove superiority of OS compared with sorafenib, with longer durable responses and tolerable safety profiles. These results suggest that combination setting with ICIs or ICI-based therapies, including atezolizumab combined with bevacizumab, may have the potential to become “a game changer” in the landscape of HCC treatment. Although TACE has been standard treatment procedure for intermediate stage HCC, ICI-based therapies strongly expect to replace from TACE in patients with intermediate stage HCC, especially limited high burden intermediate stage HCC population. This is one of the leading clinical issue in HCC. In this session, results of latest researches will be shared and this newest clinical issue will be discussed.

Optimizing Therapeutic Efficacy with Systemic Therapy & Radiotherapy in Hepatocellular Carcinoma

Jinsil Seong

Yonsei University, Seoul, Korea

For most solid cancers, multimodality treatment is a general principle particularly for locally advanced ones while single modality reserved for early cancers. However, this notion hasn't been well reflected in current therapeutic guidelines for hepatocellular carcinoma (HCC), which show a single modality as a standard of care for each stage of HCC.

HCC shows significant heterogeneity particularly in advanced stage. Although current guidelines recommend systemic agent as a standard of care, efficacy has been limited with gaining only a few months of survival. Recent studies on phylogenetic analysis[1] reported that sorafenib-targeted genetic alteration was identified in only limited case, explaining why response was less than satisfactory. It also suggests that combination strategy needs to be adopted particularly in advanced HCC. Applying a single agent to a disease with extreme heterogeneity can hardly produce therapeutic success, warranting subclassification of the disease and optimal therapy accordingly. Advanced HCC needs to be classified into 2 catogories; advanced but confined to liver and advanced to beyond liver.

In advanced HCC confined to liver, combination strategy may involve maximizing local control by local modality as well as systemic agent preventing tumor spread either intrahepatically or extrahepatically. Our group has long been practicing local radiotherapy concurrently with hepatic arterial chemotherapy (liver-directed CCRT) followed by adjuvant hepatic arterial chemotherapy for substantial period.[2,3] More recently we reported a phase 2 trial results of liver-directed CCRT followed by sorafenib.[4] The result was quite encouraging with 24.6 months of median survival time, which corresponds to double the time in those with sorafenib alone. The beauty of this approach is that 19% of the patients underwent curative surgery by tumor downsizing/downstaging. In advanced HCC beyond liver, systemic therapy is a mainstay without any argument. Now, a concept discriminating oligometastasis from full metastasis has been proposed, which has been well established in most solid cancers.[5] While systemic therapy is undergoing, local treatment, either radiotherapy or surgery, can effectively control oligometastasis that can result in prolonged overall survival.[6]

Taken together, systemic therapy and radiotherapy can be combined in various scenario, ultimately aiming at improved therapeutic efficacy in advanced Hepatocellular Carcinoma.

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DAY 1: Thursday, August 13, 2020 (14:40-15:50)

LCGSJ-KLCA Joint Symposium

Similarities and Differences in HCC Management

Chairs:

Shoji Kubo (Osaka City Univ., Japan)

Jin Wook Chung (Seoul National Univ.)

Current Approaches to the Treatment of Early HCC in Japan

Shuichiro Shiina

Juntendo University, Japan

Hepatocellular carcinoma (HCC) is the 4th most common cause of cancer-related deaths in Japan. In Japan, the most common etiology of HCC is HCV, which is different from that in most Asian countries, where HBV is the most prevalent. About a half of HCC is HCV-related, although the ratio has been gradually decreasing. Since the ethanol injection period, we have had strong argument regarding which treatment is superior for HCC, surgical resection or percutaneous ablation.

The Japanese clinical practice guidelines for HCC (4th JSH-HCC guidelines) recommends both surgery and ablation for patients with HCC who have three or fewer lesions, each 3 cm or less in diameter, and whose liver functions are in Child-Pugh grade A or B (1). Comparison of surgical resection with ablation is considerably difficult; the indications are somewhat different between the two treatments. Patients with a large lesion tend to undergo surgical resection while those with multiple lesions, advanced age, or more deteriorated liver function tend to receive ablation. Furthermore, both treatments are highly operator-dependent and their indications may be different from institution to institution. Thus, a patient who is decided by medical professionals to undergo ablation or surgical resection at an institution may not be given the same treatment at others. There were four randomized controlled trials (RCTs) to compare surgery with RFA; one showed superiority of surgery in survival while the remaining three did not show the difference in survival between the two therapies.

To compare surgery with radiofrequency ablation, we conducted a multicenter RCT (SURF trial) in Japan (2). We recruited patients with primary HCC at 49 hospitals who had three or fewer lesions, each 3 cm or less in diameter ≤ 3 cm, and whose liver functions were in Child-Pugh score of 7 or lower, age between 20 and 79 years. Before randomization, technical and liver functional feasibility for both treatment arms were confirmed by joint chart review by surgeons and hepatologists. Patients were then randomly assigned in a 1:1 ratio to surgery and RFA, stratified by age, infection of HCV, number of tumors, tumor size and institution. The primary endpoints were recurrence free survival (RFS) and overall survival (OS).

Between April 2009 and August 2015, a total of 308 patients were enrolled to this trial. Seven patients were excluded because of ineligibility, therefore 150 patients were assigned to surgery and 151 patients to RFA. There was no perioperative mortality. Under the median follow-up of 5 years, the 3-year RFSs of patients who were assigned to surgery and RFA were 49.8% and 47.7%, respectively (hazard ratio [HR] 0.96, 95% CI 0.72-1.28; p = 0.793). The RCT trial did not show difference in RFS between surgery and RFA (3).

In parallel with the RCT, we also conducted SURF Cohort trial. In this cohort trial, HCC patients who fulfilled the enrollment criteria but did not give consent to participate in the RCT were enrolled. Baseline characteristics, such as sex, HCV positivity, size, Child-Pugh score, and platelet count were significantly different between the two treatment groups. Patient's age was not significantly different between the two treatment. However, it might be due to the age limitation of 79 years in the eligibility criteria. The imbalance in background characteristics

may reflect a real-world clinical practice of choosing a treatment. In the cohort study, RFS was not significantly different, either between surgery group and RFA group after adjustment of inversed probability of treatment weighting (4). SURF trial is ongoing for the final analysis of 5-year overall survival. OS will be assessed after August 2020 as scheduled in the protocol.

New-generation MWA systems incorporating water or gas antenna cooling and high-power generation have recently attracted attention. New-generation MWA may create a more predictable ablation zone, a larger ablation volume in a shorter time period. Many high volume centers of ablation have introduced new-generation MWA for liver tumor ablation in Japan. However, its clinical data have been insufficient compared with that of RFA. There have been four RCTs to compare new-generation MWA with RFA. None of them have proved superiority of MWA over RFA from the viewpoint of overall survival. Further studies are mandatory especially in terms of long-term survival.

Both surgery and ablation are highly operator-dependent. The skills and outcomes are very different from operator to operator. In surgery, the Japanese Society of Hepato-Biliary-Pancreatic Surgery has a board-certification system for expert surgeons. On the other hand, in ablation, there is no established training system yet. Because the procedure appears to be relatively simple, we are afraid that ablation is sometimes done without sufficient training. It is mandatory to have the system which enhances acquisition of knowledge and skills for successful ablation. In Japan, more than 80% of liver tumor ablation is performed by gastroenterologists or hepatologists. The remaining are done by surgeons or radiologists.

The result of final analysis in SURF trial is not coming yet. However, we expect ablation would be proved to be the first-line treatment even for solitary HCC. Ablation would play a more important role in the aging society. In ablation, it is mandatory to establish the system to exchange knowledge and experience and standardize the procedure.

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Current Approaches to the Treatment of Early HCC in Korea

Myeong Jun Song

The Catholic University of Korea, Seoul, Korea

Introduction

For patients with early-stage hepatocellular carcinoma (HCC), potentially curative treatment options exist, including surgical resection, ablation, and liver transplantation. These treatments are associated with survival benefits, and outcomes are optimized by identification of appropriate patients. However, further studies are needed to definitely confirm optimal treatment approaches for all patients.

Treatment patterns vary in different parts of the world as a result of geographic differences in the incidence and presentation of disease. For example, difference of nationwide surveillance program or applicability of transplantation are evident between west and Asia. The aim of this topic is to review the current therapeutic options and associated outcomes for the management of patients with early HCC in Korea.

Current status and Outcomes of early HCC treatments in Korea

The decision of treatment strategy for HCC patients may vary depending on the patient's cancer stage, underlying liver function and performance status; especially, patients with early HCC are those most likely to benefit from curative treatment. Nowadays, this requires multidisciplinary treatment planning.

In Korea, early-stage HCC according to BCLC stage showed 45.4% from 2008 to 2014 in Korean Primary Liver Cancer Registry data. Within early HCC, modified UICC stage I and II and III showed 28%, 64%, and 8%, respectively. Transarterial therapy was most common 1st line treatment modality (43.4%) followed by surgical resection (29.4%) and ablation therapy (20.3%) (Fig. 1). Therefore, applicability of curative treatments varies according to geographic distribution, with 50.5 % of cases in Korea being suitable for curative treatment, compared with 25%-45% of cases in Europe and the U.S.[1]

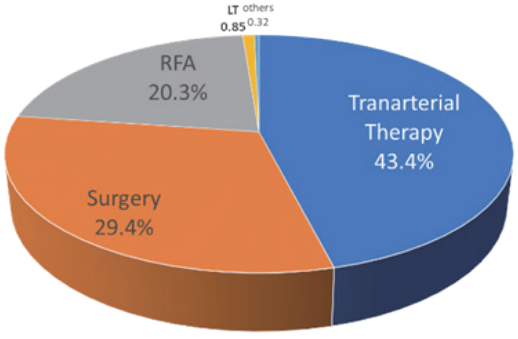

Figure 1. 1st line treatment modality in early HCC in Korea (from 2008 to 2014 in Korean Primary Liver Cancer Registry data)

2018 Korea practice guidelines for patient with HCC recommends the treatments for early HCC patients with various modified UICC stages with good liver function (Child-Pugh A class) and good performance status (Eastern Cooperative Oncology Group [ECOG] performance 0–1) without any complications of portal hypertension (Fig. 2).[2] Korea guideline also recommends curative treatments as best option in early HCC. In addition, TACE and EBRT are suggested as alternative options.

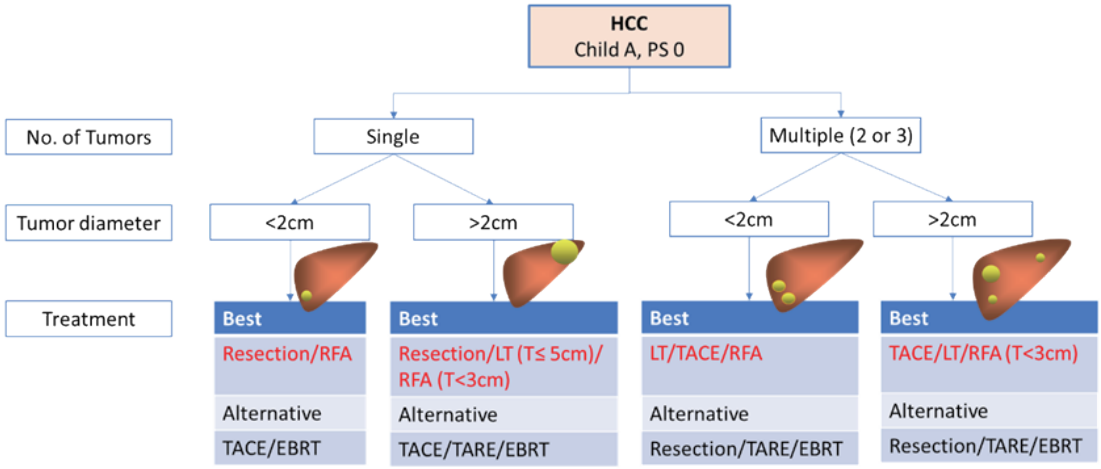

Figure 2. Treatment algorithm for HCC recommend by 2018 KLCA-NCC Korea practice guideline for patients with HCC

In Korean clinical practice, transarterial therapy was most common 1st line treatment modality (40.1%) followed by ablation and surgical resection (35% and 19.2%) in modified UICC stage I. In modified UICC stage II, transarterial therapy was also most common (44.2%). Unlike stage I, surgical resection was more applied than ablation (40.2% vs. 14.4%). Modified UICC stage III showed transarterial therapy was more common (66.9%) followed by surgical resection (16.8%) and ablation therapy (15.5%). According to modified UICC stage, applicability of curative treatment showed 54.8%, 55.6%, and 32.9% respectively. In addition, the patients with poor liver function (child-Pugh B class) showed a tendency to perform more locoregional therapy as modified UICC stage progressed (Fig. 3). However, curative treatment showed better overall survival benefit in patients compared with transarterial therapy regardless of modified UICC stage within early HCC.

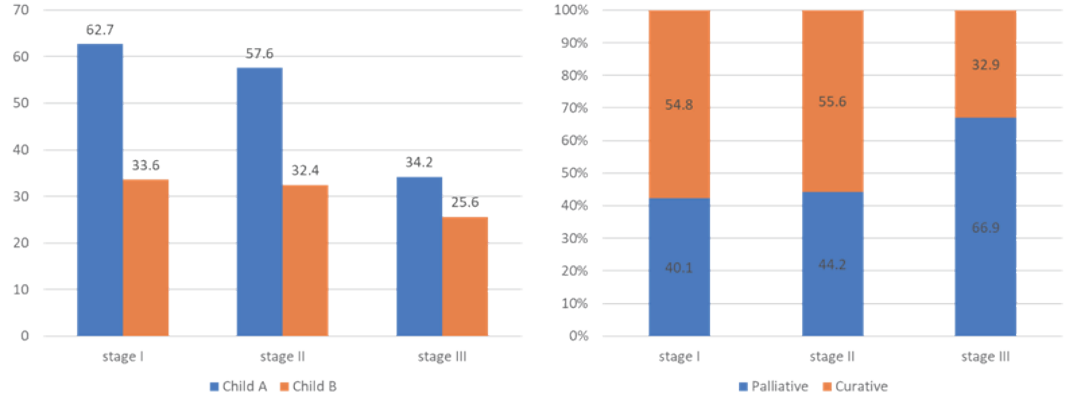

Figure 3. Applicability of curative therapy according to liver function and stage

Conclusions

Overall applicability of curative treatment was about 50.5% in patients with early HCC in Korea. Transarterial therapy was most common 1st line treatment modality. However, despite more application of locoregional therapy, patients with early HCC who perform curative treatment (surgical resection and ablation) showed better survival benefit.

Therefore, it is important to apply curative treatment as possible, and for this, more early detection will be needed. In case of ineligible curative therapy, it is needed to consider better alternative therapy through multidisciplinary approach.

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Selection of Particle Beam vs. Photon Beam Radiation Therapy for HCC: Japanese Experience

Hideyuki Sakurai, M Iizumi, S Shimizu, H. Numajiri, M. Mizumoto, K. Nakai, T. Okumura

University of Tsukuba, Japan

Radiation therapy (RT) using conventional fractionation has not been thought to be curative enough for hepatocellular carcinoma (HCC) and it has not been performed as a high priority in comparison to other standard treatments, such as surgery, percutaneous ablation and transcatheter approach. Because the liver is high sensitive to radiation, especially for patients with liver cirrhosis, non-irradiated normal liver volume must be preserved as much as possible when curative radiation is given for HCC.

Since many technological progress has been made in radiation oncology in recent years, RTs are used as an important curative treatment option for liver cancer. Stereotactic body radiotherapy (SBRT), which is included in Japanese national health insurance system, is a technique to accurately concentrate doses three-dimensionally on the target with short-term irradiation of 1-2 weeks. This technique can be used for relatively small tumors less than 5 cm with about 90% local control.[1] Recently, Hara K. et al. reported survival result of SBRT comparing radiofrequency ablation using propensity score analysis, and they concluded that SBRT appears to be an acceptable alternative treatment option for patients who are not candidates for RFA.[2] In addition, in Japan, muticenter prospective study of SBRT for untreated solitary primary HCC, so called STRSPH study, is ongoing. Eligible patients are untreated solitary, Child-Pugh score ≦7, Diameter: 1-5cm, UICC 7th. T1, T2, T3bN0M0, performance status score of 0-2, and 20-85 year-old. The primary endpoint / number of cases of this study are 3-year overall survival / 60 cases.

Particle beam therapy (PBT: proton beam therapy, heavy ion beam therapy) has unique character of radiation dose distribution, which is called Bragg peak. PBT can accumulate more dose to the target with minimizing normal liver dose. Primary liver tumor is an important indication that has been specified to be of the highest priority by the American Society for Radiology and Oncology (ASTRO). In fact, most of the studies on PBT for HCC are published by Japan, and rather highly evaluated abroad. Eighteen proton facilities and 6 heavy ion facilities are working now in Japan. The local control rate was approximately 90% and the 5-year survival rate was reported to be approximately 50%.[3] According to the results of our hospital, PBT can control 90% of a large tumor of 10 cm or more. Clinical studies of PBT report favorable therapeutic effects, even for not only large tumors[4] but also tumors in elderly patient. In addition, PBT has been clearly shown to play an important role in the treatment of HCC-related portal vein tumor thrombosis (PVTT). When applied as a curative treatment for bulky tumors with portal vein embolism, median survival time of 27 months has been obtained in our study. The clinical study comparing proton vs surgery, which is non-randomized trial using propensity score, is ongoing in Japan (JCOG1315C). Japanese Society for Radiation Oncology (JASTRO) defined identical rule for indication and treatment method in PBT for HCC, and the all data should be registered in the data-base since 2016.

We are facing an aging society, although there are indications of surgery and other local treatment, the number

of patients who choose curative radiation therapy due to aging and co-existing disease is increasing. But, the history of radical RT for HCC is still short, and sufficient consensus has not been obtained regarding the criteria for its therapeutic indication. RT may become an option for curative local treatment of HCC, but no specific role for RT has been described in the Japanese treatment guidelines. In the future, it is important to proceed with research to clarify the indication of curative radiation therapy, keeping in mind the comparison with other therapies.

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Selection of Particle Beam vs. Photon Beam Radiation Therapy for HCC: Korean Experience

Hee Chul Park

Sungkyunkwan University, Seoul, Korea

In patients with HCC where curative modalities are not feasible, radiation therapy has emerged as an alternative or combination therapy. With the development of various technologies, radiotherapy has been increasingly used for the management of HCC. Among these advances, proton beam therapy has several unique physical properties that give it a finite range in a distal direction, and thus no exit dose along the beam path. Therefore, proton beam therapy has dosimetric advantages compared with X-ray therapy for the treatment of HCC.

There were few studies directly comparing the clinical benefits of proton radiotherapy over photon radiotherapy. Study from the Massachusetts General Hospital demonstrated survival benefits with proton radiotherapy, which may be driven by a decreased incidence of radiation-related liver decompensation. The other study from the Chang Gung Memorial Hospital, which has been a propensity score-matched cohort study based on their multi-institutional medical organization research database, revealed that proton radiotherapy could deliver a higher radiation dose than photon radiotherapy without increasing the risk of radiation-induced liver disease and result in a better overall survival rate for HCC patients treated with curative intent.

Additionally, various reports in the literature have described safety of proton beam therapy for HCC patients compared with X-ray therapy.

However, there are some technical issues regarding the use of proton radiotherapy while selecting proton beam versus photon beam as a radiation modality. Impact of uncertainty of organ motion, impact of radiobiological uncertainty on tumor control and normal tissue toxicity might be different between photon beam and proton beam.

In this lecture, the brief review of previous reports comparing proton and photon radiotherapy. And several technical and biological considerations will be discussed with some case examples for better understanding from the audience.

The Liver Week 2020

August 13-14, 2020 | VIRTUAL CONFERENCE

DAY 1: Thursday, August 13, 2020 (16:00-17:30)

KASL Symposium 2

New Insights to Unanswered Issues in Treatment for Chronic Hepatitis B

Chairs:

Seung Kew Yoon (The Catholic Univ. of Korea)

Kyun-Hwan Kim (Sungkyunkwan Univ.)

Exploring Unrecognized Risks in Immune Tolerant Phase of Chronic Hepatitis B

Young-Suk Lim

University of Ulsan Seoul, Korea

Introduction

Although the universal hepatitis B virus (HBV) vaccination program has been successfully implemented for almost three decades in Korea and many Asian countries, most liver disease- and liver cancer-related deaths occur in unvaccinated middle-aged and elderly adults. Therefore, considering the birth cohort effect on HBV-related mortality from liver disease and liver cancer, the HBV vaccination program is deemed to have limited or no impact on reducing mortality from chronic hepatitis B (CHB).[1]

In these regards, secondary prevention of hepatocellular carcinoma (HCC) through antiviral therapy for patients with CHB is important and has been simulated to reduce significantly the incidence of HCC in a short-term.[2] However, there are still controversies regarding when to start the treatment.

When to start the treatment?

Chronic infection with HBV progresses through different phases. The first, which is the immune-tolerant (IT) phase, is characterized by high circulating HBV DNA and normal ALT levels. Antiviral treatment is generally not recommended for these patients by most practice guidelines because of the notion that the histologic activity is dormant, and the risk of disease progression is low in the IT phase. In our recent cohort study, the clinical outcomes of 413 untreated HBeAg-positive, non-cirrhotic IT phase patients with normal alanine aminotransferase (ALT) levels and high HBV DNA levels (≥20,000 IU/mL) were compared with those of 1497 immune-active (IA) phase patients (ALT ≥80 IU/mL and HBV DNA ≥20,000 IU/mL) treated with nucleos(t)ide analogs.[3] The untreated IT group showed a significantly higher adjusted risk of HCC (HR, 2.54; $p<0.001$) and death/transplantation (HR, 3.38; $p<0.001$) than the treated IA group; which was consistently identified through inverse probability treatment weighting, propensity score-matched, and competing risks analyses. Lower HBV DNA levels (but above 20,000 IU/mL) were independently associated with a significantly higher risk of clinical events.

In our another historical cohort study including 5414 HBeAg-negative CHB patients without cirrhosis in Korea from 2000 to 2013, compared with the treated Active phase (HBV DNA ≥2000 IU/mL and ALT ≥2xULN, n=546) group, the untreated Replicative phase (HBV DNA ≥2000 IU/mL and persistently normal ALT, n=900) group showed a significantly higher risk of HCC (HR 1.76; $P=0.05$) and death/transplantation (HR 2.14; $P=0.03$) by propensity score-matched analysis.[4]

Our results suggest that many unnecessary cancers and deaths could be prevented by earlier antiviral intervention in non-cirrhotic CHB patients with high viral load and normal ALT levels.

Moderate levels of serum HBV DNA and the highest risk of HCC

Studies have shown a higher risk of HCC with higher baseline serum HBV DNA levels in CHB patients. However, the association between very high HBV DNA levels (>6 $\log_{10}$ IU/mL) and HCC risk remains unclear, especially in middle-aged and old HBeAg-positive patients. To identify the association between broad-range HBV DNA levels and HCC risk, we conducted a historical cohort study in Korea involving 6949 non-cirrhotic, treatment-naïve CHB patients with alanine aminotransferase (ALT) <2× upper limit of normal for >1 year.[5] By multivariable Cox regression analysis, HCC risk was highest with baseline HBV DNA levels of 6–7 $\log_{10}$ IU/mL (adjusted hazard ratio [aHR] 4.98; P<0.001), and lowest with >8 $\log_{10}$ IU/mL (aHR 0.90; P=0.71) and ≤4 $\log_{10}$ IU/mL (aHR 1.00; reference), which was independent of other predictive factors. The similar association between HBV DNA levels and HCC risk was consistently observed in all age subgroups (age <40 years, 40-49 years, and ≥50 years).

These results suggests that extending treatment indication to CHB patients with medium levels of HBV DNA may be considered to further prevent HCC, regardless of ALT levels.

Conclusions

Our findings emphasize the importance of secondary prevention for HCC, including early initiation of HBV treatment for the patients with high viral load regardless of ALT levels.

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Clonal Hepatocyte Expansion and Hepatitis B Virus Integration

Patrick Kennedy

Queen Mary Univ. of London, UK

CHB remains the leading cause of hepatocellular carcinoma (HCC) worldwide and on average ~25% of patients with CHB infection will die of HCC or the complications of cirrhosis. Clonal hepatocyte expansion and HBV integration in the human genome are key events in hepatocarcinogenesis, but our understanding of these events in disease progression is limited. In this talk, I will review our previous immunological data in the early disease phases of CHB. I will show the presence of a virus-specific immune response which is no different in HBeAg positive chronic infection disease phase (formerly referred to as immune tolerant) from age-matched patients with HBeAg positive chronic hepatitis (formerly referred to as immune active). In addition, I demonstrate the presence of clonal hepatocyte expansion and HBV DNA integration in these disease phases, which are factors which should be considered in the timing of treatment initiation. As a development of this work, we have also studied integration events in patients with eAg negative CHB with low to moderate levels of viraemia, including those who currently do not meet treatment criteria. We studied the intrahepatic reservoir to investigate the association between transcriptionally active virus and integration, we were able to demonstrate HBV integration occurs in all patients with eAg negative CHB including those with low levels of cccDNA, pgRNA and intrahepatic HBV DNA. Localisation of integrants suggest these events are not restricted to carcinogenesis, but also involved in mechanisms regulating hepatocyte metabolism and antiviral/inflammatory responses. These findings underline the complexity of CHB, with its various disease phases, some of which are currently deemed not to meet treatment criteria. The growing evidence of HBV integration across all disease phases including low-viraemic patients currently not considered treatment candidates, suggests that these patients are also at risk of disease progression and HCC development. These data add to the debate around the timing of treatment in CHB and support the concept of early therapeutic intervention, an important consideration as we move forward with the HBV functional cure program.

Effect of Current and Novel Antivirals on the Prevention of Hepatocellular Carcinoma: Beyond Viral Suppression

George Papatheodoridis

Medical School of National and Kapodistrian Univ. of Athens, Greece

Hepatitis B virus (HBV) has substantial oncogenic potential promoting carcinogenesis through multifactorial and multi-route processes, which involve insertional mutagenesis following HBV DNA integration into host genome, increased genomic instability caused by HBV DNA integration and direct effects of viral proteins.[1] HBV related oncogenic activity is enhanced in patients with long-term active necro-inflammatory activity and particularly in those with established cirrhosis, but it exists even in patients with inactive chronic HBV infection, since HBV DNA integration into the host genome occurs early in the phase of chronic HBV infection.[2] Thus, it is easily understood why even non-cirrhotic chronic hepatitis B (CHB) patients carry some risk of hepatocellular carcinoma (HCC) development, which has considerable implications for their long-term monitoring.[1,3]

Current treatment options can inhibit HBV replication and prevent the progression of chronic liver injury and even achieve regression of cirrhosis in most of compliant treated patients with CHB.[4] However, since HBV cannot be eradicated, HCC may still develop after several years of effective therapy.[1,3] Therefore, HCC remains the major complication of treated CHB patients, particularly those with cirrhosis.[1,3,4] Given that persistent high HBV replication increases the risk of HCC, antiviral therapy should reasonably prevent or reduce the risk of HCC in patients with chronic HBV infection.[3,5]

Today, treatment of patients with chronic HBV infection is mostly based on therapy with an oral nucleos(t)ide analogue (NA), although interferon-alpha (IFNa), almost exclusively pegylated IFNa, may be also used in a minority of cases.[4] Treatment with any NA is usually given for long, perhaps for life, aiming to maintain on-therapy virological remission.[4] Several studies and meta-analyses including initially patients treated with lamivudine and/or adefovir (the first two licensed oral anti-HBV agents) showed that long-term NA therapy significantly reduces but does not completely eliminate the risk of HCC, particularly in patients with pre-existing cirrhosis.[5,6] Subsequent studies with the current first-line high-genetic barrier NAs, entecavir and tenofovir, reported rather variable annual incidence rates of HCC making comparisons with historical untreated controls and therefore conclusions rather complex.[3,5] However, in all studies including appropriately matched untreated chronic hepatitis B patients, treatment with entecavir or tenofovir was also found to reduce but not to eliminate the risk of HCC.[3,5] The benefit of antiviral therapy is particularly evident in patients with cirrhosis which are at increased risk for HCC, but there may be a preventive effect on the HCC incidence in non-cirrhotic patients as well.[3,5] Prolongation of therapy with entecavir or tenofovir and particularly effective therapy for more than 5-7 years seems to further reduce the risk of HCC, especially in patients with pretreatment cirrhosis.[7,8] Recently, there have been some data suggesting that the HCC risk may be lower in patients treated with tenofovir than entecavir,[9] but contradictory studies have been also reported and hidden confounding factors could not be definitely excluded leaving the issue controversial.[10]

In clinical practice, patients with chronic HBV infection who are at increased risk for HCC should be advised to remain under HCC surveillance for ever, even if they achieve complete virological remission after antiviral therapy.[1,3-5] In particular, all patients with cirrhosis should undergo HCC surveillance for life, although there are some emerging data suggesting that perhaps patients with pretreatment cirrhosis who achieve elastographic reversion of cirrhosis before the age of 40 years have minimal HCC risk and may discontinue HCC surveillance.[11] On the other hand, treated non-cirrhotic CHB patients have a low baseline HCC risk which may be further reduced under NA therapy and therefore there is a lot of interest for the accurate prediction of the HCC risk and for the identification of such patients who require HCC surveillance.[12,13] Recently, several risk scores have been reported for accurate prediction of HCC risk in treated CHB patients, one from a European Caucasian cohort (PAGE-B) and several from East Asian cohorts (South Korea: mPAGE-B, HCC-Rescue, AASL; Taiwan and Hong-Kong: APA-B, CAMD).[12,13] All these scores include similar parameters, like age, gender and a variable expressing liver fibrosis severity (combined with one more variable in some of these scores) and appear to offer similarly good HCC predictability in Asian and Caucasian patients.[12,13] The most important characteristic of all these HCC risk scores is their excellent negative predictive value, which offers identification of patient subgroups with no or negligible HCC risk (<0.2% per year) and thus no need for HCC surveillance.[12,13]

Whether novel treatment options that are currently under investigation can achieve greater reduction in the HCC risk of CHB patients is unknown. Given that all experimental treatment options aim to achieve greater rates of functional cure defined as HBsAg seroclearance,[14] which is an endpoint that has been associated with lower HCC risk,[15,16] we can only hope that the potential new treatment options will further reduce the HCC risk in this setting, particularly if they are used at an early phase of chronic HBV infection.[14,17]

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Functional Cure of Chronic Hepatitis B and Beyond

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In the past two decades, treatment of chronic hepatitis B by antiviral agents primarily targets prolonged HBV DNA suppression leading to normalization of liver biochemistry, regression of liver fibrosis/ cirrhosis and reduction of liver-related complications and mortality. To advance the treatment goal, functional cure of the disease defined by HBsAg seroclearance is now a common approach in the context of novel agents. Functional cure can be achieved spontaneously or under treatment. Studies on the former mode showed that functional cure attains at younger age e.g. younger than 50 years is associated with a significantly lower risk of development of hepatocellular carcinoma and other liver-related events. These beneficial effects are also observed in treatment-induced functional cure. Another beneficial effect would the allowance of cessation of treatment which is otherwise expected to be given long-term. It is because treatment cessation after achieving functional cure is associated with a minimal risk of disease relapse i.e. sustained HBsAg and HBV DNA negativity.

However, both spontaneous and treatment induced functional cure occur at a very low rate. It is estimated to be <1% annually and <10% over 5-10 years of treatment respectively. The HBsAg levels and/or its annual log reduction are predictive factors for functional cure.

Therefore, novel treatments are actively underway by many clinical trials to enhance the rate of functional cure. They act directly and indirectly to promote immune restoration and to enhance host control on the virus. The former group include toll like receptor agonists, therapeutic vaccines and immune checkpoint inhibitors. The latter group include agents (short interfering RNAs, anti-sense oligonucleotides) silencing viral mRNA transcriptions and hence removing the immune repressive effect exerted by high load of viral antigens, namely HBsAg. Preliminarily promising results have been shown in recent years. It is anticipated that these agents would be successful and phase III studies are warranted.

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DAY 2: Friday, August 14, 2020 (08:30-10:50)

Policy Symposium

Nationwide Policies to Eliminate Hepatitis C

Chairs:

Dong Jin Suh (Korean Liver Foundation)
W. Ray Kim (Stanford Univ., USA)
Han Chu Lee (Univ. of Ulsan)

Hepatitis C Elimination Program in Taiwan: "The Taiwan Hepatitis C Policy Guideline 2018 - 2025"

Chien-Jen Chen

Former Vice President of Taiwan, Academia Sinica, Taiwan

In 1990, the seroprevalence of antibody against hepatitis C virus (anti-HCV) in Taiwan was 0.95% in volunteer blood donors, 90% in hemophiliacs, and 81% in parenteral drug abusers. The anti-HCV seroprevalence was 17% in HBsAg-positive and 63% in HBsAg-negative patients with hepatocellular carcinoma (HCC).[1] A national program of antiviral therapy for chronic viral hepatitis was lauched in Taiwan in 2003. Mortality rates of end-stage liver diseases decreased continuously from 2000-2003 to 2008-2011 in all age and gender groups. There was 25% reduction in age-gender-adjusted mortality.[2] Recently introduced hepatitis C therapies have short treatment courses, good safety records and high success rates, presenting a new opportunity for HCV elimination.

Elimination of HCV is an ambitious task that needs national and international efforts, as indicated by World Health Organization (WHO). When the World Health Assembly adopted the Global Health Sector Strategy on viral hepatitis in 2016,[3] it immediately caught the attention of the people and government in Taiwan. Efforts towards the elimination of chronic hepatitis C were seriously considered. After two years, the efforts from experts, public health officers, legislators, and the government leaders have culminated in a consensus of reaching the WHO goals in 2025, i.e., 5 years earlier than the 2030 deadline set by WHO. Accordingly, the Taiwan Hepatitis C Policy Guideline 2018-2025 was approved and published at the beginning of 2019.[4-8]

There are currently around 400,000 hepatitis C cases in Taiwan, with nearly 7,000 new infections per year. Three main strategies including prevention, screening and therapy will be adopted in the national elimination program. The government has increased screening, lowered the threshold for treatment, and greatly expanded outlays to cover the cost of new drugs. Funding has grown from US$101.8 million in 2017 to US$219.1 million in 2019. The government will provide US$1.7 billion in the coming eight years for the elimination of HCV.

By dramatically lightening the financial burden of therapy, Taiwan aims to rapidly extend the reach of treatment and reduce infection sources and transmission of the virus. The number of people receiving new drug therapy has already more than quadrupled, from fewer than 10,000 in 2017 to about 42,000 in 2019. As many as 98.5% are successfully cured. Taiwan will accelerate its efforts to achieve WHO targets of treating 80% eligible HCV patients by 2025.

In the light of the policy guideline, treatment restrictions based on fibrosis stage were removed in 2019. More than 58,000 patients are projected to be treated in 2020. Including 80,000 CHC patients already successfully treated with peginterferon and ribavirin before the DAA era, treatment coverage is expected to reach 50% by the end of 2020. Whether from the perspective of individual patient well-being and household finances, or even overall public health, national productivity and international standing, the benefits of the program are clear.

In short, Taiwan is on track to eliminate HCV by 2025 because of aggressive measures including political commitment by the Ministry of Health and Welfare to finance this national program and remove National Health

Insurance reimbursement restrictions for treatment. The capacity of specialists in Taiwan is enough to handle the existing HCV-infected population. The Taiwan Centers for Disease Control has instituted harm reduction programs. Other measures including awareness and active screening program and funding for linkage to care programs are also reinforced. The Hepatitis C Office has been keeping monitoring and evaluation of the national program. It is expected that the Taiwan Hepatitis C Policy Guideline's triple focus – therapy spearheads prevention, screening supports therapy and prevention secures outcome will help Taiwan achieve WHO's HCV elimination goal by 2025.

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Elimination of HCV in Taiwan: What and How We Have Achieved from the Beginning till Today

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Chronic hepatitis C virus (HCV) infection is a global health threat because of the disease burden. WHO estimated that there are 71 million people with HCV infection worldwide. Of particular note, Taiwan is a country endemic for chronic HCV infection, with ~500,000 HCV patients. Annually, ~13,000 people die of chronic liver diseases and their complications. Among them, 8000 are attributable to hepatocellular carcinoma (HCC). Because of the heavy disease burden, Taiwan has been fighting hepatitis B virus (HBV) since late 1970s and HCV since early 1990s, with successful results. Taking the control of HCV infection as an example, the Taiwan National Health Insurance system reimbursed combination therapy of pegylated interferon plus ribavirin since 2003, and before the introduction of interferon-free DAA in 2017, nearly 80,000 HCV patients were treated. When the World Health Assembly adopted the Global Health Sector Strategy on viral hepatitis in 2016, Taiwanese government began to put efforts towards the elimination of HCV. The government leaders have culminated in a consensus of reaching the WHO goals in 2025, i.e. 5 years ahead of the 2030 deadline set by WHO. Accordingly, the Taiwan Hepatitis C Policy Guideline 2018–2025 was approved. The government will provide the financial support of USD 1.7 billion within 8 years for the control of HCV infection, with the following actions: lowering the barriers of access to direct-acting antivirals (DAA); screening strategies; continuum of care; preventive measures for high-risk populations; improving liver health literacy on the prevention of new infections and reinfections; liver disease management; outcome evaluation of policy and interventions. After the implementation of Hepatitis C Policy Guideline, the number of HCV patients treated has remarkably increased year by year, from 9,500 in 2017 to 46,000 in 2019. More than 58,000 patients are anticipated to be treated in 2020. Inclusion of HCV patients already cured by peginterferon and ribavirin therapy before the DAA era, the treatment coverage of HCV patients is projected to reach 50% by the end of 2020. Thus, the elimination of HCV in Taiwan by 2025 is optimistic and thus on track. A recent study using the age-period-cohort models to estimate the mortality trends of liver diseases from 1981 to 2016 and project these trends to 2035 showed that the age-adjusted mortality rates of chronic liver disease, cirrhosis and HCC for both sexes are projected to decrease by more than 30% from 2016 to 2025 and by more than 55% from 2016 to 2035. In summary, the Taiwanese experience of the successful control of HCV infection can be shared by other countries where infections are equally prevalent and the socioeconomic status is similar.

HCV Elimination in Japan: The Japanese Policy and Outcome

Tatsuya Kanto

National Center for Global Health and Medicine, Japan

In Japan, estimated number of chronic HBV infection was 1.1-1.4 million and that of chronic HCV was 1.9-2.3 million in 2000. The research on National Database (NDB) estimated number of chronic HBV infection on treatment was 0.16 million and that of chronic HCV was 0.47 million in 2015, respectively. The mortality of HCC had been increasing and hit the peak at around 2002, which subsequently started to decrease.

Real-world clinical data have proven that direct anti-viral agents (DAAs) successfully eradicate HCV from more than 95% of the infected patients. In the clinical practice in Japan, optimization of DAAs treatment has been done based on HCV genotypes, stages of liver disease (chronic hepatitis or compensated/decompensated cirrhosis), prior experience of DAAs and the pattern of resistance-associated substitutions (RAS) on treatment. Of particular importance, meticulous care is needed for the treatment of patients with prior DAA failure and decompensated liver cirrhosis. Such tailored DAA treatment is guided by the Guidelines for the management of hepatitis C virus infection, updated and issued from Japan Society of Hepatology (JSH). Most of DAAs have been approved and registered in Japan, which enables us to choose multiple treatment options. In addition, for patients on treatment, drug prices of DAAs and examination expenses should be covered by special subsidy program for viral hepatitis. The national and local government cover the amount in excess of 100-200 USD of the cost of treatment.

Japan has a national action plan for addressing viral hepatitis called, Basic Act on Hepatitis Measures, established in 2009. Basic Guidelines for Promotion of Control Measures for Hepatitis is issued in 2011 and was updated in 2016, comprising 9 principles in order to promote measures to prevent hepatitis B and C (Oza N, Kanto T et al., Hepatology Research, 2017). There are few countries like Japan that implement strategy against viral hepatitis targeting general population. According to these guidelines, national and local government share screening costs for testing hepatitis B and C for those who are over 40 years old residents. Thus, out-of-pocket expenses from examinees are free of charge or reduced to the minimum. From December 2018, special coverage program of medical expenses, shared by central and local government, has started for patients with HBV- or HCV-induced liver cancer and decompensated cirrhosis. However, in the cascade-of-care of viral hepatitis in Japan, significant gaps still remain in the diagnosis, treatment and their transition of patients in need. Questionnaire analysis for general people in Japan, which was performed in 2011 and 2017 by the government-funded research group including us, revealed that information regarding clinics and hospitals where testing is available for free has not been well disseminated. In addition, lack of correct knowledge on viral hepatitis in ordinally people sometimes induce stigma and discrimination against patients. Therefore, awareness raising in general people still in great demand for promoting hepatitis policy in Japan.

The Hepatitis Information Center (HIC), established in the Research Center for hepatitis and Immunology, National Center for Global health and Medicine in 2008. The HIC has been collaborating with 71 regional core

hospitals to promote hepatitis measures in Japan. According to the nationwide annual survey conducted by us, regional core centers have come to play varied roles in hepatitis treatment and expanded their programs, including awareness raising in general people, education of health care workers and hepatitis medical coordinators (HMC) (Setoyama H, Kanto T, et al., Hepatology Research, 2019). In order to achieve HCV elimination target by 2030, the strengthening of hepatitis care networks is needed that include regional core centers, specialized medical institutions, primary care physicians, HMCs and local governments. Several advantages have been prevailed in Japanese health care systems for patients with viral liver disease compared to those in countries in Asia and Pacific regions. Therefore, Japan should take a lead in helping the implementation of practical hepatitis action plan to each country where in need.

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National Policies on Hepatitis C in Korea

Hyungmin Lee

Korea Centers for Disease Control & Prevention

Current Status and Suggestions for Hepatitis C Control in Korea

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Globally, hepatitis C virus (HCV) infection represents a considerable burden of disease. The global annual mortality from viral hepatitis continues to increase whereas that from human immunodeficiency virus (HIV), tuberculosis, and malaria declines. Moreover, HCV imposes a substantial global burden to patients, payers and society, driven by liver-related and extrahepatic morbidity and mortality. In this situation, world health organization (WHO) announced global vision and goal for viral hepatitis. The global vision is that viral hepatitis transmission is halted and everyone living with viral hepatitis has access to safe, affordable, and effective prevention, care, and treatment services. The goal is to eliminate viral hepatitis as a major public health threat by 2030. Specifically, WHO global impact targets for eliminating viral hepatitis by 2030 is to reduce new chronic HCV infection by 90% and to reduce mortality rates from viral hepatitis by 65% until 2030. Unfortunately, 80% of high-income countries are not on track to meet the WHO's 2030 targets, and 67% are off track by at least 20 years.

There are 8 key factors for achieving HCV elimination; 1) political will, 2) financing a national program, 3) implementing harm-reduction programs, 4) expanding capacity-beyond specialists, 5) removing treatment restrictions, 6) implementing monitoring and evaluation, 7) implementing awareness and national screening program, 8) implementing national linkage-to-care program. What is the current status of South Korea? Which efforts are being done to eliminate in South Korea?

Increasing awareness and finding the undiagnosed are key elements to eliminate HCV infection. Care of cascade or linkage to care should be also highlighted in nations such as the United States, Europe, Australia and New Zealand. In Georgia, where nationwide universal screening test for hepatitis C have been done, 1/3 of HCV-infected individuals have received antiviral therapy. In Taiwan, government-initiated hepatitis C policy guidelines were released and the core strategies include precision public health, continuum of care and localized care delivery.

South Korea has an experience of successful hepatitis B virus (HBV) control under government supported vaccination program. Also, Korea has an unique national health check-up system for important diseases with payment by government. In regard to hepatitis C, anti-HCV screening test for healthy adults was not yet implemented as an item in the national health check-up due to relatively low prevalence of HCV infection and equivocal cost-effectiveness of screening program.

However, as AASLD guidelines suggested, one-time, routine, anti-HCV screening test is recommended for all individuals aged 18 years or older. This is because HCV infection can be easily diagnosed and can be cured with short duration of treatment.

In this presentation, the current status and suggestions for hepatitis C control in South Korea will be presented.

DAY 2: Friday, August 14, 2020 (08:30-09:50)

Basic Science Workshop

Transcriptomic Signature of Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) poses an impending clinical burden. Genome-wide association studies have revealed a limited contribution of genomic variants to the disease, requiring alternative but robust approaches to identify disease-associated variants and genes. We carried out a disease-specific expression quantitative trait loci (eQTL) screen to identify novel genetic factors that specifically act on NAFLD tissues on the basis of genotype. We recruited 125 Korean biopsy-proven NAFLD patients and healthy individuals without histological evidence of NAFLD and performed eQTL analysis. We then selected NAFLD-specific eQTLs that are active only under the diseased state. Among the 243 loci, *AGXT2*, encoding alanine-glyoxylate aminotransferase 2, displayed decreased expression in NAFLD patients homozygous for the non-reference allele of rs2291702, compared to no-NAFLD subjects with the same genotype. This change was replicated in an additional 165 individuals. Knockdown of *AGXT2* in cell and mouse models exacerbated fibrosis, whereas overexpression ameliorated it. Reduced *AGXT2* induced ER stress and cell death, eventually providing susceptibility to the disease in a genotype-dependent manner. Our overall approach will serve as an efficient tool for uncovering novel genetic factors that contribute to liver steatosis and fibrosis in patients with NAFLD.

Immunologic Circuits of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC), a deadly malignancy with etiologic diversity and a chronic course, is strongly influenced by the immune system and characterized by immune tolerance. HCC has a cancer-promoting tumor microenvironment (TME) comprises 1) suppressed tumor-infiltrating immune cells including $CD4^+$, $CD8^+$ T-lymphocytes, NK and NKT cells, 2) recruiting immunosuppressive cells including myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), functionally impaired dendritic cells (DCs), tumor associated neutrophils (TANs), and monocytes to tumor associated macrophages (TAMs), 3) de-regulated co-inhibitory (PD-1/PD-L1, CTLA-4, TIM3, LAG3, TIGIT, and VISTA) and co-stimulatory (CD28, OX40, 4-1BB, GITR, ICOS, and CD27) immune checkpoints, 4) complex pro-inflammatory/immunoregulatory signaling, and 5) the extracellular matrix (ECM) elements and stromal cells including fibroblasts, myofibroblasts, pericytes, adipose cells, liver sinusoidal endothelial cells (LSECs), hepatic stellate cells (HSCs), liver resident macrophages or Kupffer cells (KCs).

Apparently, interactions of HCC tumor cells and different components of TME are really intricate and multifaceted, finally determining the plasticity and heterogeneity of its both innate and adaptive immune responses and plays a key role in HCC progression and recurrence. Transcriptional and epi-genetical alterations, metabolic reprogramming and lack of co-stimulatory signals partially contribute to exhausted phenotype of tumor-infiltrating lymphocytes (TILs). The fibrotic liver favors an immune compromised TME by directly reducing cytotoxic cell ($CD8^+$ T, NK and NKT) infiltration and providing TGF-β- or IL-6-mediated immunosuppressive signals. After encountering $CD8^+$ T-cells, LSECs upregulate the co-inhibitory molecule PD-L1 (10-fold), therefore, shifting the balance from activation to tolerance induction in $CD8^+$ T-cells. MDSCs are a major host component contributing to the immune suppressive environment. In addition to their inherent immune suppressive function, MDSC amplify the immune suppressive activity of TAMs and DCs via cross-talk. It has been reported that cytokine-induced killer (CIK) cell infusion, one of strong cell-based immunotherapies, induced accumulation of tumor infiltrating MDSCs *in vivo* murine HCC models. Thus, targeting MDSCs is thought to be a good strategy to enhance the antitumor efficacy of CIK cells.

Pursuing combination therapy with immune checkpoint inhibitors (ICIs) and molecularly targeted therapies is not only justified by evidence of single-agent activity but also by the complex bidirectional relationship existing between angiogenesis and immunity. Resistance to anti-angiogenic therapy is in fact at least in part determined by an immune-suppressive TME characterized by higher Tregs infiltration and stronger PD-L1 expression. The expression of PD-L1 itself is strongly placed under the transcriptional regulation of hypoxia inducible factor 1-α. In HCC, sorafenib therapy induces tumoral PD-L1 overexpression, and pre-clinical evidence in mouse models suggests this to correlate with Tregs accumulation and M2-macrophage polarization through hypoxia, drawing a translationally appealing rationale for combination therapy. Inhibition of tumor angiogenesis, and in particular VEGF aids normalization of the endothelial barrier by regulating key adhesion molecules for immune cell hom-

ing to the tumor. VEGF also inhibits DC maturation and accentuates PD-1 expression of tumor-infiltrating $CD8^+$ T-cells highlighting the potential for synergy between VEGF inhibition and ICIs therapy. Indeed, HCC was recently found to benefit from targeted and immune-based therapies. Patients with unresectable HCC are currently included in trials exploring combinations of antiangiogenics and ICI. The phase III IMbrave150 trial evaluating atezolizumab and bevacizumab in first line vs. sorafenib showed improvement in median progression-free survival (6.8 vs. 4.3 months, $P < 0.0001$) and median overall survival (not reached vs. 13.2 months, $P = 0.0006$) in 501 patients. Objective response rate was increased with the combination therapy (27% vs. 12%, $P < 0.0001$).

Future approaches for HCC immunotherapy are to combine two or three effective systemic therapies including ICIs and/or molecular targeted therapies and the addition of innovative combination therapies targeting immune suppressive TME in order to increase immune recognition with a greater tumor response. Moreover, identification and classification of biomarkers which can predict the therapeutic responses is urgently needed to determine suitable patients for particular treatments.

Interactive Interface between Gut Microbiome and Immunome in Alcohol-Related Liver Disease

Bernd Schnabl

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Alcohol-associated intestinal dysbiosis and bacterial overgrowth can lead to a dysregulation of tryptophan metabolism and lower production of indoles. Several of these indole derivatives are aryl hydrocarbon receptor ligands that, in turn, are involved in antimicrobial defense via induction of interleukin-22 (IL-22). IL-22 increases the expression of intestinal Reg3 lectins, which maintain low bacterial colonization of the inner mucus layer and reduce bacterial translocation to the liver. Chronic alcohol consumption is associated with reduced intestinal expression of the Reg3b and Reg3g, increased numbers of mucosa-associated bacteria and bacterial translocation. Translocated microbial products and viable bacteria reach the liver and activate the innate immune system. Release of inflammatory molecules promotes inflammation, contributes to hepatocyte death and results in a fibrotic response. This talk summarizes the mechanisms by which chronic alcohol intake changes the gut microbiota and contributes to alcohol-associated liver disease by changing microbial-derived metabolites.

Microbiome Meets Cancer and Immunology

Hansoo Park

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Oxaliplatin induces tumor cell apoptosis by arrest of DNA synthesis, inhibition of RNA synthesis, and triggering of immunologic reactions. These mechanisms made Oxaliplatin to be used as a treatment for lung cancer. However, some patients respond well to Oxaliplatin treatment but others do not respond. Intestinal microbiome can influence immune pathway, so that it may affect efficacy of Oxaliplatin. We classified the patients with lung cancer into two groups according to the response of Pemetrexed and Oxaliplatin treatment and collected stool samples. We conducted sequence-based analysis for 200 lung cancer patients' Intestinal microbiome. Total DNA was extracted using the MO-BIO PowerSoil DNA Isolation Kit and PCR amplification was carried out using primers targeting the hypervariable regions V3–V4 (515f-806r) of the 16S ribosomal RNA gene on the Illumina MiSeq platform. Sequence reads processing was analyzed using the QIIME pipeline. As a result, specific strains were associated with therapeutic outcomes such as several "A" species. Using syngeneic model, we found that "A" species increased the efficacy of Oxaliplatin. Our results suggest that manipulating the microbiome can play a role in modulating cancer therapy.

DAY 2: Friday, August 14, 2020 (09:50-10:50)

Special Interest Group Forum

Clinical Issues in Autoimmune Liver Disease

Pathology of Autoimmune Liver Diseases

Masayoshi Kage

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Introduction

A diagnosis of autoimmune liver disease cannot be made from the morphological features of a liver biopsy alone; however, autoimmune liver diseases have morphologic characteristics which can be distinguished from liver diseases associated with other etiologies. Histological examination of autoimmune liver diseases is important not only to establish the diagnosis, but also to precisely assess the status of inflammation and fibrosis. Here we describe the pathological characteristics of two representative autoimmune diseases; autoimmune hepatitis or AIH, and primary biliary cholangitis or PBC. Overlap between these two diseases is also discussed.

I. AIH

AIH is a disease of unknown etiology associated with the progressive destruction of the hepatic parenchyma, and may progress toward cirrhosis and liver failure.[1,2,3]

1. Basic pathology of AIH

The basic morphologic features of all forms of chronic hepatitis, including AIH, are generally the same; however, the presence of increased plasma cells and strong necroinflammation with parenchymal collapse are hallmarks of AIH. These findings, however, are not always observed, particularly in patients under immunosuppressive therapy.

1-1. Hepatic fibrosis and cirrhosis

The wide spectrum of hepatic fibrosis in AIH is similar to that in chronic viral hepatitis, and the degree varies from mild fibrosis to cirrhosis. Fibrosis initially extends from the portal tracts, and then to bridging fibrosis between portal tracts, and finally extends between portal tracts and central veins.

The presence of liver cirrhosis is an important indicator of poor prognosis. Hepatocellular carcinoma is exceptionally rare but has been documented in the cirrhotic stage.

1-2. Necroinflammatory reaction

Strong necroinflammatory reactions are characteristic of AIH, although the reactions and the histological patterns of the reactions vary as follows.

1) Interface hepatitis and inflammatory cells

Interface hepatitis is a characteristic necroinflammatory reaction in the periportal area with disruption of the limiting plate. The periportal hepatocytes show hydropic swelling, and are sometimes associated with rosette formation,[4] which is noted mainly in cases of severe necro-inflammatory reactions. Although these changes are characteristic of AIH, they are also noted in chronic hepatitis B and C with severe inflammation, and are not spe-

cific to AIH.[4]

Inflammatory cell infiltration mixed with lymphocytes and plasma cell infiltration in interface hepatitis are also characteristic features. Plasma cell infiltration in the hepatic lobules, along with interface hepatitis, is very valuable in AIH diagnosis, although plasma cells are not always noted in AIH.

2) Focal necrosis and bridging necrosis

Focal necrosis and acidophilic bodies are found in AIH as well as in viral hepatitis. In general, plasma cells are more frequently observed in focal necrosis than in viral hepatitis.

3) Massive and submassive hepatic necrosis

AIH may rarely present with fulminant hepatitis. Histologically, these cases represent massive or submassive hepatic necrosis. The histology is the same as that of viral hepatitis or drug-induced hepatic injury, but mixed lympho-plasmocytic infiltration is pronounced in some cases of AIH.

1-3. Emperipolesis

Emperipolesis is a characteristic feature of AIH which is often seen in conjunction with interface hepatitis, plasmocytic infiltration, hepatocytes resetting and more advanced fibrosis. The finding that emperipolesis is mediated by CD8T cells suggests a mechanism of autoimmune-mediated hepatocyte injury.[5]

1-4. Bile duct change

The main lesion of AIH occurs in hepatic parenchyma, but bile duct lesions similar to PBC may also develop.[6,7]

1-5. Phlebitis

Phlebitis is also an important finding in AIH, although it is not specific to AIH. Phlebitis is mainly noted in the central vein in association with severe lobular inflammation, but is also seen in the intrahepatic portal vein, although it is rare.

1-6. Irregular distribution of hepatic change

In AIH, the distribution and degree of necro-inflammatory reactions and regenerative activity of hepatocytes may vary, even in the same liver. Marked inflammation including interface hepatitis and collapsed parenchyma are commonly found in some lobuli, while minimal inflammatory activity is present in other lobuli. An uneven distribution of hepatic changes from one lobule to another, especially irregular necro-inflammatory reaction, is a characteristic of AIH, and an important finding in the evolutionary process from chronic hepatitis to cirrhosis.

2. Acute-onset AIH

2-1. Clinical profile

It has recently been clarified that AIH sometimes develops with symptoms similar to acute hepatitis, such as jaundice and rapid elevation of the transaminase level. Such AIH patients have been designated as recent–onset hepatitis or acute-onset AIH.[8,9,10,11]

According to the report of Okano N et al.[9], the clinical features of acute-onset AIH showed significantly higher serum ALT levels, lower IgG levels and AIH score than those of classical AIH, so the clinical diagnosis is not easy. Liver biopsy may be very important to establish the diagnosis.

2-2. Histopathology of acute-onset AIH

The histopathology is also similar to that of acute hepatitis in some cases,[8,9,10,1]1 however, about one third of the

cases that develop acute hepatitis-like symptoms already have liver cirrhosis. From a histological point of view, AIH of this type can be interpreted as either acute hepatitis or acute exacerbation of chronic hepatitis. Acute-onset AIH is characterized by regularly distributed centrizonal necrosis with mild inflammatory cell infiltration, macrophages phagocytosed to ceroid and slight hemorrhage, resembling passive congestion at first glance. The portal tracts have interface hepatitis with lympho-plasmocytic infiltration as in classic AIH, but in some cases interface hepatitis is slight or even absent in spite of accentuated necroinflammation in the lobuli.[10,11] Rosette formation of hepatocytes is usually absent in cases with no or mild fibrosis in the portal tracts. It is important when diagnosing liver specimens to keep in mind that acute-onset AIH may present with histology different from that of chronic hepatitis in classical AIH.

Regarding the differential diagnosis, AIH of this type may present with a histopathology resembling acute viral hepatitis. The feature of increased plasma cells is helpful in diagnosing AIH. Another important aid to differential diagnosis is drug-induced hepatic injury. Drugs sometimes cause hepatic dysfunction simulating AIH, or may act as a trigger to induce AIH.

II. PBC

PBC is an uncommon disorder of unknown etiology involving the intrahepatic biliary system.[12,13]

1. The basic pathology of PBC

PBC develops its main lesions in the biliary system. It is characterized by chronic destructive inflammation of small interlobular bile ducts and fibrosis, subsequently leading to liver cirrhosis. It also shows a characteristic fibrosis morphologically different from that in chronic viral hepatitis. This fibrosis is called biliary fibrosis or cirrhosis. Biliary cirrhosis with regenerative nodules arranged in an irregular, geometric pattern. There is a decrease or loss of small to intermediate-sized interlobular bile ducts.

1-1. Changes of the bile duct and inflammation in portal tract

The most important pathological change of the bile duct is nonsuppurative destructive cholangitis, involving small interlobular bile ducts 40 to 80 μm in diameter.[12] The bile duct changes are characterized by infiltrated lymphocytes and variable cytologic distortion of the epithelial cells, resulting in death of the epithelial cells.

Portal tracts in PBC have inflammatory cells, mainly consisting of lymphocytes and plasma cells, and occasional eosinophils and neutrophils. Interface hepatitis usually found in AIH is absent or generally mild if present.

These features are the basis of the pathological diagnosis of PBC, however, not all portal areas show this feature. This feature is usually noted in intermediate-sized portal areas, and is unlikely to appear in the most peripheral portal areas. Thus, when only the most peripheral portal areas are included in a needle liver biopsy specimen, this feature may not be noted.

1-2. Epithelioid granuloma

Epithelioid granulomas are occasionally found in portal tracts and parenchyma. The granulomas are generally small in size without caseous necrosis.[13,14]

1-3. Lobular changes of necroinflammatory reaction

Necroinflammatory reactions are generally absent or mild, showing only scattered focal necrosis.

1-4. Cholestasis

Cholestasis is noted in about 30-50% of cases, but the degree of cholestasis is generally mild.

1-5. Copper-binding protein in hepatocytes

In the majority of pediatric patients with PBC, copper-binding protein may be proven to accumulate in hepatocytes in the periportal area by copper staining or orcein staining.[15,16] This finding reflects chronic cholestasis. The presence of copper-binding protein has proved valuable for distinguishing between PBC and chronic hepatitis of viral or autoimmune etiology, although it is not specific for PBC.

2. Classification of the staging for PBC

There have been a few classifications about the staging for PBC. Recently a new staging and grading system that takes into account necro-inflammatory activity and histological heterogeneity has been proposed for PBC.[16] This new system appears to be more practical and useful than those used before.

III. Autoimmune overlap variants

Variants of AIH are not infrequen t. Overlap syndromes of AIH with other known liver diseases have been well documented. They present with characteristics of AIH and the variants that show the histology and clinical and serological indicators of more than one liver disease. The overlap variants include the following liver diseases: primary biliary cholangitis, primary sclerosing cholangitis and chronic hepatitis C.

1. Overlap of AIH and PBC

AIH-PBC is the most common form of overlap syndrome, affecting almost 10% of adults with AIH or PBC.[17,18] Overlap syndromes include simultaneous or consecutive occurrence of AIH-PBC. Transitions from PBC to AIH-PBC overlap syndrome have been reported. Overlap syndromes show a progressive course without treatment.

2. Pathology of overlap of AIH and PBC

Liver pathology of the overlap of AIH and PBC shows characteristics of both AIH and PBC as described above.[18] In a typical case with overlap of AIH and PBC, marked inflammatory reaction with plasmo-lymphocytic infiltration in the lobulus coexist with destructive bile duct changes in the portal tract.

Liver biopsy sometimes is crucial to establish the diagnosis of overlap of AIH and PBC.

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Autoimmune Hepatitis: From Bench to Clinic

Xiong Ma

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Primary Biliary Cholangitis: Unsolved Issues and New Treatment

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Primary biliary cholangitis (PBC) is an infrequent autoimmune liver disease. It is classically autoimmune in origin but clinically manifests as a progressive cholestatic syndrome. Much is known about PBC as regards diagnosis, prognosis and treatment, but equally there remains questions related to disease pathophysiology and optimal treatment of disease and associated symptom complexes.

PBC is chronic, seropositive and female-predominant. It has inflammatory and cholestatic liver disease phenotypes, with a variable rate of progression towards biliary cirrhosis. The disease biology spans genetic risk, epigenetic changes, dysregulated mucosal immunity and altered biliary epithelial cell function, all of which interact and arise in the context of ill-defined environmental triggers. A current focus of research on nuclear receptor pathway modulation that specifically and potently improves biliary excretion, reduces inflammation and attenuates fibrosis is redefining therapy. Patients are benefiting from pharmacological agonists of farnesoid X receptor and peroxisome proliferator-activated receptors. Immunotherapy remains a challenge, with a lack of target definition, pleiotropic immune pathways and an interplay between hepatic immune responses and cholestasis, wherein bile acid-induced inflammation and fibrosis are dominant clinically. In this short lecture I will:

a) Aim: To provide an overview of the disease characteristics of PBC and review a patient-centred management approach for the clinical team caring for those with PBC;

b) Summarise practice: A confident diagnosis of PBC is usually made based on serum liver tests and immune serology. Management of PBC should focus on 3 main 'process' pillars: (1) treat and risk stratify through use of biochemical and prognostic criteria; (2) manage concurrent symptoms and other associated diseases; and (3) stage disease, monitor progression, and prevent complications. With ongoing complexities in management, including newly licenced therapy (obeticholic acid), alternative non-licenced treatments (e.g. bezafibrate), and emerging clinical trial agents (e.g. elafibrinor, seladelpar). I will provide an up-to-date disease summary in the context of latest clinical scientific understanding;

c) Highlight future opportunities: I will demonstrate how PBC is a dynamic disease wherein current treatment goals have become appropriately ambitious. Goals of care should prioritise prevention of end-stage liver disease and amelioration of patient symptom burden for all, and such aspirations are accessible through current practice as well as a number of evolving trial opportunities for patients.

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DAY 2: Friday, August 14, 2020 (13:00-14:10)

KLTS-KAHBPS-KLCA Joint Symposium

Treatment Options for HCC beyond the Milan Criteria in Patients with Marginal Liver Function

Chairs:

Jong Young Choi (The Catholic Univ. of Korea)

Shin Hwang (Univ. of Ulsan)

Locoregional Therapy

Yoon Jun Kim

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There are conflicting data on the best management for patients with hepatocellular carcinoma (HCC) who are not candidates for transplantation or hepatic resection. Also the optimal approach for HCC patients with marginal liver function is still unclear. Optimal surgical candidacy is based on a multiparametric evaluation including compensated Child-Pugh class A liver function with MELD score <10. Therefore, the optimal treatment for the patients with HCC beyond Milan criteria and marginal liver function is controversial. Traditionally, several locoregional treatment modalities, such as TACE, TABE, TARE, HAIC, RFA, RT and combinational treatment, are used for the treatment of those patients. In this lecture, current guidelines, recent data and the treatment options for HCC beyond the Milan criteria in patients with marginal liver function will be reviewed.

Down-Staging Living Donor Liver Transplantation

Jae Geun Lee

Yonsei University, Seoul, Korea

Curative surgical treatments for patients with hepatocellular carcinoma include resection and transplantation. Resection can be performed in patients with good liver function and localized hepatocellular carcinoma, while transplantation is favored in selected patients with decreased liver function and/or multiple nodules.

The word down-staging is used loosely to qualify any type of treatment aiming to control tumor growth prior to surgery, with a confusing overlap with the term neo-adjuvant treatment. Down-staging have the aim or the result of a treatment that intends to facilitate or make possible a surgical procedure that would otherwise be too risky or unfeasible. Finally, down-staging prior to transplantation is used as a selection tool to detect patients with low rates of recurrence among those that would be excluded according to recognized number-size criteria.

Currently one third to one half of all HCC patients on the waiting list undergo local HCC treatment prior to transplantation. The type of treatment varies according to center, but TACE is the most frequently used, followed by RFA.

Neo-adjuvant treatments (in contrast to down-staging) are primarily used to decrease the risk of drop-out from the waiting list. They may be linked to a better post-transplant patient survival, as shown by a large UNOS-based study. This data is also supported by the observation that patients with full HCC necrosis after TACE have better post-transplant survivals than those with partial response. Overall, a broader use of local neo-adjuvant HCC treatment in patients within transplant criteria appears justified (without delaying transplantation), as the risk of significant side-effects of these treatments is limited, with potential lower drop-out and higher survival rates.

When patients have HCCs beyond the accepted transplant criteria, the application of treatments aiming at down-staging tumors appears appropriate, as this is often the only hope of potential cure with a subsequent transplantation. In addition, tumor response to TACE could be used as a selection tool to help identify patients with an outcome that may be superior to that suggested by morphological criteria alone.

More recent reports have demonstrated that down-staging can be successful in 24 to 90% of patients. This wide range of observed rates is primarily related to the use of different criteria to include patients in down-staging protocols and different criteria to subsequently decide on listing for transplantation. Some groups consider patients for listing as soon as HCCs have decreased in size by 30 or 50%, while others will require full necrosis (absence of any uptake on CT) prior to doing so. In addition, some centers follow Milan transplant criteria, while others use expanded ones.

Despite these limitations, recent prospective studies have demonstrated that down-staging is a valid strategy prior to transplant: following successful down-staging, post-transplant disease-free survivals have been reported at over 70% at 3 years, and intention-to-treat post-HCC treatment survivals between 60 and 70% at 3 years. Such outcomes have been substantially better than anticipated in a group of patients with such an advanced cancer, in some series not just beyond Milan criteria, but beyond UCSF criteria as well. In addition, they appear to compare

favorably with the generally accepted minimal long-term post-transplant survival of 50% at 5 years, an unrefined and arbitrary target that holds consensus.

For these reasons, it appears legitimate to attempt down-staging in any patient beyond transplant criteria and without distant metastasis, even more so as down-staging treatments are identical to palliative ones. The down-side of a too liberal access to down-staging strategies (and subsequent transplant) could be an enhanced competition for donor livers with patients within standard transplant criteria (with or without HCC) and should be countered by defining reasonable inclusion criteria.

Is There a Role for TKIs and Immune Checkpoint Inhibitors?

Thomas Yau

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The Liver Week 2020

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The Liver Week 2020

DAY 2: Friday, August 14, 2020 (13:00-14:00)

KLCA Symposium 2

Updates in Diagnosis and Biomarkers of Hepatocellular Carcinoma

Biomarkers of HCC with Focus on Recent Clinical Trials

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National Cancer Center, Korea

A biomarker is any substance, structure, or process that can be measured in the body and can influence or predict the incidence of outcomes or disease. A cancer biomarker may measure the risk of developing cancer, or the risk of cancer progression or potential response to therapy. Cancer biomarkers can be classified into three categories based on their usage: (i) predictive biomarkers predicting response to specific therapeutic interventions, (ii) prognostic biomarkers associated with the risk of clinical outcomes, and (iii) diagnostic biomarkers.

The well-known serum biomarkers for hepatocellular carcinoma (HCC) include alpha-fetoprotein (AFP), des-γ-carboxy prothrombin (DCP; protein induced by vitamin K absence or antagonist-II, PIVKA), lens culinaris agglutinin-reactive AFP (AFP-L3), and α-1-antitrypsin. In HCC, the most studied biomarker is AFP, but this biomarker has several limitations. Serum levels of AFP do not correlate well with other clinical features of HCC, such as size, number, or stage. Elevated serum AFP levels may also be seen in patients without HCC, such as acute or chronic viral hepatitis. The heterogeneity of the biology of HCC may change over time from the first expression.

In the sub-analysis of SHARP trial, a high level of baseline Angiopoietin-2 (Ang-2) was independently predictive of survival both in the sorafenib and placebo arms. Additionally, baseline vascular endothelial growth factor (VEGF)-A plasma levels correlated with prognosis, but not with tumor response. Recent studies have shown a correlation between polymorphisms of VEGF, VEGFR, endothelial nitric oxide synthase (eNOS), peptide transporter SLC15A2, and clinical outcome of sorafenib treatment in HCC patients. In several retrospective studies, adverse events, such as hand-foot-skin reaction predicted a positive tumor response better than serum biomarkers.

In addition to sorafenib, recently several drugs, including other multikinase inhibitors (regorafenib, lenvatinib, cabozantinib), monoclonal antibodies (ramucirumab, bevacizumab), and immune checkpoint inhibitors (nivolumab, pembrolizumab, ipilimumab, atezolizumab), alone or in combination have demonstrated activity in HCC. If we have a predictive biomarker, we may be able to choose the best drug among these drugs for a patient with HCC. However, unfortunately, there are no remarkable predictive biomarkers found during clinical trials. Post-hoc analysis showed that serum AFP or inflammation-related factors, and tumor tissue expression of PD-1/PD-L1 might be associated with tumor response and prognosis.

Many biomarkers have been evaluated in order to predict the efficacy of all available treatments; however, at present, there are no biomarkers that allow us to define the best patient-specific treatment. Validated biomarkers that capture the heterogeneity of the biology of HCC are urgently needed.

Imaging Biomarkers in the Era of Precision Medicine

Sun Young Lee

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We discuss MR imaging features that have been reported to be related to aggressiveness and poor prognosis of hepatocellular carcinoma (HCC) but not included in the current staging systems: findings associated with worse histologic grade, microvascular invasion, presence of satellite nodules, and progenitor cell marker. Current evidence suggests that non-smooth tumor margin, irregular rim-like enhancement in the arterial phase, peritumoral enhancement in the arterial phase, hypointense HCC in the hepatobiliary phase, peritumoral hypointensity in the hepatobiliary phase, and restricted diffusion are related to poor prognosis of HCC, reflecting aggressive tumor biology.

Pathologic Biomarkers that Indicate the Aggressiveness and Prognosis of Hepatocellular Carcinoma

Young Nyun Park

Yonsei University, Seoul, Korea

Pathological features related to prognosis of hepatocellular carcinoma (HCC) include tumor differentiation grade, tumor size, vascular invasion and intrahepatic metastasis. HCCs are classified into early HCCs and progressed HCCs. Early HCCs are suggested to be the earliest lesion of HCC, corresponding to carcinoma in situ of the other organs. Early HCCs are well differentiated without vascular invasion and its prognosis is very good. In contrast, progressed HCCs are usually moderate to poor differentiated, even in the small sized (< 2cm) HCCs, and vascular invasion and intrahepatic metastasis are found in 27 % and 10%, respectively. The changes in transcriptomes of early HCCs are modest and homogenous, whereas extensive genetic alterations and subsequent activation of prognostic adverse signaling pathways occur only late during hepatocarcinogenesis, and are centered on TGF-ß, WNT, NOTCH, and epithelial-mesenchymal transition (EMT)-related genes highlighting the molecular diversity of progressed HCCs.

Recently, new HCC subtypes have been reported based on pathological-molecular classification, and some of them have been reported to be related to poor prognosis. HCCs expressing stemness markers including K19 have been reported to have an aggressive behavior. HCCs with high expression of stemness markers (K19, EpCAM) show activation of YAP pathway, TP53 mutation, FGF19 amplification, and they correlate with aggressive gene expression signatures including S2 (Hoshida et al.) and G1 (Boyault et al.) subclasses. There are some characteristic clinicopathological features that have been more frequently seen in HCCs expressing stemness-related markers compared to those without these markers. HCCs with K19 expression, approximately 10-28% of HCCs show high serum alpha-fetoprotein (AFP) levels, chronic hepatitis B, and decreased overall and recurrence-free survival. HCCs with K19 expression are less frequently encapsulated compared to those without, imparting a more infiltrative growth pattern. Vascular invasion is more frequent in HCCs with K19 expression compared to those without. A fibrous stromal component is more frequently identified in HCCs with K19 expression compared to those without. There is a crosstalk between tumor epithelial cells and stromal cells, and K19 expression is regulated by fibroblast-derived HGF via a MET-ERK1/2-AP1 and SP1 Axis. HCCs with K19 expression are associated with increased expression of EMT-related genes and their proteins, and they are also associated with longer telomeres, increased hTERT expression and increased chromosomal instability, suggesting that HCCs with K19 expression have a survival advantage over those without by maintaining telomeres despite the increased chromosomal instability. Hypoxic microenvironment is known to be important in the generation and maintenance of stemness, and we found that HCCs with stemness (K19, EpCAM) and hypoxia (CAIX)-related markers showed more resistance to transarterial chemoembolization (TACE) and poorer outcome compared those without, and their tumor microenvironment was found to be altered under TACE-induced hypoxia, which might promote the aggressive biology of HCC. The expression of stemness and hypoxia-related markers were

correlated each other, and evaluation for both markers of stemness and hypoxia may have an additional value in predicting HCC outcome, especially for TACE-treated HCCs.

Scirrhous HCC subtype, which frequency is 4% of HCCs shows dense intratumoral fibrosis > 50% of tumor, and correlates with aggressive gene expression signature of G2 subclass (Boyault et al.). Its key molecular features are TSC1/2 mutations, and TGF-ß signaling activation. The fibrous stroma of scirrhous HCC contains abundant cancer-associated fibroblasts and tumor-infiltrating macrophages, suggesting a possible role for this complex tumor microenvironment in the aggressive behavior of scirrhous HCC. In fact, the majority of scirrhous HCCs have been demonstrated to express K19 or other "stemness"-related markers, and therefore, K19-positive HCCs and scirrhous HCCs may lie on the same spectrum of HCCs, with the latter being defined as containing more intratumoral fibrous stroma.

Mactrotrabecular massive (MTM) HCC subtype is defined as trabecular pattern with more than 6-10 cells thickness in 50% of tumor. Its frequency is 5% of HCCs and reported to have a poor prognosis. It correlates with aggressive gene expression signature of G3 subclass (Boyault et al.). Its key molecular features are TP53 mutations and FGF19 amplication. Vessels that encapsulate tumor clusters (VETC), which is defined as ≥ 55% tumor area by CD34 immunostaining is a new HCC subtype related to poor prognosis. VETC was significantly associated to high serum AFP level, tumor size >5 cm, poor differentiation, macrotrabecular pattern, and frequent microvascular invasion.

Therefore, the identification of pathologic biomarkers related to aggressiveness and poor prognosis on HCC tissues obtained by biopsy, resection or transplantation could provide useful information for treatment of HCC patient. Moreover, the recent accumulation of molecular-pathological data will hopefully lead to the development of targeted therapy for this aggressive subset of HCCs.

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The Liver Week 2020

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DAY 2: Friday, August 14, 2020 (14:10-15:10)

KAHBPS-KLTS Joint Symposium

Optimal Use of ICG Fluorescence Technology in Daily Practice

Tumor Localization in Oncologic Surgery

Masaki Ueno

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1. Introduction

Indocyanine green (ICG) is well utilized for estimating liver function and, nowadays, also for a near infrared (NIR) fluorescent imaging. ICG is excited by around 760nm NIR wavelength and emits around 830nm NIR wavelength. Using this characteristics, specialized cameras for ICG fluorescence imaging has been developed for open and laparoscopic surgeries. Using this imaging system, several ICG fluorescence guided surgical procedures have been established such as sentinel node navigation, vascular patency imaging, blood flow evaluation around intestinal anastomosis, and so on. In the field of liver surgery, ICG fluorescence imaging is utilized for tumor detecting, bile leakage detection, liver segmentation, etc. In this session, utility and limitations of ICG fluorescence imaging on tumor localization during surgery are reviewed.

2. Tumor localization by ICG fluorescence imaging

2.1. Hepatocellular carcinoma (HCC)

Regarding the tumor localization by ICG fluoresce imaging, Ishizawa et al would firstly reported in 2009 that characteristics of ICG fluorescence among various HCC nodules and classified three fluorescence patterns; total fluorescent, partial fluorescent, and rim fluorescent type.[1] In the same year, Gotoh et al reported utility of detecting small intrahepatic metastasis around target tumor lesion.[2]

As the HCC is originated from hepatocytes, HCC tends to maintain a character of hepatocyte. Ishizawa et al analyzed about the mechanism of ICG fluorescence in HCC tissues using gene set enrichment analysis. They found that Na+/taurocholate co-transporting polypeptide (NTCP) and organic anion-transporting polypeptide 8 (OATP8) were highly expressed in total or partial fluorescence type of HCC compared to the rim fluorescent type.[3] In general, these NTCP and OATP are recognized as the ICG transporters. Well or moderately differentiated HCC tends to maintain the character of hepatocyte. While, inside the cancerous tissue, the normal biliary system has disappeared, and therefore the cancerous tissue lost the function of excreting ICG. As a result, well or moderately differentiated HCC shows total or partial ICG fluorescence in the tumor.

Regarding the rim fluorescent type, it correlates with poorly differentiated HCC and with suppressed expression of ICG transporters. Therefore, it does not emit ICG fluorescence itself. Moreover, the biliary systems around a tumor are compressed and deteriorated ICG draining locally. As a result, poorly differentiated HCC is recognized to show rim fluorescence type.[4]

The Issue of ICG fluorescence imaging in detecting HCC is high incidences of false-positive. Benign lesions including cyst, dysplastic nodule, bile plug also shows ICG fluorescence signal. Previous studies reported that false-positive rate of ICG fluorescence was around 40%.[3] Therefore, in diagnosing small nodules intraoperatively,

we must recognize that the accuracy will not be so high and must check the nodule by another imaging modality.

Another issue is that NIR signal does not penetrate far deep. The depth of tissue penetration of ICG fluorescence signals was reported to be up to 8~10mm.[3,4] Therefore, we can only detect subcapsular lesions. In this meaning, both utilize of ICG fluorescence imaging and intraoperative ultrasonography (IOUS) will be good combination.[5]

Last issue is that appropriate ICG injection timing is not confirmed. ICG was usually injected intravenously as part of liver functional test (0.5 mg/kg body weight). Interval between ICG injection and operation was various and ranged from three days to 28 days. If a patient does not have sufficient liver function, short interval might cause retention of ICG in surrounding liver tissue and result in fluorescent noise or false positive lesions. Moreover, fluorescence detection will depend on the performance of imaging sensor. Therefore, an appropriate injection timing will be differed by these factors. In general, the longer interval may reduce the false positive rate of tumor detection.

2.2. Metastatic liver tumor (adenocarcinoma)

Regarding the adenocarcinoma, same as the poorly differentiated HCC, it shows rim fluorescent type. As intestinal cells do not have transporter of ICG, adenocarcinoma tumor itself does not emit ICG fluorescence. van der Vorst JR et al surveyed the mechanism of ICG fluorescence in colorectal liver metastasis and reported that immature hepatocytes surrounding metastasis lesion had decreased bile excretion ability and resulted in ICG retention around the metastatic lesion.[6] Moreover, if a metastatic tumor shows bile stasis around the tumor, we can observe the tumor existence as ICG stasis area even when the tumor is located slightly deeper form the liver surface.[7]

3. Usefulness of ICG fluorescence imaging in clinical practice

3.1. Salvage hepatectomy for patients with local HCC recurrence after thermal ablation therapy

As previously described, ICG fluorescence imaging may be helpful in detecting small HCC dissemination. We sometimes perform salvage hepatectomy after local recurrent HCC after thermal ablation therapy. These recurrent lesions sometimes spread to a portal territory area. Moreover, preoperative imaging diagnosis becomes complicated as the original tumor was ablated. In such a situation, this ICG fluorescence imaging might be helpful and provide us visual information about the distribution of small HCC nodules around the ablated area. Extrahepatic metastasis also can be observed by ICG fluoresce imaging. We previously reported a case who was incidentally detected a needle tract implantation of HCC after thermal ablation therapy.[8]

3.2. Hepatectomy for patients after neoadjuvant chemotherapy

If a preoperative chemotherapy is effective, some small metastatic lesions may be disappeared radiologically. In such a situation, it is sometimes difficult to search these small lesions intraoperatively. However, if the bile stasis around the small tumor still remains, we can easily detect the bile stasis area and confirm the lesion under ICG fluorescence imaging [5].

4. Advances of fluorescence imaging in a future

ICG alone is currently approved for clinical use in performing NIR imaging. In laboratory, development of a

complex substance with ICG is in progress. ICG is used as a tag and conjugations with various substance has been developed. For example, anti-CEA antibody labeled ICG complexes were reported to detect gastric cancer [9].

Moreover, novel fluorescent agents with different structure to ICG have also been developed such as the γ-glutamyl hydroxymethyl rhodamine green (gGlu-HMRG) [10]. This system uses the cancer specific enzyme, γ-Glutamyl transpeptidase (GGT), and the novel fluorophore emitting light at around 520 nm following enzymatic reaction with GGT. This fluorescence agent can be used as intraoperative navigation tool and, as the signal intensity was correlated with prognosis, also can be used for prognostic prediction.

5. Summary

Intraoperative ICG fluorescence imaging is useful for detecting small HCC or metastases, even though it is disseminated nodules or a nodule with response to neoadjuvant chemotherapy. However, we must recognize that false positive is relatively high and, therefore, we must distinguish malignant lesion from benign lesion by another imaging modality such as IOUS. In future, addition to ICG, novel cancer specific fluorescence agent will be developed and will be provided to our clinical practice.

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Anatomical Liver Resection

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Fluorescence imaging using indocyanine green (ICG) had been used clinically to visulalize the vascular as well as lymphatic anatomy in realtime during surgery. This technique also has been utilizing for anatomical liver resection not only for conventional open surgery but also for minimally invasive liver resection. The fluorescent property of ICG as well as its biliary excretion property can be used for anatomical liver resection. Since approval of ICG by Food and Drug Administration (FDA) in 1954, ICG has been used mainly to evaluate the liver function in the field of liver surgery. The fluorescence property of ICG was characterized in detail in the 1970s. Protein-bound ICG emits fluorescence that peaks at about 840 nm when illuminated with near-infrared light between 750 and 810 nm. Near-infrared (NIR) fluorescent light has several advantageous properties for intraoperative imaging. The wavelength of NIR light is between 700 and 900 nm, which is invisible to the naked human eye, and therefore does not alter the look of the surgical field.

In the meantime, anatomical liver resection is essential surgical technique for liver surgeon. Especially for the treatment of hepatocellular carcinoma, anatomical liver resection might reduce the intrahepatic metastases comparing with non-anatomical resection. Bleeding during operation also might be reduced under anatomical liver resection. Moreover, there were lack of ischemic area in the remnant liver which may be the source of postoperative complication. However, it is quite difficult to distinguish the exact anatomical dissection plane through the liver which is invisible solid organ. Although various surgical technique such as ischemic demarcation line after blocking of inflow blood flow of future-resected liver, injection of dye such as methylene blue into the portal pedicle, determination of anatomical plane according to intraoperative ultrasonography, and preoperative 3 dimensional reconstruction of hepatic vasculature were adapted to perform the exact anatomical liver resection, the performance of each technique had some limitations. Mapping with vital blue dyes under intraoperative ultrasound can sometimes yield indistinct results, and it is much more difficult to reproduce in laparoscopic procedure. Ischemic demarcation also indistinguishable especially in the liver with jaundice or covered by connective tissue from adhesion. Liver dome area is also somewhat difficult to distinguish the ischemic demarcation line. In the contrary, ICG fluorescence technique may be useful to find out the exact anatomical dissection line. It is easy to apply. Demarcation line is clear. Anatomical plane may be identified during parenchymal dissection. Moreover, adaptation to minimally invasive liver resection seems to be convenient. Therefore, ICG fluorescence technique may be useful for anatomical liver resection.

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Donor Hepatectomy

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The indocyanine green (ICG) has been used to determine the cardiac out. Hepatic function, liver blood flow, and for the ophthalmic angiography. ICG fluorescence images can be obtained in the process of hepatic inflow, hepatocyte uptake, and outflow and its biliary excretion because ICG is removed from circulation exclusive by the liver to bile juice. Besides, plasma binding ICG emits light with a peak wavelength of around 840 nm when illuminated with near-infrared light (750-810nm). Biliary excretion starts within minutes after injection. Its peak is within 2 hours and continues for as long as 20 hours. Even though the most effective timing of ICG injection is not to be established, ICG should be given 20 minutes before taking images. In addition, Fluorescence intensity is peak around 0.1mg/mL. Considering its peak time of fluorescence, 2 hours before applying the ICG Fluorescence camera, Intravenous ICG about 5mg should be injected for adults of 50kg. By using theses ICG characteristics, we can obtain the optimal ICG fluorescence images.

ICG fluorescence images are easily applicable in donor hepatectomy, especially in laparoscopic living donor hepatectomy; Liver mapping with guiding the anatomical resection, visualizing the extrahepatic bile duct, checking the vascular flow, bile leak after resection and so on. ICG fluorescence technique allows visualization of the bile duct, anatomical territory as well as vascular structure with its flow in donor hepatectomy; Determining the division point of the bile duct can be performed smoothly by the guidance of ICG fluorescence images.

Intraoperative cholangiography has been considered the gold standard in most centers, with bile duct division under the guidance of a C-arm fluoroscope or using the rubber band tagging method. This procedure involves a significantly increased operating time, inherent risk of biliary duct injury associated with IOC, radiation exposure, and requires additional human resources. With preoperative MR cholangiography and probing, the method needs surgeons' experience, and the bile duct division point is unclear under these methods; therefore, there is a high chance of bile duct injury. Compared to these things, ICG fluorescence images show a real-time visualization of the bile duct in relation to the surrounding structures. This method saves operation time and avoids bile duct injury associated with the insertion of a tube for injection of contrast material. As ICG can penetrate the tissue of 5-10mm depth only, the biliary tract should be exposed adequately.

The Liver Week 2020

August 13-14, 2020 | VIRTUAL CONFERENCE

DAY 2: Friday, August 14, 2020 (15:20-16:40)

KASL Symposium 3

Exploration of Biomarkers in Liver Diseases

New and Old Biomarkers for Diagnosis and Management of Chronic Hepatitis B Infection

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Chronic hepatitis B virus (HBV) infection is a public health threat along with socio-economic burden affecting more than 250 million individuals worldwide and accounting for over 600,000 liver-related deaths every year. Especially, highly endemic regions, such as China, Southeast Asia, and sub-Saharan Africa, lead the majority of new HBV infection. Chronic HBV infection is a debilitating complex disease leading to chronic hepatitis, advanced fibrosis/cirrhosis, portal hypertension-related deterioration, hepatic decompensation/failure, and hepatocellular carcinoma. Despite advanced progress of anti-HBV therapeutics that has been made in a few last decades, long-term treatment with nucleos(t)ide analogues (NAs) is usually required.

Functional cure, defined by serum hepatitis B surface antigen (HBsAg) loss and persistent undetectability of serum HBV deoxyribonucleic acid (DNA), is the classic endpoint of antiviral management in patients with chronic hepatitis B (CHB). Current treatment with NAs effectively suppress viral replication by blocking reverse transcriptase of HBV in most CHB patients, however, rarely achieve functional cure. Furthermore, complete cure, defined by elimination of HBV covalently closed circular DNA (cccDNA) on the sero-status of functional cure, is not possible due to the persistence of cccDNA in the nucleus of infected hepatocytes, which is not targeted by current NAs. HBV cccDNA is a minichromosome that acts as a template for the transcription of viral ribonucleic acid (RNA), resulting in translation of viral proteins and reverse transcription of replicative double-stranded DNA. The assessment of the cccDNA amount and its transcriptional activity is known to be necessary to monitor treatment response of antiviral agents and to assess disease progression. Although routine serum viral markers, such as HBsAg, hepatitis B e antigen (HBeAg), and HBV DNA, are still valuable biomarkers to diagnose the patients, to classify the different phases of infection, to select the patients who need the antiviral therapy, and to monitor the patients on treatment, they do not accurately reflect the pool and transcriptional activity of cccDNA.

New viral markers, such as quantitative HBsAg (qHBsAg), hepatitis B core-related antigen (HBcrAg), and HBV RNA, are novel representative runners of non-invasive biomarkers that have the potential role in guiding the cure of viral hepatitis B. According to the results of the recent studies, these biomarkers seem to be superior than conventional biomarkers for evaluating intrahepatic cccDNA status. Clinically, the most important issue for CHB patients with virologic suppression during treatment is to decide whether to continue or stop taking the medicine, and if so, when to stop, based on the reliable risk to benefit assessment for both sides of relapse requiring retreatment and HBsAg loss. For actually clinical application of diagnostic tools using these novel biomarkers, standardization and availability in the limit of detection should be required. In the future, therapeutic endpoints of antiviral management using these emerging biomarkers will be re-addressed for research and development of excavating novel compounds against HBV.

The natural and therapeutic course of CHB is mainly depending on the mutual interaction between viral rep-

lication and host immune response. In other words, HBV-induced host immune responses make an influence on the outcome of HBV infection, disease progression, and therapeutic response to antiviral agents. The immunologic biomarkers are, however, in a primitive stage of development. To date, there are no established immunologic biomarkers to guide clinical management for HBV infection.

Non-Invasive Diagnosis and Biomarkers in Alcohol-Related Liver Disease

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Alcohol-related liver disease (ALD) represents a spectrum of clinical illness and pathological change in individuals with acute and chronic alcohol consumption. Patients may have minimal abnormalities from steatosis or may develop more severe signs and symptoms of liver disease associated with inflammation seen in alcoholic hepatitis or cirrhosis.[1] The risk of ALD is closely related with the per capita alcohol consumption;[2,3] however, careful study of the relationship between development/natural history of ALD and the quantity of alcohol consumed is almost impossible, because data collection always involves numerous broad assumptions and rough estimates.[4,5] Drinking becomes excessive when it causes or elevates the risk for alcohol-related problems or complicates the management of other health problems. According to the National Institute on Alcohol Abuse and Alcoholism **(**NIH/NIAAA), excessive drinking is defined as men who drink more than 4 standard drinks in a day (or more than 14 per week) and women who drink more than 3 drinks in a day (or more than 7 per week).[6] Early studies in France suggested that a long-term consumption of 80 grams per day or more was associated with increased risk of cirrhosis but subsequent estimates of the threshold for harm have been below this level, especially for women.[7,8] Screening for excessive alcohol use is important in the diagnosis of ALD. Besides questionnaires, several laboratory tests have been used to screen for excessive alcohol use (EAU) in clinical practice. Determination of the breath and blood alcohol concentration (BAC) or by the highly specific direct markers ethyl glucuronide (EtG) and ethyl sulphate (EtS) in blood and/or urine has been used, but they are only specific to very recent alcohol ingestion; its use may not be useful in clinical situation.[9] Other lab tests to screening for chronic alcohol use are gamma glutaryl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and mean corpuscular volume (MCV).[10] Despite their common use, these tests revealed low sensitivities and specificities.[11] Transferrin molecules in the blood usually contain several carbohydrate components, which is reduced, resulting in an increase in %CDT, among excessive alcohol users.[12] Phosphatidylethanol (PEth) represents a group of phospholipids present in cell membranes, which are formed directly after alcohol intake[13] via the enzyme phospholipase D from phosphatidylcholine in the presence of alcohol.[14]

ALD is rarely detected at the early stage. In a study of 3,500 patients worldwide with chronic liver disease, only 3.8% of patients with ALD were seen at early stages defined as those without any signs of chronic liver disease or complications from portal HTN. Whereas the majority of patients were seen at advanced stages were those with ALD compared with viral hepatitis such as HCV and HBV. These results indicate that ALD is normally detected at later stages when patients require hospitalization owing to liver-related complications.[15] Early detection or screening for ALD is therefore important. The diagnostic tool depends on the disease stage in the spectrum of ALD. For hepatic steatosis, liver ultrasound is accepted as an initial screen for fatty liver because it is non-invasive, inexpensive and widely available. Controlled attenuation parameter is a simple and promising new bedside technique for diagnosing steatosis in patients with ALD, but it requires further validation.[16] For evaluation of

fibrosis, several blood tests are available; however, the sensitivity and specificity are varied (depending on the cut off values). The use of transient elastography to determine the degree of fibrosis is promising. There are 2 important components for the diagnosis of alcoholic hepatitis, history of alcohol consumption and clinical presentation/laboratory tests. Excessive alcohol use should have occurred for>6 months, with <60 days of abstinence before the onset of jaundice. Jaundice should be accompanied by malaise, tender hepatomegaly, or with hepatic decompensation.[17] Serum bilirubin cutoff is >3 mg/dL with the AST (>50 IU/mL), and AST to alanine aminotransferase (ALT) ratio of >1.5. Liver biopsy is not always required unless the clinical diagnosis is unclear.[17] To date, no specific non-invasive diagnosis and biomarkers in ALD are reliable and validated. Systematic studies in a large and well characterized patients with ALD are needed to address these shortcomings.[16]

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Quantitative Imaging Biomarkers: Assessment of Hepatic Fibrosis and Steatosis

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Quantitative imaging (QI) is the emerging tool that the extraction of quantifiable features from medical images for the assessment of normal of the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal. The QI could be applied to various imaging modalities such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Ultrasound elastography including transient elastography and 2D-shear wave elastography (SWE) is one of the QI methods using ultrasound. It has been widely used for prediction of hepatic fibrosis since a decade before. Not only it correlates with the grade of hepatic fibrosis, but it also well correlates with hepatic venous pressure gradient, a surrogate of portal hypertension. Through deep learning technology, there have been recent attemps to increase the accuracy and reproducibility of ultrasound elastography. Texture analysis using imaging features extracted from the CT and MRI images can be used to predict hepatic fibrosis. Radiomics is a representative method of the QI, and it can support clinical decision making and precision medicine.

Steatosis is a health problem highlighted recently, and non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western countries. Because liver biopsy has many limitations including selection bias, imaging study is widely used to evaluate the degree of fatty liver. Hyperechogenicity of liver parenchyma compared with renal cortex is a representative finding of fatty liver, but subjective. Hepatorenal ratio and controlled attenuation parameter (CAP) are quantifiable parameter of hepatic echogenicity, and it is robust to measure the degree of fatty liver by the CAP. In CT, Hounsfield unit is a reference measurable value that reflects the composition of the liver, especially the compostion of intracellular fat. However, the MR-based QI, such as MR spectroscopy and MRI-proton density fat fraction (PDFF) are the most accurate and reproducible method of measuring fatty liver.

Although the potential of the QI is expected, there are several challening issues like other emerging techniques. The QI is less subjective than conventional imaging study, but reproducibility issue is still remained. In many studies, data extraction process is still performed manually. For example, an examiner should choose the location of region of interest for measuring liver stiffness on the shear wave elastography and MR elastography. Interoberver variability is still a remaining problem of these techniques. Standardization of the QI methodology should be established, and a quanlity control system of the QI is also needed. The radiomics is very attractive as a QI method, but it needs abundant (big) data (1,000 to over 10,000) to get accurate results. Lastly, it is necessary that the QI model should be fairly validated with internal and external datasets. Overfitting issue is also a problem to be solved.

In 2007, Radiologic Society of North America (RSNA) organized the QI biomarker alliance to unite researchers, healthcare professionals and industry to advance the QI. It is an expert group trying to solve the several issues of the QI. After overcoming various problems, at last, the QI will be used as a universal diagnostic tool with reference standards and reproducibility.

Clinical Application of Liquid Biopsy as a Prognostic Biomarker in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and remains the third most frequent cause of cancer death.[1] Although alpha-fetoprotein (AFP) is most well-known biomarkers in diagnosis for HCC. Due to the promising results, it has since been shown that AFP is relatively insensitive under certain circumstances, and often elevated in non-tumorous conditions.[2] Extensive efforts have been made to find more useful biomarkers in HCC, Unfortunately, available data has shown similar or only slightly better sensitivities and specificities when compared to AFP, with none being used in clinical practice.

The development of current molecular technologies has allowed us to detect molecules of carcinogenesis and specific genetic mutations in tumor specimens, which may be able to diagnosis of cancer and predict response or resistance to cancer therapies.[3] These technologies have also highlighted the significance of morphological and genetic tumor heterogeneity in a liver biopsy for diagnostic or prognostic purposes. However, biopsy in clinical field is mostly recommended when radiological diagnosis is not conclusive but not for diagnostic or prognostic purposes.

The concept of liquid biopsy was developed for reliable, minimally invasive methods of diagnosis, prognosis and overall disease monitoring by analyzing body fluids samples, instead of solid tissue, for the purpose of pathophysiological or molecular analyses. It has been introduced for many clinically relevant fields, including cancer research and, blood samples are most investigated as potential samples for liquid biopsy.[4] The term liquid biopsy can apply to cancer by-products including circulating tumor cells (CTC), cell-free DNA (cfDNA), cell-free RNA (cfRNA), microRNA (miRNA), extracellular vesicles (EVs), and tumor-derived metabolites. As biomarkers for liquid biopsy are generally present in low levels, effective separation and enrichment methods with high specificity and practicability are key points in liquid biopsy

When EVs are firstly identified, they were regarded as cellular wastes or debris, without any biological function. However, the current finding is that EVs are a new cellular dimension of the so-called microenvironmental cell-cell communication, traveling to proximal and distal spaces with the ability of altering intracellular pathways with pathophysiological consequences. Exosomes contain a variety of cellular components, including a range of proteins such as heat shock proteins (HSPs), lipids, RNAs, mRNAs and DNA molecular cargoes, with surface protein markers.[5] The contents of exosomes and their effects on recipient cells mainly depend on the cell types from which they are derived. Therefore, these EVs can be more useful to reflect the microenvironment and prognosis of tumors.

Recent studies have shown that both miRNA-21 and lncRNA-activated by tumor growth factor-beta (TGF-β) (lncRNA-ATB) are involved in cell proliferation and epithelialmesenchymal transition (EMT) of HCC by targeting tumor suppressor genes.[6-8] When exosomes containing miRNA-21 and lncRNA-ATB are collected, it has

been shown that the overall survival and progression-free survival were significantly lower in patients with higher circulating levels of exosomal miRNA-21 (≥0.09) and lncRNA-ATB (≥0.0016) (log-rank test: $p < 0.05$).[9]

With high incidence, the researches for non-invasive biomarkers are very important in current diagnosis and treatment of HCC. Liquid biopsy is not only useful in early diagnosis of HCC but also more important in prognosis and monitoring its course and treatment.

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DAY 2: Friday, August 14, 2020 (15:30-17:00)

KASL-KAHBPS-KLTS Joint Symposium

How to Improve Outcome in Critically Ill Patients Awaiting Liver Transplantation

Chairs:

Soon Ho Um (Korea Univ.)

Hee Chul Yu (Chonbuk National Univ.)

Liver Transplantation for Alcoholic Hepatitis

Philippe Mathurin

Chu De Lille, France

KEY POINTS

- For patients with severe alcoholic hepatitis failing to medical therapy can be early identified and have a 6-month survival around 30%.
- Expert guidelines no longer recommended a fixed period of abstinence prior to transplantation.
- Early liver transplantation in those patients is attractive but highly controversial as it challenges the 6-month abstinence rule prior to LT.
- Several recent studies provided more data supporting early LT as a rescue therapy in patients with SAH failing to respond to medical therapy and confirmed low rates of alcohol use post-LT

RECOMMENDATIONS

- Duration of abstinence before listing should rely on severity of liver insufficiency in selected patients with a favourable addiction profile and supportive relatives (Grade A1)
- Multidisciplinary approach evaluating medical and psychological suitability for transplantation is required before and after LT (Grade A1)
- Early LT should be proposed to highly selected patients with severe AH not responding to medical therapy after a rigorous evaluation process

Does the 6-month rule limit access to liver transplantation for the most severely ill patients?

Optimal timing for liver transplantation in alcoholic patients varies drastically between transplant programs, and decisions on transplant eligibility should be made on an individual basis, with careful prediction of short-term survival. In the particular setting of non-responders to corticosteroids, strict application of a period of sobriety as a policy for transplant eligibility is unfair to such patients, as most of them will have died prior to the end of the 6-month sober period.

It is well established that doctors and the public do not share the same viewpoint on graft allocation. It is important to make the public aware that most philosophers and ethicists feel that patients with self-inflicted diseases should have the same access to medical resources, and that personal responsibility should not influence the decision to transplant.

Early liver transplantation improves survival of patients

In severe alcoholic hepatitis, patients with severe alcoholic hepatitis failing to medical therapy can be early identified and have a 6-month survival around 30%. As most deaths occur within 2 months, early liver transplan-

tation in those patients is attractive but highly controversial as it challenges the 6-month abstinence rule prior to LT. The first study evaluating early liver transplantation in patients with severe alcoholic hepatitis failing to medical therapy undergoing their first episode of liver disease showed a drastic improvement of survival in patients who were early transplanted. Patients were drastically selected using those criteria: absolute consensus of paramedical and medical staff, no co-morbidities, social integration and supportive family members.[1] These results support future evaluation in drastically selected patients with severe alcoholic hepatitis failing to medical therapy.[2] Early Liver transplantation was associated with low rate of recidivism to alcohol use and good adherence to medical regiments in the absence of graft dysfunction. Two recent American studies provided additional data supporting early liver transplantation as a rescue therapy in patients with SAH failing to respond to medical therapy and confirmed low rates of alcohol use post-LT.[3,4]

The fear of early LT may decrease organ donation is not supported by a survey showing that most of potential donors were supportive or neutral with regard to this new indication.[5] Only ethical principles recommending active treatment of patients without discrimination, and according to best scientific knowledge should be applied in the evaluation of changes in clinical practices.[6] However, due to organ shortage, selection process of patients with S

AH should remain stringent in order to limit transplant availability. The use of a combination of baseline MELD score[7] and Lille score at 7 days[8] seems to be most efficient approach to identify patients with the highest risk of short-term mortality in order to limit the number of unnecessary procedures.[9]

Nowadays expert guidelines no longer recommended a fixed period of abstinence prior to transplantation[10,11] and stopped listing alcoholic hepatitis as an absolute contraindication[10] to LT contrary to the recommendations from the preceding decade.[12]

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Risk Stratification and Optimal Management for Liver Transplantation in Acute-on-Chronic Liver Failure

Dong Hyun Sinn

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Liver transplantation (LT) is indicated for patients with acute liver failure and in patients with end-stage liver disease when the limits of medical therapy have been reached.[1,2] Emergent adult living donor LT (LDLT) has been shown to improve the survival rate greatly in patients with acute liver failure.[3] However, the role of LT in patients with acute-on-chronic liver failure (ACLF) is controversial. ACLF is a syndrome characterized by acute decompensation of chronic liver disease associated with organ failure that includes extrahepatic organ failure.[4-6] Although extrahepatic organ failure is not an absolute contraindication for LT, it does confer high risks for LT.[7] Donor livers are a scarce, life-saving resource. Hence, the posttransplant mortality risk should also be considered in decision to proceed emergent LT in very sick patients.[8] The low post-LT survival rates among ACLF patients with multiple organ failure suggests that ACLF patients with multiple organ failure need careful consideration for LT to prevent futile LT. This critical question is more challenging in the setting of living donor LT (LDLT), as the timing of LT can be selected by the doctor in LDLT.[9] Hence, in a region where LDLT is a major mode of LT, finding optimal timing and selection and delisting criteria for transplants in patients with ACLF is needed. In this presentation, factors that could be used to guide management plans for patients with ACLF will be discussed.

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Risk Stratification and Optimal Management for Liver Transplantation in Acute Liver Failure

Young-dong Yu

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Acute liver failure (ALF) is a potentially reversible syndrome characterized by hepatic encephalopathy within 8 weeks of severe liver injury in a patient without underlying liver disease. The prognosis in these patients is highly variable and depends on the etiology, interval between jaundice and encephalopathy, age, and the degree of coagulopathy. Determining the prognosis for this population is vital. Unfortunately, prognostic models with both high sensitivity and specificity for prediction of death have not been developed. Liver transplantation has dramatically improved survival in patients with acute liver failure. Still, 25% to 45% of patients will survive with medical treatment. The identification of patients who will eventually require liver transplantation should be carefully addressed through the combination of current prognostic models and continuous medical assessment. The concerns of inaccurate selection for transplantation are significant, exposing the recipient to a complex surgery and lifelong immunosuppression. In this challenging scenario, where organ shortage remains one of the main problems, alternatives to conventional orthotopic liver transplantation, such as living-donor liver transplantation, auxiliary liver transplant, and ABO-incompatible grafts, should be explored. Although overall outcomes after liver transplantation for acute liver failure are improving, they are not yet comparable to elective transplantation.

How to Improve Post-Transplant Outcomes in Patients with High MELD Scores

Dong-Hwan Jung

University of Ulsan, Seoul, Korea

Patients with high MELD scores have prioritized access to liver transplantation (LT) and are therefore transferred to the LT center. The prognosis of the high MELD score patients is accurately assessed by sequential evaluation of the presence of hepatic and/or extrahepatic organ failures in the early period of admission. General management of patients with high MELD scores is based on organ support, treatment of precipitating events and prevention of complications, with a particular focus on prevention of infectious events. There is the increased risk of losing a graft in the initial postoperative period when performing LT in "too sick to transplant" patients. Transplantation window must be identified swiftly after admission given the poor short-term survival of patients with high MELD scores. Given the limited availability of donor organs in deceased donor liver transplantation, the benefit of transplantation in high MELD score patients must also be balanced against the risk of poor posttransplant outcomes. Recipient and donor factors affecting posttransplant survival among patients with high MELD scores must be considered to aid the clinician in determining who may and may not benefit from organ transplantation. Objective measures to score risk of death and major morbidity based on accessible physiological and laboratory values would be pragmatic to guide clinical decision making for liver organ allocation and transplantation among LT candidates. Preoperatively, we should attempt to optimize the condition of transplant candidates with liver failure so that the patient remains eligible for transplantation.

Postoperatively, the targets of critical care are both the posttransplant patient and the newly implanted allograft. Essentially, postoperative care has to be provided to 2 different biological systems that require individual attention and may not always align with respect to treatment options. The leading cause of mortality following liver transplantation is infection. Infections increase with increased intensity of immunosuppression. "Net state of immunosuppression" must be estimated based on clinical status, doses or levels of immunosuppressive drugs, and recent treatment of rejection.

The Liver Week 2020

August 13-14, 2020 | VIRTUAL CONFERENCE

DAY 1: Thursday, August 13, 2020 (10:20-11:20)

Plenary Session 1

Chairs:

Kwan Sik Lee (Yonsei Univ.)
Kwan Soo Byun (Korea Univ.)
Ho Seong Han (Seoul National Univ.)

PS 1-1

ROS-Induced Activation of YAP-1 through a c-Myc Pathway is a Therapeutic Target in Hepatocellular Carcinoma

Yuri Cho[1,2], Minji Park[1], Sun Woong Kim[1,2], Wonjin Kim[1], Jung-Hwan Yoon[2]

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Aims: The Hippo signaling pathway regulates organ size by controlling both cell proliferation and apoptosis via effectors such as yes-associated protein (YAP). Dysregulation of the Hippo pathway has been suggested as one of the therapeutic target in hepatocarcinogenesis. Reactive oxygen species (ROS) levels increase during the progression from early to advanced hepatocellular carcinoma (HCC). Activated YAP-1 by ROS-induced damage has been hypothesized to aggravate progression of HCC, but it remains unclear which signaling pathway is involved.

Methods: The expression of YAP-1 was quantified using real-time PCR and immunoblotting. Human HCC cells (Huh-7, HepG2, SNU-761) were grown under H_2O_2 treatment which is a major component of ROS in living organisms, either with YAP-1 siRNA or with control siRNA. MTT assays were performed to evaluate the role of YAP-1 in HCC under H_2O_2 treatment. To investigate the signaling pathway responsible for the activation of YAP-1, immunoblotting was performed. 88 surgically resected frozen HCC and 88 non-tumor liver tissue samples were used for gene expression analyses.

Results: H_2O_2 treatment increased the mRNA and protein expressions of YAP-1 in HCC cells (Huh-7, HepG2, and SNU-761). Suppression of YAP-1 using siRNA transfection resulted in significant decrease in tumor proliferation under H_2O_2 treatment, both in vitro and *in vivo*. The oncogenic action of YAP-1 occurred via activation of the c-myc pathway, leading to up-regulation of unfolded protein response (UPR), including the 78-kDa glucose-regulated protein (GRP78/BiP) and activating transcription factor 6 (ATF-6). YAP mRNA levels in human HCC tissues were upregulated 2.6-fold compared with non-tumor tissues and positively correlated with ATF-6 levels.

Conclusions: ROS-induced activation of YAP-1 via the c-myc pathway, which leads to activation of the UPR pathway, might be a therapeutic target in HCC.

Funding: This study was supported by the Research Supporting Program of the Korean Association for the Study of the Liver and The Korean Liver Foundation in 2017.

Keywords: Hepatocellular carcinoma, YAP, C-myc, ROS

PS 1-2

Oral L-Carnitine on Quality of Life and Cognition in Covert Hepatic Encephalopathy: A Randomized, Double-Blind, Placebo-controlled (HELIOS) Study

Eileen L. Yoon[1], Dae Won Jun[2*], Sang Bong Ahn[3*], Yong Kyun Cho[4], Do Seon Song[5], Jae Yoon Jeong[6], Hee Yeon Kim[7], Young Kul Jung[8], Myeong Jun Song[9], Sung Eun Kim[10], Hyoung Su Kim[11], Soung Won Jeong[12], Sang Gyune Kim[13], Tae Hee Lee[14]

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Aims: To evaluate the impact of L-carnitine on the improvement of quality of life (QOL) and cognitive function in liver cirrhosis patients with covert hepatic encephalopathy (HE).

Methods: We conducted a multi-center, double-blind, randomized, phase III clinical trial in patients with covert HE. A total of 150 covert HE patients were randomized 1:1 to L-carnitine (1 g) or placebo for 24 weeks. Changes in QOL and cognitive function were assessed at 6 months. West Haven criteria, 36-Item Short Form Health Survey (SF-36), psychometric hepatic encephalopathy score (PHES), and the Stroop Test were evaluated in all patients.

Results: The L-carnitine supplement improved QOL compared to baseline. PHES scores were improved and normalization rates of minimal HE were increased in the L-carnitine group compared to baseline; however, median PHES scores and normalization rates were not different between the L-carnitine group and the placebo group at Week 24. Assessment of cognitive inhibition via the Stroop test showed significant improvement following 24 weeks of treatment in the L-carnitine group. Model for end stage liver disease scores were increased in the placebo group and significantly decreased in the L-carnitine group. Changes in

total carnitine level positively correlated with rate correct scores of the Stroop test in the L-carnitine group. The incidence of adverse events was not different between the treatment groups.
Conclusions: L-carnitine supplement was safe and effective for the improvement of QOL and cognitive dysfunction in covert HE patients with liver cirrhosis. (Clinical trial No. KCT0002029)
Keywords: Hepatitis B, Chronic, Hepatic encephalopathy, Carnitine, Stroop test

PS 1-3

Impact of Existing Liver Disease on Clinical Outcomes of COVID-19: A Multicenter Study

Yu Rim Lee[1], Min Kyu Kang[2], Jeong Eun Song[3], Hyun Jung Kim[4], Young Oh Kweon[1], Won Young Tak[1], Se Young Jang[1], Jung Gil Park[2], Changhyeong Lee[3], Jae Seok Hwang[4], Byoung Kuk Jang[4], Jeong Ill Suh[5], Woo Jin Chung[4], Byung Seok Kim[3], and Soo Young Park[1]

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Aims: Although coronavirus disease 2019 (COVID-19) has spread rapidly worldwide, the implication of pre-existing liver disease on the outcome of COVID-19 remains unresolved.
Methods: A total of 1,005 patients who had laboratory-confirmed COVID-19 admitted to five tertiary hospitals in South Korea were included in this study. Clinical outcomes in COVID-19 patients with coexisting liver disease and predictors of disease severity and mortality in COVID-19 were assessed.
Results: Of the 47 patients (4.7%) who had liver-related comorbidities, 14 patients (1.4%) had liver cirrhosis. Liver cirrhosis was more common in COVID-19 patients with severe pneumonia than in those with non-severe diseases (4.5% vs. 0.9%, *P*=0.006). Compared to patients without advanced liver fibrosis, a higher proportion of patients with significant fibrosis (presence of liver cirrhosis or FIB-4 >3.25) needed oxygen therapy; were admitted to the intensive care unit; had septic shock, acute respiratory distress syndrome, acute kidney injury; succumbed to death (*P*<0.05). Presence of liver cirrhosis and higher FIB-4 value were found to be independent predictors of severe disease (OR 4.52, 95% CI 1.20–17.02, *P*=0.026; OR 6.09, 95% CI 3.76–9.86, *P*<0.001) and death (HR 2.86, 95% CI 1.04–9.30, *P*=0.042; HR 4.30, 95% CI 2.56–7.23, *P*<0.001) in COVID-19, along with old age and diabetes. FIB-4 index showed a high predictive power for disease severity and mortality of COVID-19 (AUROC=0.858, AUROC=0.870, respectively).
Conclusions: This study suggests advanced liver fibrosis is a significant risk factor of COVID-19. Stronger personal protection and more intensive treatment for COVID-19 are recommended in these patients.
Keywords: Liver disease, Liver cirrhosis, Mortality, COVID-19

PS 1-4

Adverse Effect of Sarcopenic Obesity on Postoperative Complications after Major Hepatectomy in Patients with Hilar Cholangiocarcinoma

Youngju RYU[1], Chang-Sup LIM[2], Yong Chan SHIN[3], Naru KIM[1], Yung hun YOU[1], Sang Hyun SHIN[1], Jin Seok HEO[1], Dong Wook CHOI[1], In Woong HAN[1]

[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [2]Seoul Metropolitan Government - Seoul National University Boramae Medical Center, Seoul, [3]Ilsan Paik Hospital, Inje University College of Medicine, Goyang

Aims: Recently, it is well known that sarcopenia is one of the risk factors on post-hepatectomy outcomes in patients with hepatocellular carcinoma. However, there were seldom reports for effect of sarcopenia or sarcopenic obesity (SO) on postoperative outcomes in patients with perihilar cholangiocarcinoma (CCC). The purpose of this study is to evaluate the effect of preoperative sarcopenia or SO on postoperative outcomes in patients with hilar CCC following major heptectomy.
Methods: Preoperative sarcopenia and SO was assessed in 328 patients undergoing hepatectomy for hilar CCC at three institution between 2006 and 2016, retrospectively. The sarcopenia was calculated from cross-sectional visceral fat and muscle area on preoperative CT imaging (muscle area/height2 = skeletal muscle index, SMI). SO was defined by visceral fat area/SMI.
Results: Preoperative sarcopenia and SO was present in 97 (29.6%) and 98 (29.9%) of the patients. Preoperative sarcopenia itself was not associated with postoperative outcomes. However, the rate of major complication in patients with SO was higher than in those without SO (54.1 vs. 37.0%, *P*=0.004). Also, postoperative hospital stay was prolonged in patients with SO (18.5 vs. 16.5 days, *P*=0.038). After multivariable analysis, male sex (OR1.937, 95%CI:1.182-3.174, *P*=0.009) and SO (OR1.866, 95%CI:1.148-3.034, *P*=0.012) were independent risk factors for occurrence of major complication. There was no statistically significant in overall survival with sarcopenia or SO.
Conclusions: SO was an independent risk factor of major complication after hepatectomy in hilar CCC. As a result, careful postoperative management would be needed after major hepatectomy in patients with hilar CCC in case of SO.

The Liver Week 2020

August 13-14, 2020 | VIRTUAL CONFERENCE

DAY 2: Friday, August 14, 2020 (11:00-12:00)

Plenary Session 2

Chairs:

Jin Mo Yang (The Catholic Univ. of Korea)
Chul Ju Han (Korea Cancer Center Hospital)
Yang Won Nah (Univ. of Ulsan)

PS 2-1

Serum miRNA as a Useful Diagnostic Biomarker for Diagnosis of NASH and a Clue for Disease Progression Pathway in NAFLD Patients

Young-Sun Lee[1], Jeong-An Gim[2], Haein Bak[1], Sehwa Kim[1], Young Kul Jung[1], Ji Hoon Kim[1], Yeon Seok Seo[1], Hyung Joon Yim[1], Jong Eun Yeon[1], Soon Ho Um[1] and Kwan Soo Byun[1]

[1]Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea; [2]Medical Science Research Center, Korea University College of Medicine, Seoul, South Korea

Aims: Non-alcoholic steatohepatitis (NASH), as subtype of non-alcoholic fatty liver disease (NAFLD), is progressive disease that can result in advanced fibrosis and cirrhosis. The aim of this study was to evaluate diagnostic value using serum miRNA to For distinguish ing NASH from simple steatosis (SS).

Methods: RNA extraction and small RNA sequencing were done using sera from 24 patients who were diagnosed with NAFLD by biopsy. miRNA expression levels were compared between 12 SS patients and 12 NASH patients. After selecting miRNAs showing significantly increased expression in NASH group comparing to SS group, diagnostic accuracies of each miRNA and a combination of miRNAs were analysed. For functional relationship between specific signalling pathway and miRNAs that were significantly elevated in sera of NASH patients compared to those in sera of SS patients, miEAA database was used.

Results: A total of 2,588 mature miRNA reads were obtained from miRDeep2 Quantifier module. Expression levels of 26 miRNAs were significantly increased in NASH group than in SS group, whereas those of 12 miRNAs were significantly decreased in NASH group than in SS group. Among 38 significant miRNAs, eight miRNAs that showed high expression within the top 25% of all miRNAs were selected and compared. Only four miRNAs showed meaningful area under receiver operating characteristic (AUROC) values for NASH diagnosis (P<0.05). When AUROC values for diagnosis of NASH were compared between a combination of 8 miRNAs (AUROC: 0.924; 95% CI: 0.739-0.992) and a combination of 4 miRNAs (AUROC: 0.875; 95% CI: 0.676-0.973), there was no significant difference (P=0.26). Among 26 miRNAs that showed significantly increased expression in NASH group, 10 miRNAs were included in 17 miRNA group, such as adipocytokine signalling pathway and thyroid hormone signalling pathway (Figure).

Figure. miRNA to category heatmap

Conclusions: Combination of serum circulating miRNAs could be used as novel biomarker for diagnosis of NASH. The expression of circulating miRNAs is correlated with specific signalling pathway.

Keywords: MiRNA, NASH, NAFLD, Biomarker

PS 2-2

Association of Metabolic Risk Factors with Risks of Cancer and All-Cause Mortality in Patients with Chronic Hepatitis B Virus Infection: A Korean Nationwide Cohort Study

Yun Bin Lee[1], Hyemi Moon[2], Jeong-Hoon Lee[1], Eun Ju Cho[1], Su Jong Yu[1], Yoon Jun Kim[1], Fabien Zoulim[3], Juneyoung Lee[2], Jung-Hwan Yoon[1]

[1]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea; [2]Department of Biostatistics, College of Medicine, Korea University, Seoul, Korea; [3]Cancer Research Centre of Lyon, INSERM U1052, Lyon University, Hospices Civils de Lyon, Lyon, France

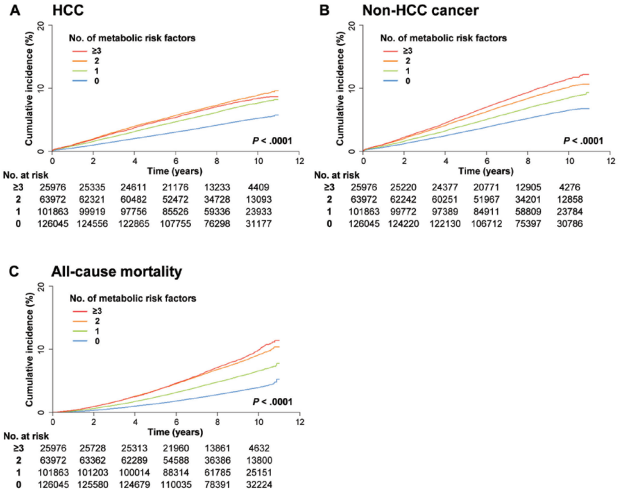
Aims: Long-term antiviral therapy can effectively suppress viral replication and improve clinical outcomes in chronic hepatitis B patients, but it cannot eliminate the risk of hepatocellular carcinoma (HCC). We investigated the association of metabolic risk factors with the risks of cancer and all-cause mortality in chronic hepatitis B patients using the Korean National Health Insurance Service database.

Methods: We collected baseline data on metabolic risk factors, including obesity, hypercholesterolemia, insulin resistance, and hypertension. The risks of developing HCC, non-HCC cancer, and overall death were analyzed according to the metabolic risk profile. The risks of HCC and non-HCC cancer were analyzed after adjusting death as a competing risk event.

Results: The study population consisted of 317,856 adults with chronic hepatitis B. A total of 18,850 HCCs, 22,164 non-HCC cancers, and 15,768 deaths were observed during a median follow-up period of 8.5 years. The cumulative incidences of HCC (P<.0001; panel A), non-HCC cancer (P<.0001; panel B), and death (P<.0001; panel C) rose with increasing number of metabolic factors. The metabolic risk factor burden was positively associated with the risks of HCC, non-HCC cancer, and all-cause mortality (all P<.0001 for trend). Patients with ≥3 metabolic risk factors, compared to those without metabolic risk factors, showed adjusted hazard ratios of 1.23 (95% confidence interval [CI], 1.16–1.31) for HCC, 1.34 (95% CI, 1.27–1.41) for non-HCC cancer, and 1.31 (95% CI, 1.23–1.39) for all-cause mortality. Among patients receiving antiviral therapy for over 5 years, the risk-increasing association of the sum of metabolic risk factors with the risks of HCC and overall death was consistent.

Conclusions: In this Korean nationwide cohort study, the burden of metabolic risk factors was associated with increased risk of HCC, non-HCC cancer, and all-cause mortality in patients with

chronic HBV infection.



Keywords: Hepatitis B, Metabolic risk factor, Hepatocellular carcinoma, Cancer, Survival

PS 2-3

Regorafenib versus Nivolumab after Sorafenib Failure: Real-World Data in Patients with Hepatocellular Carcinoma

Won-Mook Choi[1], Jonggi Choi[1], Danbi Lee[1], Ju Hyun Shim[1], Young-Suk Lim[1], Han Chu Lee[1], Young-Hwa Chung[1], Young-Sang Lee[1], Sook Ryun Park[2], Min-Hee Ryu[2], Baek-Yeol Ryoo[2], So Jung Lee[3], and Kang Mo Kim[1]

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Aims: Regorafenib and nivolumab are drugs approved for second-line treatment of patients with hepatocellular carcinoma (HCC) after sorafenib failure. However, the effectiveness of regorafenib and nivolumab following sorafenib has not been directly compared.

Methods: This study retrospectively evaluated 373 patients with HCC who were treated with regorafenib (n=223) or nivolumab (n=150) after sorafenib failure between July 2017 and February 2019.

Results: Progression-free survival (PFS; hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.69–1.06; *P*=0.150), time to progression (TTP; HR, 0.95; 95% CI, 0.77–1.19; *P*=0.680), and overall survival (OS; HR, 0.83; 95% CI, 0.64–1.07; *P*=0.154) did not differ significantly between groups of patients treated with regorafenib and nivolumab, findings consistently observed by multivariable-adjusted, propensity score-matched, and inverse probability treatment weighting (IPTW) analyses. However, the objective response rate was significantly higher in the nivolumab than in the regorafenib group (13.3% vs, 4.0%; *P*=0.002). When the effectiveness of regorafenib and nivolumab was compared in non-progressors to treatment, defined as patients who achieved complete response, partial response, or stable disease after first response evaluation, PFS (HR, 0.50; 95% CI, 0.33–0.75; *P*=0.001), TTP (HR, 0.48; 95% CI, 0.31–0.73; *P*<0.001), and OS (HR, 0.51; 95% CI, 0.31–0.87; *P*=0.013) were significantly longer in the 59 non-progressors to nivolumab than in the 104 non-progressors to regorafenib, findings also observed by multivariable-adjusted and IPTW analyses.

Conclusions: Survival outcomes in patients treated with regorafenib and nivolumab after sorafenib failure did not differ significantly. However, nivolumab may be more effective than regorafenib in non-progressors.

Keywords: Liver cancer, Second-line therapy, Effectiveness, Safety

PS 2-4

Circulating Cancer Stem Cells in Hepatocellular Carcinoma: A Pilot Study of Prediction for Tumor Recurrence after Living Donor Liver Transplantation

Hyeo Seong HWANG[1], Gi Hong CHOI[1], Jeong Eun YOO[2], Dai Hoon HAN[1], Jin Sub CHOI[1], Jae Geun LEE[1], Myoung Soo KIM[1], Soon Il KIM[1], Young Nyun PARK[2], Dong Jin JOO[1]

[1]Department of Surgery, Yonsei University College of Medicine, Korea, [2]Department of Pathology, Korea

Aims: The optimal indication of LT in HCC patients has evolved from Milan criteria to morphologic criteria with biologic markers. The role of circulating cancer stem cells has not been reported in patients who underwent LT for HCC.

Methods: From April 2014 to March 2017, 25 patients who underwent LDLT for HCC were prospectively enrolled. EpCAM, CD90 and EpCAM/CD90 were sorted by FACS and mRNA expression of EPCAM, KRT19, THY1 were analyzed by RT-PCR in peripheral blood at preoperative, postoperative day 1 and 7, respectively. The median follow-up duration was 40 months.

Results: The mean age was 55.9 years, and HBV was the most common underlying liver disease (88%). 10 patients were above Milan criteria at diagnosis, and 20 patient received preoperative treatments before LT. HCC recurred in 4 patients. The detected numbers of EpCAM (+) cells and CD90 (+) cells were well correlated with their mRNA expression levels in the peripheral blood (*P*<0.05). EpCAM protein in HCC tissue was highly expressed in patients with recurrence (66% vs. 20%) but didn't reach statistical significance (*P*=0.172). HCCs with EpCAM (+) protein expression showed more detection of EpCAM (+) circulating cells than EpCAM (-). The detection of EpCAM (+) or EpCAM(+)/CD90(+) cells before surgery and at postoperative day 1.

Conclusions: Detection of EpCAM (+) or EpCAM(+)/CD90(+) cells in the peripheral blood before surgery and at postoperative day 1 was the only variable significantly associated with HCC recurrence after LDLT but should be validated in a large-scale prospective study.

The Liver Week 2020

August 13-14, 2020 | VIRTUAL CONFERENCE

DAY 2: Friday, August 14, 2020 (14:20-15:20)

KASL Plenary

Chairs:

Seong Gyu Hwang (CHA Univ.)

Kwon Yoo (Ewha Womans Univ.)

KP 1-1

Therapeutic Effects of Function-Enhanced PRL-1 in Placenta-Derived Mesenchymal Stem Cells on Accelerating Hepatic Functions via Mitochondrial Dynamics in Liver Diseases

Jae Yeon Kim[1], Se Ho Kim[1], Ji Hye Jun[1], Hee Jung Park[1], Jong Ho Choi[2], Si Hyun Bae[3], and Gi Jin Kim[1*]

[1]Department of Biomedical Science, CHA University, Seongnam, Republic of Korea; [2]Department of Oral Pathology, College of Dentistry, Gangneung-Wonju National University, Gangneung, Republic of Korea; [3]Department of Internal Medicine, Catholic University Medical College, Seoul, Republic of Korea

Aims: Placenta-derived mesenchymal stem cells (PD-MSCs) have been highlighted as an alternative cell sources because their several advantages, including therapeutic effects in regenerative medicine and potential as vehicles for targeted gene delivery systems. Phosphatase of regenerating liver-1 (PRL-1), an immediate early gene, plays a critical role during liver regeneration. However, whether enhanced PRL-1 expression in cirrhotic liver accelerates the mitochondrial metabolic state for hepatic regeneration remains unknown. Here, we generated enhanced PRL-1 in PD-MSCs (PD-MSCs^{PRL-1}) using lentiviral and nonviral gene delivery systems and investigated mitochondrial functions by PD-MSC^{PRL-1} transplantation for hepatic functions in a rat model with bile duct ligation (BDL).

Methods: PD-MSCs^{PRL-1} were generated by lentiviral and non-viral AMAXA gene delivery systems and analyzed for their characteristics and mitochondrial metabolic functions. Sprague-Dawley (SD) rats induced liver cirrhosis using common BDL for 10 days. PKH67 labeled naïve PD-MSCs and PD-MSCs^{PRL-1} using a non-viral system ($2x10^6$ cells/animal) were intravenously administered into cirrhotic rats. The animals were sacrificed at 1, 2, 3, and 5 weeks after transplantation. Engraftment of stem cells, and histopathological analysis and hepatic mitochondrial functions were performed.

Results: PD-MSCs^{PRL-1} using lentiviral and non-viral AMAXA systems were successfully generated, and they maintained characteristics similar to those of naïve cells. PD-MSCs^{PRL-1} improved respirational metabolic states in mitochondria compared with naïve cells. In particular, compared with mitochondria in PD-MSCs^{PRL-1}generated by the nonviral AMAXA system, mitochondria in PD-MSCs^{PRL-1} generated by the lentiviral system showed a significant increase in the respirational metabolic state, including ATP production and mitochondrial biogenesis (*P<0.05). Furthermore, transplantation of PD-MSCs^{PRL-1} using a nonviral AMAXA system promoted engraftment into injured target liver tissues of a rat cirrhotic model with BDL and enhanced the metabolism of mitochondria via increased mtDNA and ATP production, thereby improving therapeutic efficacy.

Conclusions: These findings will help the understanding of the therapeutic mechanism of enhanced MSCs (PD-MSCs^{PRL-1}) and provide useful data for the development of next-generation MSC-based cell therapy and therapeutic strategies for regenerative medicine in liver disease.

Funding: This research was supported by a grant of the Ministry of Health & Welfare, Republic of Korea (HI17C1050) and by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2020M3A9B302618221).

Keywords: Phosphatase of regenerating liver-1, Liver disease, Placenta-derived mesenchymal stem cells, Mitochondria

KP 1-2

The Role of Urinary Biomarkers in Cirrhotic Patients with Acute Kidney Injury: Multicenter, Prospective Cohort Study

Jeong-Ju Yoo[1], Jung Hyun Kwon[2], Young Seok Kim[1], Soon Woo Nam[2], Ji Won Park[3], Hee Yeon Kim[2], Chang Wook Kim[2], Seung Kak Shin[4], Young Eun Chon[5], Eun-Sun Jang[6], Sook-Hyang Jeong[6], Jin Woo Lee[7], Do Seon Song[2], Jin Mo Yang[2], Sung Won Lee[2], Hae Lim Lee[2], Young Kul Jung[8], Hyung Joon Yim[8], Sang Gyune Kim[1*], Ju Hyun Kim[4*]

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Aims: Current AKI criteria using serum creatinine (Cr) has some limitations to predict reversibility of renal function and discriminate renal parenchymal injury in cirrhotic patients. The aim of this study is to evaluate whether urine biomarkers [N-acetyl-ß-D-Glucosaminidase (NAG)] can predict survival and response to terlipressin in cirrhotic patients with AKI.

Methods: Two hundred sixty two cirrhotic patients who developed AKI were prospectively enrolled from 11 tertiary medical centers in Korea during 2016 to 2019. AKI was defined as increase in serum Cr (SCr) of 0.3mg/dL or 50% increase of baseline in SCr according to guideline. The patients with SCr ≥ 2.5 mg/dL were diagnosed as hepatorenal syndrome (HRS-AKI) and treated with terlipressin plus albumin. Urine and blood samples were collected at the diagnosis of AKI and/or HRS.

Results: The mean MELD score was 25.27 ± 9.11, and mean SCr was 2.27 ± 0.87 mg/dL. The baseline urine NAG (AKI stage I, 17.22 ± 24.66 mg/dL; stage II, 32.12 ± 52.71 mg/dL; stage III, 53.23 ± 63.28 mg/dL, P<0.001) increased as the baseline AKI stage increased. Urine NAG level was significantly lower in survival group than who underwent death or transplant in

3-months (22.34 ± 36.73 mg/dL vs. 38.80 ± 55.90 mg/dL, *P*=0.005). In multivariate analysis, urine NAG was a significant risk factor for 3-month transplant free survival (TFS), especially in patients with Child-Pugh class ≤ B or MELD < 24. However, urine NAG did not predict the response to terlipressin or recovery of renal function.

Conclusions: Urine NAG is strongly associated with severity of AKI in patients with liver cirrhosis and may be helpful to predict 3-months TFS in these patients.

Keywords: Acute kidney injury, Hepatorenal syndrome, N-acetyl-ß-D-Glucosaminidase

KP 1-3

Lean Non Alcoholic Fatty Liver Disease Increases Cardiovascular Risk more than Obese Non Alcoholic Fatty Liver Disease

Yuna Kim[1,3], Eugene Han[2], Jae Seung Lee[1,3,5], Hye Won Lee[1,3,5], Beom Kyung Kim[1,3,5], Jun Yong Park[1,3,5], Do Young Kim[1,3,5], Sang Hoon Ahn[1,3,5], Yong-ho Lee[4], and Seung Up Kim[1,3,5]

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Aims: Nonalcoholic fatty liver disease (NAFLD) and obesity are independently associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD) and ASCVD is the leading cause of mortality in patients with NAFLD. A significant subset of NAFLD patients are lean, but their ASCVD risk compared to obese NAFLD subjects is not well known.

Methods: Data from the 2008–2011 Korean National Health and Nutrition Examination Surveys database were analyzed (n=4,786). NAFLD was defined as a comprehensive NAFLD score (CNS) ≥40 or a liver fat score (LFS) ≥-0.640. ASCVD risk was evaluated using ACC/AHA guidelines. High probability of ASCVD was defined as ASCVD risk >10%.

Results: Prevalence of subjects without NAFLD, obese subjects with NAFLD, and lean subjects with NAFLD was 62.4% (n=2,987), 26.6% (n=1,274) and 11.0% (n=525), respectively. Subjects with lean NAFLD had a significantly highest ASCVD score and prevalence of high ASCVD risk (mean 15.6±14.0 and 51.6%), whereas subjects with obese NAFLD was in the middle and those without NAFLD was in the lowest (mean 11.2±11.4 and 39.8% in obese NAFLD and mean 7.9±10.9 and 25.5% in control without NAFLD, all *P*<0.001). Lean NAFLD subjects with significant liver fibrosis showed significantly higher OR for risk of high probability of ASCVD than obese subjects with significant fibrosis, compared with subjects without significant liver fibrosis (OR=2.60 versus 1.93; *P*=0.023).

Conclusions: Despite partially a more favorable metabolic profile, subjects with lean NAFLD had a significantly higher ASCVD score and prevalence of high ASCVD risk than subjects with obese NAFLD. Similarly, lean subjects with significant liver fibrosis showed higher OR for risk of high probability of ASCVD than obese subjects in the sub-population with NAFLD.

Table. Odds ratio and 95% confidential intervals of high probability of ASCVD according to obesity and NAFLD using comprehensive NAFLD score

Models	Subjects without NAFLD	Obese subjects with NAFLD	Lean subjects with NAFLD
Crude	1.00 (ref.)	1.93 (1.68-2.22) *P*<0.001	3.12 (2.58-3.77) *P*<0.001
Model 1	1.00 (ref.)	3.68 (2.89-4.69) *P*<0.001	3.71 (2.68-5.14) *P*<0.001
Model 2	1.00 (ref.)	2.05 (1.37-3.07) *P*=0.001	2.63 (1.61-3.58) *P*<0.001

Model 1: adjusted for age and sex
Model 2: adjusted for age, sex, smoking, exercise, waist circumference, hypertension, diabetes, HOMA-IR, chronic kidney disease, and hyper-LDL cholesterolemia

Keywords: Nonalcoholic fatty liver disease, Liver fibrosis, Cardiovascular risk, Fatty liver

KP 1-4

Multicenter Analysis of Clinical Features and Treatment Outcomes of COVID-19 Patients with Hepatic Impairment

Jeong Eun Song[1], Chang Hyeong Lee[1], Jae Seok Hwang[2], Woo Jin Chung[2], Byoung Kuk Jang[2], Heon Ju Lee[3], Jung Gil Park[3], Min Kyu Kang[3], Young Oh Kweon[4], Won Young Tak[4], Soo Young Park[4], Se Young Jang[4], Yu Rim Lee[4], Jeong Ill Suh[5], Byung Seok Kim[1]

[1]Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, South Korea; [2]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, South Korea; [3]Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, South Korea; [4]Department of Internal Medicine, Kyungpook National University College of Medicine, Daegu, South Korea; [5]Department of Internal Medicine, Dongguk University College of Medicine, Gyeongju, South Korea

Aims: Coronavirus disease 2019 (COVID-19) has spread worldwide, resulting in an ongoing pandemic. Limited data are available for liver function in patients with COVID-19. We aimed to evaluate the clinical features and treatment outcomes in COVID-19 patients with liver enzyme abnormality.

Methods: Clinical records and laboratory results were obtained from 874 patients (female, 566; male, 308; median age, 62 years) diagnosed of COVID-19 who were admitted to four tertiary hospitals in Daegu from February 20 to April 14, 2020 and followed up to April 30, 2020. Clinical features and treatment outcomes were compared between patients with elevated aminotransferase or not.

Results: 362 of 874 (41.1%) COVID-19 patients had elevated aminotransferase. The median levels of ALT were 51 (37-79) U/

L vs. 19 (14-24) U/L, respectively, AST were 44 (34-69) U/L vs. 20 (17-24) U/L, respectively in abnormal and normal aminotransferase groups. Males were more likely to have elevated liver enzymes when infected with COVID-19 (P<0.001) compared with normal aminotransferase group. No significant differences were found regarding to underlying liver diseases between two groups. The prevalence of initial symptoms was also similar in both groups except the COVID-19 patients with elevated liver enzymes had greater proportion of fever (52.2% vs. 39.9%, P=0.001) and dyspnea (34.3% vs. 19.6%, P<0.001). Liver enzyme abnormality was associated with disease severity (P<0.001) and bilateral involvement on chest radiographs (P<0.001). A significantly higher proportion of patients with elevated liver enzyme had received lopinavir/ritonavir (64.9% vs. 50.0%), hydroxychloroquine (63.0% vs. 48.4%) and antibiotics (87.6% vs. 70.1%). Patients with elevated liver enzyme had longer median hospital stays (22 days vs. 26 days, P=0.001) and higher mortality rate (12.4% vs. 2.9%, P<0.001) than patients with normal liver enzyme.

Conclusions: Liver enzyme abnormality is common in COVID-19 patients. It is related to disease severity and poor treatment outcomes.

Keywords: COVID-10, Liver enzyme abnormality, SARS-CoV-2 infection

DAY 1: Thursday, August 13, 2020 (14:00:15:10)

General Oral 1

Chairs:

Myung Seok Lee (Hallym Univ.)

Byung Ik Kim (Sungkyunkwan Univ.)

GO 1-1

Kahweol Activates the NRF2/HO-1 Pathway by Decreasing Keap1 Expression Independently of p62 and Autophagy Pathways

Hye-Young Seo, So-Hee Lee, Ji-Ha Lee, Jae Seok Hwang, Mi Kyung Kim, Byoung Kuk Jang

Department of Internal Medicine, Keimyung University School of Medicine, Republic of Korea

Aims: Kahweol is a diterpene found in coffee beans and unfiltered coffee drinks. Several studies have demonstrated that kahweol induces the nuclear factor erythroid-2 related factor 2/hemeoxygenase-1 (NRF2/HO-1) pathway; however, the mechanisms involved are currently unknown. Kelch-like ECH-associated protein 1 (Keap1) is a major regulator of NRF2 expression and is degraded mostly by autophagy. Here, we examined the role of Keap1 regulation in the effect of kahweol on the NRF2/HO-1 pathway in hepatocytes.

Methods: Hepatocyte-specific ATG7 knockout mice were generated by crossing ATG7 Flox/Flxo mice with albumin Cre mice. We isolated and cultured ATG7 K/O mouse primary hepatocyte, mouse primary hepatocyte and AML12 cells. The expression levels of HO-1, p62 and keap1 were measured by real-time RT-PCR analysis. The expression levels of HO-1, Nrf2, p62, keap1 and autophagye marker were measured by western blot analysis.

Results: In AML12 cells and primary mouse hepatocytes, kahweol increased the levels of HO-1 and NRF2, as well as that of p62, which binds to Keap1 and contributes to the activation of NRF2. In addition, kahweol decreased Keap1 protein but not mRNA levels. Kahweol increased the expression of HO-1 in cells treated with a p62-specific siRNA and did not affect the levels of ubiquitin or autophagy-related markers. Furthermore, kahweol decreased Keap1 protein expression in primary hepatocytes from ATG7-knockout mice.

Conclusions: This study shows that kahweol decreased keap1 protein expression in primary hepatocyte and AML12 cells. The keap1-Nrf2-pathway by p62 dependent autophagy is well known. However, it was confirmed that the reduction of keap1 by kahweol was not due to p62, ubiquitin and autophagy degradation. Further research is needed to determine whether kahweol regulates the translation of keap1.

Keywords: Kahweol, Keap1, HO-1, NRF2

GO 1-2

TIP-47 Accelerates Fatty Change of Liver during Alcohol Ingestion in HBx Transgenic Mice

Eun Young Cho[1], Hoon Gil Jo[1], Keum Ha Choi[3], Hyung Jin Kim[2], Ki Soo Oh[2], Hong-Seob So[2]

Departments of Internal Medicine,[1] Microbiology,[2] Pathology,[3] Wonkwang University, Iksan, Republic of Korea

Aims: In chronic hepatitis B patients, alcohol is known to accelerate the progression of liver fibrosis and increase the incidence of hepatocellular carcinoma. However, little is known about the exact mechanism of this disease progression. This study aimed to investigate the direct effect of alcohol on hepatitis B.

Methods: The experiment was performed using HBx transgenic and control C57BL/6 (B6) mice(4 groups; control-liquid diet[LD], control-ethanol, HBx-LD, HBx-ethanol). Real-time PCR, histologic and serologic exam were performed for analysis.

Results: 1. As for liver histology, there was no difference in degree of steatosis and ballooning between the control-ethanol group and the HBx-ethanol group, but PMNL infiltration showed a significant increase in the HBx-control group(P<0.005). Also, the macrovesicular fatty change was predominant in the control-ethanol group whereas the microvesicular fatty change was mainly observed in the HBx-ethanol group. Besides, the nuclear hyperchromasia and irregularity of nucleus were observed in hepatocytes only in the HBx-ethanol group. 2. To identify factors affecting the fatty change of liver, RT-PCR was performed on Peroxisomal and mitochondrial beta oxidation enzymes. As a result, mRNA for Peroxisomal beta oxidation enzymes(ACOX1, DBP, EHHADH, PEX11a) were not significantly different between groups(control-ethanol vs. HBx-ethanol). However, mRNA results for mitochondrial beta oxidation enzymes(CPT1A, CPT1B, MCAD) showed a significant decrease in the HBx-ethanol group(P<0.05). 3. In the results of analyzing the mRNA expression level of the factors related to the fat vacuole size(perilipin, TIP47, Fsp27, Seipin), TIP47 was significantly increased in the HBx-ethanol group(P<0.001) 4. When suppressing the expression of TIP47 using TIP47-siRNA, there was no change in degree of oil-red O staining in HBV-free Hep G2 cells, but it was showed that oil-red O staining was significantly reduced in HBV-genome containing Hep3B cell(P<0.001).

Conclusions: This study showed that alcohol exacervated pathologic change (microvesicular fatty change and dysplastic change in hepatocyte) in liver of HBx transgenic mice. TIP47 can contribute to this process, especially microvesicular fatty change of liver.

Keywords: HBV, TIP47, Alcohol

GO 1-3

Hepatitis B Core-Related Antigen is a Satisfactory Marker in Differentiating Hepatitis B e Antigen-positive Chronic Infection and Hepatitis B e Antigen-Positive Chronic Hepatitis

Han Ah Lee[1], Hyun Woong Lee[2], Jihwan Lim[1], Young-Sun Lee[1], Young Kul Jung[1], Ji Hoon Kim[1], Jung Il Lee[2], Young Kul Jung[1], Hyung Joon Yim[1], Jong Eun Yeon[1], Kwan Soo Byun[1], Kwan Sik Lee[2], Soon Ho Um[1], and Yeon Seok Seo[1]

[1]Departments of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea; [2]Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Republic of Korea

Aims: We investigated the clinical impact of Hepatitis B core-related antigen (HBcrAg) level in defining different phases of patients with chronic hepatitis B (CHB).
Methods: Stored residual serum samples from longitudinal cohorts of CHB patients in Korea University College of Medicine were studied. Patients were divided into four phases of CHB based on the histology result: hepatitis B e antigen (HBeAg)-positive chronic infection (EPI), HBeAg-positive chronic hepatitis (EPH), HBeAg-negative chronic hepatitis (ENH), HBeAg-negative chronic infection (ENI).
Results: In total, 425 patients followed up for 83.1 months were included. The number of patients in each phase are as follows: 26 in EPI, 243 in EPH, 137 in ENH, and 19 in EHI. To evaluate the clinical impact of HBCrAg in differentiating EPI and EPH, patients older than 60 years old, patients with clinically or ultrasonographically evident liver cirrhosis or fibrosis-4 index (> 3.25), and HBV-DNA ≤ 20,000 IU/mL were excluded. In 145 selected patients, 26 patients were in EPI and 119 patients were in EPH. HBCrAg level was significantly higher in EPI than in EPH (8.22 log U/mL vs. 7.57 log U/mL, *P*=0.003). On multivariate analysis, only higher HBCrAg level (HR 0.447, *P*=0.013) was significantly associated with an increased probability of EPI. To evaluate the clinical impact of HBCrAg in differentiating ENH and ENI, patients with clinically or ultrasonographically evident liver cirrhosis or fibrosis-4 index (> 3.25), and HBV-DNA > 20,000 IU/mL were excluded. In 33 selected patients, 21 patients were in ENH and 12 patients were ENI. HBCrAg level was significantly higher in ENH patients than in ENI patients (5.24 log U/mL vs. 3.98 log U/mL, *P*<0.001). Only elevated ALT according to the KASL criteria (HR 4.875, *P*=0.049) was significantly associated with increased probability of ENH.
Conclusions: HBcrAg level is a useful marker in differentiating EPI and EPH in patients with CHB.
Keywords: Hepatitis B Core-related Antigen, Hepatitis B e Antigen-positive Chronic Infection, Hepatitis B e Antigen-positive Chronic Hepatitis, Chronic Hepatitis B

GO 1-4

All Cause of Mortality and Incidence of Hepatocellular Carcinoma Among Chronic Hepatitis C Patients in South Korea: A Prospective, Multicenter Cohort Study

Gwang Hyeon Choi[1*], Eun Sun Jang[1*], Young Seok Kim[2], Youn Jae Lee[3], In Hee Kim[4], Sung Bum Cho[5], Han Chu Lee[6], Jang Jeong Won[7], Moran Ki[8], Hwa Young Choi[8], Dahye Baik[8], Sook-Hyang Jeong[1]

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Aims: This study aimed to elucidate the all-cause mortality and the incidence hepatocellular carcinoma (HCC), and their related factors among the patients with chronic hepatitis C virus (HCV) infection in South Korea.
Methods: A total 2,369 patients with HCV RNA positivity and no HCC at diagnosis (mean age 57.5 years, 47.6% male, 29.8% cirrhosis) were prospectively enrolled in 6 university hospitals from May 2007 to March 2019 and followed until February 2020. The patients were classified into untreated group (n=753, 31.8%), interferon (IFN)-based treated group (n=698, 29.5%), and direct-acting antivirals (DAA)-treated group (n=918, 38.8%). Kaplan-Meier curve analysis and Cox regression analysis were performed.
Results: During 4.3 years (IQR 2.5–7.6) of median follow-up, 245 patients died and 147 developed HCC. The 3-, 5-, and 10-year cumulative mortality in the HCV patients was 4.6%, 8.0%, and 12.8%, respectively. The 3-, 5-, and 10-year cumulative incidence of HCC was 4.5%, 8.5%, and 18.3%, respectively. The SVR rate was 68.7% in IFN-based treated group and 95.2% in DAA-treated group, by per-protocol analysis. After multivariate analysis, achievement of SVR was an independent factor for decreased risk of HCC (adjusted hazard ratio [aHR] 0.22, 95% confidence interval [CI] 0.12–0.39, *P*<0.001 for IFN based-treated group and aHR 0.29, 95% CI 0.17–0.50, *P*<0.001 for DAA-treated group, respectively). SVR was an independent factor for decreased risk of all cause of mortality (aHR 0.27, 95% CI 0.17–0.44, *P*<0.001 for IFN based-treated group and aHR 0.23, 95% CI 0.12–0.45, *P*<0.001 for DAA-treated group, respectively) along with other factors.
Conclusions: In Korea HCV cohort, 5-year cumulative incidence of HCC and mortality was 8.0% and 8.5%, respectively. The overall treatment rate was 70% with overall SVR rate of 86%. Achievement of SVR was a strong factor for better outcomes, which support active screening and treatment of HCV infection.
Keywords: Hepatitis C virus, Direct acting antivirals, Hepatocellular carcinoma, Survival

GO 1-5

Weight Gain during Early Adulthood, Trajectory of Body Shape and the Risk of Non-Alcoholic Fatty Liver Disease Among Women : A Prospective Cohort Study

Mi Na Kim[1,2], Chun-Han Lo[3], Kathleen E. Corey[1,4], Mingyang Song[1,3], Tracey G. Simon[1,4], and Andrew T. Chan[1,5]

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Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA; [5]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA

Aims: Obesity is established as a major risk factor for the development of nonalcoholic fatty liver disease (NAFLD). However, the influence of changes in adiposity over the life course on NAFLD risk remains poorly understood.
Methods: This study included 110,054 women in the Nurses' Health Study II cohort without NAFLD at baseline (in 1995), who were followed prospectively through 2015. Early adulthood weight change was defined as the difference between early adulthood weight (at age 18 years) and the weight reported in the current questionnaire cycle. We used a group-based modeling approach to identify five trajectories of body shape from age 5 years up to 50.
Results: We documented 3,798 incident cases of NAFLD over 20 years of follow-up (1,842,560 person-years). An elevated early adulthood body mass index (BMI) and weight gain since early adulthood were significantly and positively associated with the risk of incident NAFLD (all P trend <0.0001). Compared to women who maintained stable weight (+/-2 kg), women with ≥20 kg of early adulthood weight gain had the multivariable adjusted hazard ratio (aHR) of 6.96 (95% confidence interval [CI], 5.27-9.18), and this remained significant after further adjusting for updated BMI (P trend <0.0001). Compared to women with a medium-stable body shape trajectory, the multivariable aHRs for NAFLD risk were, 2.84 (95% CI, 2.50-3.22) for lean-marked increase, 2.60 (95% CI, 2.27-2.98) for medium-moderate increase, and 3.39 (95% CI, 2.95-3.89) for medium-marked increase.
Conclusions: Both early adulthood weight gain and lifetime body shape trajectory were significantly and independently associated with excess risk of developing NAFLD. Maintaining both lean and stable weight throughout life may offer the greatest benefit for the prevention of NAFLD.
Keywords: Nonalcoholic fatty liver disease, Weight change, Trajectory of body shape

GO 1-6

Bedside Risk-Scoring Model for Prediction of 30 days' Mortality in Patients with Cirrhosis Underwent Endoscopic Band Ligation for Acute Variceal Bleeding

Jung Hee Kim[1], Se Woo Park[1], Jang Han Jung[1], Jae Gun Park[2], Chang Suk Bang[3], Ji Won Park[4], Da Hae Park[1], Jin Lee[1], Dong Hee Koh[1]

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Aims: Acute variceal bleeding is a fatal complication for cirrhotic patients and endoscopic band ligation (EVL) is recommended for treatment. But there are sporadic data for mortality in patients underwent EVL of acute variceal bleeding. We developed a novel bed-side scoring model to predict 30 days' mortality for cirrhotic patients who underwent EVL of acute variceal bleeding.
Methods: From a Cox-regression model for 30 days' mortality, variables were developed among baseline characteristics, history of complication, the presence of hepatocellular carcinoma, ascites and endoscopic finding from the derivation cohort (n=1372) underwent EVL for acute variceal bleeding. The model's prognostic performance was compared with CTP and MELD score and assessed in validation cohort. (n=200).
Results: Among 1372 patients, rebleeding or death within 5 days was observed in 51 patients (3.7%) and 72 patients (5.2%), respectively. The validation cohort showed more aggressive clinical outcome than derivation cohort in term of endoscopic active bleeding, shock at presentation and treatment failure.From a multivariate Cox-regression model, four objective variables (the presence of HCC, CTP class (A/B vs. C), the shock at presentation and the history of hepatic encephalopathy) were developed and scored to generate an 11-point risk prediction model. The scoring model was able to stratify patient 30 days' mortality as low (4.25%), medium (20.9%) and high (42.3%) risk group. (P<0.001) The time-dependent area under receiver-operating characteristics curves (AUROCs) for 30days mortality were higher in risk prediction model than CPT score. (derivation cohort: 0.79 vs 0.73, validation cohort:0.82 vs 0.75, P<0.001). Even in the group of same MELD (<15 or ≥15), new scoring model also stratified 30 days' mortality to three groups with statistically significant in derivation and validation cohort.
Conclusions: New simplified scoring system was useful in estimating 30days mortality for patients who underwent EVL for acute variceal bleeding. This score can be useful in planning and guiding further strategies after EVL which warrants prospective validation.
Keywords: Liver cirrhosis, Varix bleeding, Endoscopic band ligation, Risk scoring

GO 1-7

Population-Based Epidemiology of Primary Biliary Cholangitis in South Korea

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Aims: As a rare disease, only a few population-based epidemiology studies of primary biliary cholangitis (PBC) have been reported. After designation of PBC as a rare disease in 2009

in South Korea, the trend of prevalence and incidence of PBC were not reported. This study aimed to elucidate the nationwide prevalence, incidence, and outcomes of PBC in South Korea from 2009 to 2017.

Methods: The Korean National Health Service database and Rare Intractable Disease registration data on PBC, identified with the International Classification of Diseases 10 code of K74.3, were obtained from 2009 through 2017. Age and gender-specific prevalence and incidence rates of PBC were calculated, and data on complications, comorbidities, prescribed drugs, therapeutic procedures, and were analyzed.

Results: A total of 2,458 patients over 20 years old were identified as an incident PBC in 2009~2017 (female-to-male ratio 5.8, median age 58 years old). The average age and sex-adjusted incidence from 2009 to 2017 was 7.81 per million per year and annual incidence tends to decrease for recent 2 years (3.42~4.69 per million per year). The annual age and sex-adjusted prevalence increased from 38.18 per million population in 2009 to 84.27 in 2017. The average age and sex-adjusted prevalence demonstrated geographic variation. About 15% of patients had liver-related complications including ascites (14.9%), variceal bleeding (6.6%) and/or hepatocellular carcinoma (1.9%). Liver transplantation was undertaken in 55 patients (2.2%), and all-cause mortality was 9.3% among 2,458 incident cases incident PBC cases for 9 years. The annual case-fatality was 1.94% and was higher in male (3.62% vs 1.71%).

Conclusions: During 2009-2017, the incidence of PBC was 7.81 per million per year with recent decreasing trend, and the prevalence of PBC in 2017 was 84.3 per million population with increasing trend in South Korea, which suggests improved outcomes with UDCA treatment. However, liver-related complication was observed in 15% of the PBC patients, and remarkable geographic disparity of epidemiology warrants nationwide efforts for enhancing awareness and diagnosis.

Keywords: Primary biliary cholangitis, Prevalence, Incidence, Liver-related complication

The Liver Week 2020

August 13-14, 2020 | VIRTUAL CONFERENCE

DAY 2: Friday, August 14, 2020 (13:30-14:40)

General Oral 2

Chairs:

Young Oh Kweon (Kyungpook National Univ.)

Sang-Jae Park (National Cancer Center)

GO 2-1

Serum Small Extracellular Vesicle-Derived *LINC00853* as a Novel Diagnostic Marker for Early Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) accounts for approximately 90% of the primary liver cancers and represents a major global health problem. This study aimed to identify novel long non-coding RNA (lncRNA) biomarkers for hepatocellular carcinoma (HCC) using publicly available tissue genomic datasets, and validate their diagnostic utility for early-stage HCC. Differentially expressed lncRNAs between 371 HCC and 50 non-tumor tissues were obtained from The Cancer Genome Atlas liver hepatocellular carcinoma (TCGA_LIHC) project.

Methods: Expression of the serum- and the extracellular vesicles (EV)-derived lncRNA was assessed in 10 patients with HCC and 10 healthy controls using RT-PCR. The candidate lncRNAs were validated in 90 HCC and 92 non-HCC (29 healthy control, 28 chronic hepatitis, 35 liver cirrhosis) patients. The sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) were calculated for candidate lncRNAs and the current HCC biomarker, alpha-fetoprotein (AFP).

Results: *SFTA1P, HOTTIP, HAGLROS, LINC01419, HAGLR, CRNDE*, and *LINC00853* were markedly up-regulated in HCC in TCGA_LIHC dataset. Among them, *LINC00853* has not been reported in relation to HCC before. In patients with HCC, only expression of small EV-derived *LINC00853* (EV-*LINC00853*) was increased. EV-*LINC00853* showed excellent discriminatory ability in the diagnosis of all-stage HCC (AUC=0.934, 95% CI=0.887-0.966). Moreover, using a 14-fold increase and 20 ng/mL as cut-offs for EV-*LINC00853* expression and AFP level, respectively, EV-*LINC00853* was found to have a sensitivity of 93.75% and specificity of 89.77%, while AFP showed only 9.38% sensitivity and 72.73% specificity for the diagnosis of early-stage HCC (mUICC stage I). EV-*LINC00853* had a positivity of 97% and 67% in AFP-negative and AFP-positive early HCC, respectively.

Conclusions: Serum EV-derived LINC00853 may be a novel potential diagnostic biomarker for early HCC, especially for AFP-negative HCC.

Keywords: Early hepatocellular carcinoma, Diagnostic marker, Exosome extracellular vesicles, Long noncoding RNAs

GO 2-2

Current Status of Ultrasonography Examination Operated by National Cancer Surveillance Program for Hepatocellular Carcinoma: Multi-center Large-Scale Research

Jeong-Ju Yoo[1], Sun Hong Yoo[2], Jung Hyun Kwon[2], Han-Ah Lee[3], Yeon Seok Seo[3], Young Kul Jung[4], Hyung Joon Yim[4], Do Seon Song[5], Seong Hee Kang[6], Moon Young Kim[6], Young-Hwan Ahn[7], Jieun Han[7], Young Seok Kim[1], Young Chang[8], Soung Won Jeong[8], Jae Young Jang[8], Soon Sun Kim[7*], Sang Gyune Kim[1*]

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Aims: Abdominal ultrasonography (USG) is recommended as a surveillance test for the high-risk group of hepatocellular carcinoma (HCC). However, there is lack of information about how USG examination is actually performed in clinical practice, and how the quality control related to USG examination is managed. We investigated the incidence of HCC by a reference point of 6 months after USG was conducted.

Methods: We collected data of surveillance USG from high-risk group of HCC (liver cirrhosis, or chronic hepatitis B or C over 40 years) group during 2017 in 8 tertiary hospitals. To determine the accuracy of the ultrasound examination itself, patients who had a prior history of HCC or who had CT or MRI scan within 6 months of ultrasound were excluded. If ultrasound was performed more than twice during 2017, the results of the first test were used.

Results: In 2017, 45 experienced hepatologists or radiologists performed 8,512 ultrasounds. Mean age was 53.5 ± 11.0 years and, 4817 (56.6%) were males. Chronic hepatitis B was the most common indication (6319, 74.2%), and 2429 patients (28.5%) had liver cirrhosis. Doctors had 15.0 ± 8.3 years of experience, and proportion of hepatologists was higher than that of radiologists (61.4% vs. 38.6%). The time taken for the ultrasound scan was 4.1 ± 3.3 minutes excluding the preparation time. The detection rate of HCC through surveillance USG was 0.3% (29 patients). During 27 months of follow-up, a total of 60 patients (0.7%) developed new HCC. Of these, 15 patients (0.2%) were diagnosed with HCC within 6 months of the surveillance USG, and 45 patients (0.5%) were diagnosed after 6 months of the surveillance test.

Conclusions: This is the first study on the current status of USG examination as a surveillance modality for HCC. It is necessary to develop quality indicator and quality assessment of USG to increase the detection rate of HCC.

Keywords: Ultrasonography, Surveillance, Hepatocellular carcinoma

GO 2-3

Development of Machine Learning-Based Clinical Decision Support System for Hepatocellular Carcinoma

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Aims: There is a significant discrepancy between the actual choice for initial treatment option for hepatocellular carcinoma (HCC) and recommendations from the currently used BCLC staging system. The aim of this study is to develop a machine learning-based clinical decision support system (CDSS) for recommending initial treatment option in HCC and predicting overall survival (OS).

Methods: From hospital records of 1021 consecutive patients with HCC treated at a single center in Korea between January 2010 and October 2010, we collected information on 61 pretreatment variables, initial treatment, and survival status. Twenty pretreatment key variables were finally selected. We developed the CDSS from the derivation set (N=813) using random forest method and validated it in the validation set (N=208).

Results: Among the 1021 patients (mean age: 56.9 years), 81.8% were male and hepatitis B virus was positive in 77.0%. Patients with BCLC stages 0, A, B, C, and D were 13.4%, 26.0%, 18.0%, 36.6%, and 6.3%, respectively. The 6 multistep classifier models were developed for treatment decision in a hierarchical manner, and it showed good performance with 76.6–88.4% of accuracy. We also developed 7 survival prediction models for each treatment option, which showed good prediction ability for OS with C-index values ranging from 0.684–0.959.

Conclusions: Our newly developed HCC-CDSS model showed good performance in terms of treatment recommendation and overall survival prediction. Our HCC-CDSS model may be used as a guidance in deciding the initial treatment option for HCC.

Keywords: Hepatocellular carcinoma, Survival, clinical decision support system, Machine learning

GO 2-4

Proton Beam Radiotherapy versus Radiofrequency Ablation Treatment in Patients with Recurrent Hepatocellular Carcinoma: A Randomized Controlled phase 3 Non-Inferiority APROH Trial

Joong-Won Park[1], Tae Hyun Kim[1,2], Young-Hwan Koh[1,3], Bo Hyun Kim[1], Min Ju Kim[3], Ju Hee Lee[1,3], Boram Park[4]

[1]Center for Liver and Pancreatobiliary Cancer; [2]Center for Proton Therapy; [3]Department of Radiology; [4]Biostatistics Collaboration Team, National Cancer Center, Goyang, South Korea

Aims: Radiofrequency ablation (RFA) is the standard of care for patients (pts) with Barcelona Clinic for Liver Cancer stage 0 and A hepatocellular carcinoma (HCC) not suitable for surgery. The role of external proton beam radiotherapy (PBT) is under investigation and a phase 2 study of PBT showed promising local control and safety. Herein, we conducted an investigator-initiated phase 3 non-inferiority trial to evaluate the clinical outcomes of PBT on recurrent or residual HCC (rHCC).

Methods: Patients (pts) with rHCC (size < 3 cm, number ≤2) were randomly assigned (1:1) to receive PBT or RFA according to the Child-Pugh score and tumour stage. If the randomly assigned method was not technically feasible, pts were allowed to enroll in the other treatment. Eligible pts of PBT arm received a total of 66 Gray equivalent in 10 fractions and those of RFA arm received RFA with a monopolar electrode. The primary endpoint was 2-year (y) local progression-free survival (LPFS) rate with a non-inferiority margin of 15%; secondary endpoints included overall survival, progression-free survival, tumor response rate and safety profile (NCT01963429).

Results: Between December 2013 and December 2017, 144 pts in PBT arm (n=72) and RFA arm (n=72) comprised the intention-to-treat (ITT) population and the trial was concluded on January 2020. The baseline characteristics of pts were well balanced. In PBT arm, six pts switched to RFA and five pts received another treatment, while in RFA arm, 19 pts switched to PBT and three pts received another treatment. Thus, the per-protocol (PP) population comprised 80 patients receiving PBT and 56 undergoing RFA. In the PP population, the 2-year LPFS rate associated with PBT vs. RFA was 94.8% vs. 83.9% (90% confidence interval [CI], 1.8-20.0%; $P<0.001$); in the ITT population, the 2-year LPFS rate associated with PBT vs. RFA was 92.8% vs. 83.2% (90% CI, 0.7-18.4%; $P<0.001$), meeting the criteria for non-inferiority. The 3- and 4-year LPFS rates for PBT were also significantly non-inferior to those for RFA. Efficacy outcomes are shown in the figure. The most common adverse events (AEs) were radiation pneumonitis (32.5%) and decreased leukocyte counts (23.8%) for PBT and increased alanine aminotransferase levels (96.4%) and abdominal pain (30.4%) for RFA. No Grade 4 AEs or mortality were noted.

Conclusions: PBT was non-inferior to RFA in terms of LPFS in pts with rHCC, and PBT was tolerable and safe, consistent with the known profile.

Keywords: Hepatocellular carcinom, Proton beam therapy, Radiotherapy, Radiofrequency ablation

GO 2-5

Clinical Significance of Intraoperative Bile Culture in Surgery Including Bile Duct Resection

Youngju RYU, Naru KIM, Yung hun YOU, In Woong HAN, Jin Seok HEO, Dong Wook CHOI, Sang Hyun SHIN

Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Aims: It is widely accepted that intraoperative bacterial infection may potentially result in a worse postoperative outcomes. The purpose of this study is to analyze the microbiology of intraoperative bile smear culture test and the correlation between the results of culture and postoperative outcomes in bile duct resection operation.
Methods: The data was prospectively collected from 235 patients who underwent bile duct resection at Samsung Medical Center for one year from October 2018 to September 2019. The diseases included in the data are periampullary cancer, gallbladder cancer, hilar cholangiocarcionoma, and intrahepatic cholangiocarcinoma. Intraoperative bile smear test was performed in operation, and the included operation was pancreaticoduodenectomy and liver resection surgery with bile duct resection. Specimens were obtained from culture swab of bile drained during bile duct resection.
Results: Of the 235 patients, microorganism was isolated in 141 patients (60%). The predominant microorganisms grown from the intraoperative bile cultures were Enterococcus faecalis (38 cultures, 27.0%), Enterococcus faecium (32 cultures, 22.7%), Klebsiella pneumoniae and Enterobacter cloacae (28 cultures, 19.9%). In postoperative complication, the positive results of intraoperative bile cultures was related with Clavien-Dindo Classification≥Ⅲ (OR3.117, 95%CI:1.498-6.485, *P*=0.002). Also, it was a risk factors for occurrence of surgical site infection (OR3.266, 95%CI:1.237-8.621, *P*=0.013) and intra-abdominal abscess (OR1.145, 95%CI:1.057-1.240, *P*=0.003). In addition, the incidence of postoperative pancreatic fistula was increased in patients with microorganisms grown in bile (OR1.974, 95%CI:1.098-3.549, *P*=0.022).
Conclusions: Smear positivity of intraoperative bile fluid is associated with occurrence of major complication. It was risk factor for surgical site infection and intra-abdominal abscess.

GO 2-6

Medium not Too High Intensity versus Medium not Too Low Intensity Exercise Effect on Fatty Liver – Post Cholecystectomy with Metabolic Syndrome: A Comparison Study

Alvin WIHARJA

Sports Medicine, Svarga e-Motion Sanctuary, Indonesia

Aims: To measure the effectiveness of medium not too high (MNTH) and medium not too low intensity (MNTI) exercise using callisthenic method in adult with fatty liver-post cholecystectomy and risk of metabolic syndrome.
Methods: 2 groups of each 25 adults with fatty liver, post cholecystectomy history and risk of metabolic syndrome were treated with 2 different method of exercise prescription, specifically in-group of MNTH and MTHI, for 12 weeks. To practice, the exercise prescription was structured and supervised by sports medicine specialist. The intensity was measured with heart rate during exercise with cut off point 64-69% of maximum heart rate (MHR) for MNTH and 69-74% for MNTI. Thus it contained strength, flexibility, balance and cardiorespiratory exercise that were suitable with patient conditions. A subjective Borgs' Scale, Blood pressure and GPT, HbA1C, Fasting Glucose, profile lipid, bodyweight examination were used as controlling parameter.
Results: Exercise was done 3 times a week regularly with average duration of 58 (SD±4.66) minutes on MNTH and 55 (SD±6.19) minutes on MNTI. Borgs' scale obtained during of intervention (Score 11 (SD±2.15) of 20) was in the target level, medium intensity. Subjectively and objectively no clinical symptoms, led to cardiovascular and complication of disease, were found. There was a significant improvement in the MNTL group on GPT (improvement 27 (SD±4.73)U/L[*P*=0.031]), HbA1C (improvement 1(SD±0.81)%[*P*=0.048]) and bodyweight (improvement 5 (SD±2.84)kg[*P*=0.036]). Fasting glucose, total cholesterol and LDL-cholesterol concentration were improved on both groups clinically.
Conclusions: The MNTL exercise gives better significant results compared with MNTI exercise on GPT, HbA1C also bodyweight in adult patients.

GO 2-7

Development of Novel Multivariable Logistic Regression Model for Predicting Graft Failure within 2 Weeks and 4 Weeks after Liver Transplantation

Jinsoo RHU, Jong Man KIM, Gyu-Seong CHOI, Jae-Won JOH

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Aims: This study designed a prediction model for graft failure after liver transplantation.
Methods: Multivariable logistic regression including AST, TB, and PT/INR for predicting graft failures within 2 and 4 weeks, respectively, were performed. The models were evaluated with area under receiver operating characteristic curve (AUC) and net reclassification improvement (NRI). Decision curve analysis was performed to evaluate the clinical usefulness.
Results: 1539 patients were included. Univariable logistic regression with maximum INR≥2.53 during 3 to 7 (AUC=0.9224,-CI=0.8726-0.9721, *P*<0.0001) and maximum INR≥2.6 during 3 to 14 post-transplantation (AUC=0.900, CI=0.8518-0.9482,

P<0.0001) showed relationship to 2- and 4-week graft failure, respectively. Multivariable model including log2-scaled maximum AST during 0 to 7, log_2-scaled maximum TB and log_2-scaled maximum INR during 3 to 7 post-transplantation day were related to 2-week graft failure (AUC=0.9715,CI=0.9428-0.9993,*P*<0.0001) while model with log_2-scaled maximum AST during 0 to 14, log2-scaled maximum TB and log2-scaled maximum INR during 3 to 14 post-transplantation day, were related to 4-week graft failure (AUC=0.9669,CI=0.9476-0.9863, *P*<0.0001). The multivariable model showed 128.1% and 110.5% improvement in NRI compared to INR model for 2- and 4-week graft failure, respectively. Based on Youden's index method, predictive probability of 5.62% (sensitivity=92.1%,specificity=95.8%) and 6.69% (sensitivity=87.0%,specificity=95.2%) were cut-offs for within 2- and 4-week graft failure, respectively. Net benefit analysis showed that 72.7% and 76.9% were cut-offs with a net-zero benefit for 2- and 4-week graft failure, respectively.

Conclusions: Predicted probability of 5.62% and 6.69% calculated by our model can be considered as cut-offs where decision for re-transplantation shows highest advantages.

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Free Paper Session

O-001~O-005	Basic
O-006~O-011	HBV
O-012~O-017	HBV
O-018~O-022	HCV, COVID
O-023~O-028	NAFLD
O-029~O-034	Liver Cirrhosis
O-035~O-040	Alcoholic Liver Disease/Autoimmune Liver Disease/Drug and Toxic Injury/Genetic
O-041~O-045	Liver Cancer, Basic
O-046~O-050	Liver Cancer, Clinical
O-051~O-056	Liver Cancer, Clinical
O-057~O-061	Liver Cancer Surgery
O-062~O-069	Biliary and Pancreatic Disease
O-070~O-077	Surgery, Technical Issues
O-078~O-084	Liver Transplantation

1. Basic

O-01

MicroRNA-101-3p Is a Key Regulator In the Therapeutic Potential of Human Bone Marrow-Derived Mesenchymal Stem Cells on Liver Fibrosis

Jung Hoon Cha[1], Na Ri Park[1], Sung Woo Cho[1,3], Pil Soo Sung[1,4], Gi Jin Kim[5], Jong Young Choi[1,3], Seung Kew Yoon[1,3,4], Si Hyun Bae[1,2,3*]

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Aims: Although the therapeutic mechanisms of bone marrow-derived mesenchymal stem cells (BM-MSC) are still unclear, BM-MSCs play key therapeutic roles in liver fibrosis. Furthermore, microRNAs (miRNAs) are regulators in hepatic differentiation and liver fibrosis. miR-101-3p is upregulated during hepatic trans-differentiation, whereas miR-101-3p is downregulated in a stage of liver fibrosis. The purpose of this study is to investigate miR-101-3p's roles in the hepatic differentiation of human BM-MSC (hBM-MSCs) and in hepatic stellate cell (HSC) activation.

Methods: miRTarBase and miRDB were used to predict targets EZH2 of miR-101-3p selected by the next-generation sequencing. hBM-MSC was treated with miR-101-3p mimic, inhibitor, or EZH2 siRNA during the hepatic differentiation. hHSC LX2 was treated with TGF-ß1, and with or without miR mimic and siRNA. BM-MSCs and PRL-1(+) BM-MSCs were injected into the tail vein in the BDL rat model. The role of miR-101-3p was identified through the change of liver-specific genes, EMT markers, and fibrosis genes using the quantitative real-time PCR and western blotting.

Results: miR-101-3p showed a higher expression level in PRL-1(+) BM-MSCs transplantation group than the BDL group and in differentiated hepatocyte-like cells than hBM-MSC but lower expression level in liver fibrosis than the normal liver. miR-101-3p caused the increase in the liver-specific genes in hBM-MSC, while mesenchymal markers, fibrosis markers, and apoptosis inhibitor genes decreased in LX2. At this time, the expression of EZH2 has decreased and the same result as miR-101-3p overexpression was obtained by knockdown of EZH2. As a result, miR-101-3p mimic promoted the hepatic differentiation of hBM-MSC and inhibited the TGF-ß1 mediated LX2 activation via regulating EZH2.

Conclusions: In this study, we identified miR-101-3p that can regulate the hepatic differentiation of hBM-MSC and the hepatic fibrosis. Our results demonstrate that miR-101-3p may be a biomarker, monitoring the response to therapeutic effect by BM-MSC in liver fibrosis.

Keywords: Human bone marrow-derived mesenchymal stem cells (hBM-MSCs), Hepatic differentiation, Next-generation sequencing (NGS), microRNAs (miRNAs), Fibrosis

O-02

Therapeutic Effect Of KS-356, A Novel Small Compound Targeting CD147, on Mice with NAFLD through Modulating the Inflammatory Crosstalk between Liver and Visceral Adipose Tissue: An 18F-FDG PET/CT Study

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Aims: Inflamed and dysregulated visceral adipose tissue (VAT) secretes pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) thereby promoting systemic inflammation and insulin resistance which further lead to exacerbate the progression of nonalcoholic fatty liver disease (NAFLD). CD147 has been known to play key roles in mediating the inflammatory activation of macrophages through the activation of matrix metalloproteinase-9 (MMP-9). We identified that a novel drug KS-356 could bind to CD147 and inhibit its subsequent MMP-9 activation. Here, we investigated the suppressive effects of a novel drug KS-356 on NAFLD and inflamed VAT using high-fat induced mouse model and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET/CT), which is a well-known non-invasive imaging modality for measurement of inflammatory activity, especially M1 macrophage.

Methods: NAFLD was induced by a high-fat diet (HFD) (60% fat) for 20 weeks using the C57BL/6 mice. KS-356 (50 mg/kg) was orally given daily for 20 weeks. Both insulin tolerance- and glucose-tolerance were performed to assess the status of insulin-resistance and glucose-intolerance. Before sacrifice, blood serum was acquired to analysis of C-reactive protein (CRP) levels and ^{18}F-FDG PET/CT was taken. After sacrifice, histomolecular analysis was performed on harvested liver and VAT.

Results: KS-356 significantly improved insulin sensitivity with glucose homeostasis and reduced the progression of NAFLD. Furthermore, KS-356 also ameliorated VAT inflammation and its related systemic inflammation. There was no significant difference of daily food intake between HFD and HFD with KS-356 group.

Conclusions: Owing to its beneficial effect across the liv-

er-VAT-metabolic continuum, KS-356 could be a potential therapeutic drug candidate for NAFLD and related metabolic disorder.

Keywords: NAFLD, Obesity, Visceral fat, Inflammation, Insulin resistance

O-03

Hepatoprotective Effects of 17β Estradiol on Glucose Transporter and Oxidative Stress in Aging Female Rat Liver

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Department of Biochemistry, F H Medical College & Hospital, India

Aims: Free radical production and oxidative stress are known to increase in liver during aging, and may contribute to the oxidative damage. These changes increase during menopausal condition in females when the level of estradiol is decreased. The objective of this study was to observe the changes in activities of membrane linked ATPases antioxidant enzymes, hepatic enzymes, lipid peroxidation levels and glucose transporters 2 (GLUT 2) expression occurring in livers of female rats of 3, 12 and 24 months age groups, and to see whether these changes are restored to 3 months control levels rats after exogenous administration of 17-ß-estradiol (E2).

Methods: The aged female rats (12 and 24 months old) (n= 8 for each group) were given subcutaneous injection of 17ß estradiol (0.1 µg/g body weight) daily for one month. Controls animals received an equal volume of vehicle. After 30 days of hormone treatment, experimental animals of all the groups were sacrificed and livers were isolated for further study. Biochemical parameters including serum transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] and alkaline phosphatase (ALP) in serum were analyzed. A detailed study was carried on membrane linked enzymes (Na^+ / K^+ ATPase, Ca^{2+} ATPase), antioxidant enzymes (superoxide dismutase, glutathione-S-transferase) and GLUT2 expression with immunohistochemistry to identify the antiaging role of E2 using biochemical, molecular and histochemical study.

Results: The results obtained in the present work revealed that normal aging was associated with significant decrease in the activities of membrane linked ATPases, antioxidant enzymes, GLUT 2 expression and an increase in lipid peroxidation and hepatic enzymes in livers of aging female rats. Our data showed that exogenous administration of E2 brought these changes to near normalcy in aging female rats.

Conclusions: The present study showed that E2 treatment reversed the changes to normal levels. E2 treatment may be beneficial in preventing some of the age related changes in the liver by increasing antioxidant defenses.

Keywords: Aging rat liver

O-04

Enhanced Liver Regeneration of the Secretome Released from ASCs by PGC-1α-Driven Upregulation of Mitochondrial Proliferation

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Aims: Peroxisome proliferator activated receptor λ coactivator 1a (PGC-1a) is a potent regulator of mitochondrial biogenesis and energy metabolism. In this study, we investigated the therapeutic potential of the secretome released from the adipose-derived stem cells (ASCs) transfected with PGC-1a (PGC-secretome).

Methods: We first generated PGC-1a-overexpressing ASCs by transfecting ASCs with the plasmids harboring the gene encoding PGC-1a. Secretory materials released from PGC-1a-overexpressing ASCs were collected and their therapeutic potential was determined using *in vitro* (thioacetamide [TAA]-treated AML12 cells) and *in vivo* (70% partial hepatectomized mice) models of liver injury.

Results: In the TAA-treated AML12 cells, the PGC-secretome significantly increased cell viability, promoted expression of proliferation-related markers, such as PCNA and p-STAT, and significantly reduced the levels of ROS. In the mice, PGC-secretome injections significantly increased both liver tissue expression of proliferation-related markers than did normal secretome injections ($P<0.05$). We demonstrated that the PGC-secretome does not only have higher antioxidant and anti-inflammatory properties, but also has a potential of significantly enhancing liver regeneration in both *in vivo* and *in vitro* models of liver injury.

Conclusions: Reinforcing the mitochondrial antioxidant potential by transfecting ASCs with PGC-1a could be one of the effective strategies to enhance the therapeutic potential of ASCs.

O-05

Effect of Overexpressed PRL-1 in Placenta-Derived Mesenchymal Stem Cells on Lipid Metabolism in a TAA-injured Rat Model

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Aims: In our previous report, alterative expression of CPT1A by placenta-derived mesenchymal stem cells (PD-MSCs) is involved in lipid metabolism in a rat model with bile-duct ligation (BDL). Phosphatase regenerating liver-1 (PRL-1) has known to be regeneration factor in the liver. However, there are no reports the PRL-1 is involved in lipid metabolism. Therefore, the purpose of this study is to demonstrate the effect of overexpressed PRL-1 in PD-MSCs (PD-MSC^{PRL-1}) and analyze the factors related to ROS, hepatic function and fibrosis, and lipid metabolism in TAA-injured rat model.

Methods: TAA-injured model (300 mg/kg/twice a week) was administrated by intraperitoneal (IP) injection for 12 weeks. At 8 weeks, PD-MSCs and PD-MSCPRL-1 ($2x10^6$) were transplanted by intravenous (IV) injection. Their therapeutic effects were analyzed by blood analysis, qRT-PCR, western blot, and histological staining.

Results: The blood analysis including ALT, AST, bilirubin, IL-6, TNF-α, total cholesterol, and LDL was significantly decreased in PD-MSC^{PRL-1} group compared to non-transplanted group (NTx), while the albumin level was increased (P<0.05). Also, the ROS level by mitosox staining was dramatically decreased in PD-MSC^{PRL-1} group and the expression of peroxiredoxin-1, known as inhibitor of ROS, was significantly increased in PD-MSC^{PRL-1} group versus other groups (P<0.05). Furthermore, the mRNA expressions of adipogenic factors (e.g., PPAR γ , adiponectin, FABP4, adipsin, and LPL) were significantly decreased in PD-MSC^{PRL-1} group compared to other groups (P<0.05).

Conclusions: PD-MSC^{PRL-1} decreased activated ROS level by TAA administration and inhibited the adipogenesis in a rat model with BDL. Therefore, PD-MSC^{PRL-1} could be used as a therapeutic source and it is helpful to understanding therapeutic mechanism in a chronic hepatic disease.

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Keywords: Phosphatase regenerating liver-1

2. HBV

O-06

A Cross Sectional Study of Knowledge, Attitude and Practice towards Hepatitis B and C among Adolescents in Chitwan, Nepal

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Aims: Adolescence age is a period of challenges and opportunities for understanding oneself within social context. Adolescents are more exposed to infectious diseases, like hepatitis B and C. Knowledge of hepatitis B and C has been reported to be low among respondents in different studies. We conducted cross-sectional study among adolescents of Chitwan, Nepal to ascertain their knowledge, Attitude, and practices regarding hepatitis B and C.

Methods: A self-administered questionnaire consisting of questions to assess the knowledge, attitude and practices regarding hepatitis B and C infection, was duly filled by 150 adolescents. The data were entered and analyzed using Statistical Package for Social Sciences (SPSS) software version 25.

Results: Of the total 150 respondents, 63.3% were males. Only 65.3% of adolescents had knowledge on causative agent, 62.0% and 65.3% have knowledge on prevention from vaccination. Minority, had knowledge about transmission through unsterilized needle, mother to child during pregnancy and through blood and blood product I.e. 30.7%, 38.7% and 62% respectively. Only 17.3% respondent that, case can remain asymptomatic .More than 50% of adolescent had proper knowledge about Hepatitis B and C could be prevented by proper disposal of needle and sharp instruments, can be prevented by avoiding multi sexual partnership. Likewise, 54.7%, 62.0% adolescent respond that Hepatitis B can be severe and fatal, and can persist in body lifelong. Most of the adolescents reported they do not used globes while handling different body fluids and did not proper disposal of needle and sharps. Of total, 25.3% had history of needle stick injury but only 8.7% reported for the injury. Of total, 22.7% adolescents had been ever screened for hepatitis B or hepatitis C; 38% of the total had ask for new needle during piercing/tattooing. Of total, only 15.3% asked barber for new blade, 25.3% asked for new syringe to medical staffs, 23.3% ask dentist for sterilized instrument. Likewise, majority 90% and 80% respectively had used other used tooth brush/ razor, earrings and nail clippers.

Conclusions: : Most of the adolescents were not aware about the hepatitis B and C. Attitude and Practice on mode of transmission and preventive measures were lacking.

Keywords: Hepatitis, Practice, Knowledge, Adolescents

O-07

Genotype and Serotype Analysis on Potential Hepatitis B Virus as a Candidate Sequence for Hepatitis B Vaccine in Web-Based Bioinformatics

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Aims: Currently there are 10 types of hepatitis B virus geno-

types, from A to J, and 4 types of serotypes namely adw, adr, ayw, and ayr. This study aims to determine the genotype and serotype of the hepatitis B virus that has potential as a hepatitis B vaccine candidate. One effective method at present is bioinformatics, a multidisciplinary web-based biological science that can explore various sequences and see phylogeny.

Methods: The first stage is the collection and selection of nucleotide DNA sequences or hepatitis B virus amino acids. All data on nucleotide DNA sequences and hepatitis B virus amino acids with the target genotype and serotype are accessed and collected from Genbank. Next, a kinship tree is made. This kinship tree is designed with multiple alignments, phylogeny, and tree viewers using phylogeny.fr.

Results: The data obtained shows that there are 43 sequences with the same subtype, Adw, but the genotype and distribution of the spread of the hepatitis B virus are different. Genotype A originates from Somalia (Africa), and the Philippines (Asia), genotype B originates from Indonesia and China. Genotype C explains that genotype C is found around South Asia and East Asia, genotype H obtained information from America and Mexico, and genotype I originates from China.

Conclusions: Sequence data that can be candidates for hepatitis B vaccine design are hepatitis B virus genotype B with subgenotype B3, genotype C with subgenotype C6 for the scope of Indonesia, while for the scope of the world obtained the potential of the Adw serotype.

Keywords: Genotype, Serotype, HBV, Candidate Sequence

O-08

Persistence of Intrahepatic HBV DNA Integration in Patients Developing Hepatocellular Carcinoma after HBsAg Seroclearance

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Aims: The role of hepatitis B virus (HBV) integration into the host genome in hepatocarcinogenesis following HBsAg seroclearance remains unknown. The aim of our study was to investigate and characterize HBV integration events in patients with chronic hepatitis B (CHB) who developed hepatocellular carcinoma (HCC) after HBsAg seroclearance.

Methods: Using probe-based HBV capturing followed by next generation sequencing technology, HBV integration was examined in 11 samples (eight HCC tumors and three non-tumor tissues) from 8 chronic carriers who developed HCC after HBsAg loss. Genomic locations and patterns of HBV integration were investigated.

Results: HBV integration was observed in seven (87.5%) patients and 9 (81.8%) of 11 tested samples. HBV integration breakpoints were detected in all of the non-tumor (3/3, 100%) and six of the eight (75.0%) tumor samples, with an average number of breakpoints of 4.00 and 2.75, respectively. Despite the lower total number of tumoral integration breakpoints, the tumor samples harbored more genic integrations than the non-tumor samples, with preferential targets of cancer-associated genes. In contrast, intergenic integration was more frequent in non-tumor than in tumor tissues. The integration of viral subgenomes corresponding to Pre/S and X genes was found more often in the tumor versus the non-tumor samples. The integrated HBV subgenomic fragments were verified by Sanger sequencing.

Conclusions: The biological functions of HBV integration are almost comparable between HBsAg-positive and HBsAg-seroclearred HCCs, with continuing pro-oncogenic effects of HBV integration. Thus, ongoing HCC surveillance and clinical management should continue even after HBsAg seroclearance in patients with CHB.

Keywords: Hepatitis B virus, Virus integration, Liver cancer, HBsAg seroclearance

O-09

A Novel Mathematical Model Precisely Predict HBsAg Kinetics during Antiviral Therapy in HBeAg-Positive Chronic Hepatitis B

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Aims: The kinetics of serum hepatitis B surface antigen (HBsAg) during nucleos(t)ide analog (NA) treatment might provide clues for the prediction of off-treatment durability of response in patients with chronic hepatitis B (CHB). The aim was to develop a novel method of mathematical modeling for HBsAg kinetics under long-term NA treatment.

Methods: We reviewed viral decay patterns and HBsAg kinetics in 114 HBeAg-positive CHB patients from a tertiary hospital in Korea who were treated with entecavir or tenofovir as their initial NAs, without evidence of antiviral resistance. Of these, 74 patients with ≥8 valid HBV DNA and HBsAg titers were included in the analysis. HBsAg and immune effectors were incorporated in the model equations for viral dynamics as additional compartments. Parameter estimation was performed using the non-linear least square minimization method and non-linear Kalman filter algorithm.

Results: Modeling for HBsAg kinetics was successful in 70 out of 74 patients (94.6%). Mean age was 50 years, and 39 patients (55.7%) were male. Patients received either entecavir (47, 67.1%) or tenofovir (23, 32.9%). Median follow-up duration was 91.5 months. Baseline alanine aminotransferase (ALT) was 97.5 IU/L (interquartile range [IQR], 52.3–196.3). Baseline liver stiffness by transient elastography was 6.1 kPa (IQR, 4.3–11.3).

Baseline HBV DNA and HBsAg titers were 7.32 Log_{10}IU/mL (IQR, 6.24–7.94) and 2697.68 IU/mL (IQR, 1432.87 – 6333.67), respectively. The model equations for viral and HBsAg dynamics during antiviral treatment were developed as follows, considering i) both cytolytic and non-cytolytic clearance of infected cells, and ii) cccDNA and integrated HBV DNA in the host genome as dual sources of HBsAg:

$dT_1/dt = S_{T1} - d_{T1}*T_1 - (1-\eta)\, b*V*T_1$

$dT_2/dt = S_{T2} - d_{T2}*T_2 - (1-\eta)\, b*f_b*V*T_2 + a*f_a*I*E$

$dI/dt = (1-\eta)\, b*V(T_1 + f_2*T_2) + m_1*I - d_I*I - a*I*E$

$dV/dt = (1-e)p*d_I*I - c*V$

$dE/dt = S_E + b_E*I*E/(I+k_E) - d_E*E$

$sAg = \gamma*T_2 + (d+\gamma)*I$

(NOTE. T, target cell; I, infected cells; V, virus; E, immune effectors; sAg, HBsAg; d, death rate; η, treatment efficacy of inhibiting de novo infection; b, de novo infection rate of T; f, calibration coefficient of a for T; m, mitotic production rate of I; a, E-induced clearance rate of I; e, treatment efficacy of inhibiting viral production; p, viral production rate by I; c, clearance rate of free virions; S, production rate of T_1, T_2, and E; b_E, maximum birth rate for E; k_E, Michaelis-Menten type coefficient for E; γ, sAg production rate; d, additional factor for infected cells in HBsAg production rate)

Patients with HBeAg loss during NA treatment had significantly higher HBV DNA levels at baseline (7.51 vs. 7.32 Log_{10}IU/mL, *P*=0.035) than those without HBeAg loss. Parameter estimation showed that d value was significantly lower in patients with HBeAg loss had than in those without (0.537 vs. 1.166, *P*=0.043).

Conclusions: Our novel mathematical model for hepatitis B viral dynamics showed precisely predicted HBsAg kinetics during long-term NA treatment. Outcome prediction including HBeAg loss needs prospective validation.

Keywords: Hepatitis B, HBsAg, Mathematical modeling, Parameter estimation

O-10

Development of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B according to Cirrhotic Findings Evaluated by Ultrasonography and Transient Elastography

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Aims: In patients with chronic hepatitis B (CHB), cirrhosis evaluated by ultrasonography (US) or transient elastography (TE) is considered to be the main risk factor for hepatocellular carcinoma (HCC), and in fact, various HCC prediction models include cirrhosis assessed by these two methods as a constituent variable. This study investigated largely whether the cirrhosis evaluated by TE or US predicts HCC.

Methods: Between April 2006 and December 2018, a total of 9479 patients with CHB in two tertiary care centers were enrolled. Cirrhosis evaluated by TE was defined as ≥13kPa, and the index date was set to the date of initial TE. Patients were divided four groups as follows: US(+)TE(+) [cirrhosis defined by US and FS]; US(+)TE(-) [cirrhosis defined by US, but not by FS]; US(-)FS(+) [cirrhosis defined by TE, but not by US]; US(-)FS(-) no cirrhosis defined by US or FS]

Results: Mean age was 47.5 years, and male was predominant (n=5624, 59.3%). During follow-up (median 60.0 months), HCC was developed in 551 patients (5.8%). These four groups were well stratified to predict HCC (overall *P*<.001, log-rank test). HCC occurred most frequently in the US(+)TE(+) group, and least in the US(-)TE(-) group. HCC was developed more in FS(+)US(-) group than FS(-)US(+) group.

Conclusions: Cirrhosis assessed by both TE and US can be used as a major indicator to predict HCC in patients with CHB, and TE can better predict HCC than US when cirrhotic findings measured by TE and US do not match.

Keywords: Hepatocellular carcinoma, Transient elastography, Ultrasonography, Chronic hepatitis B

O-11

Association of Aspirin with Hepatocellular Carcinoma in Patients with Chronic Hepatitis B with or without Cirrhosis

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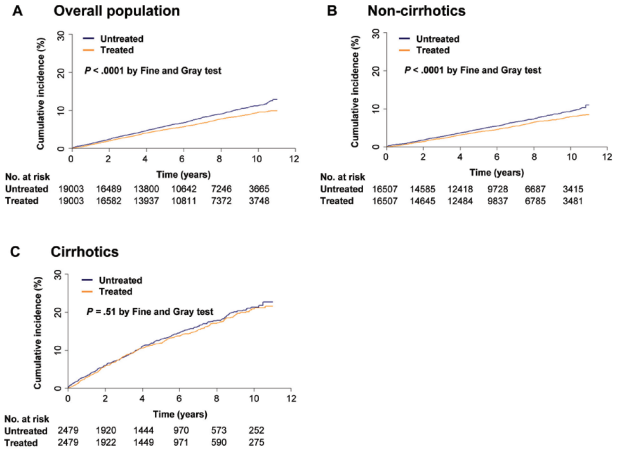
Aims: Aspirin therapy has been shown to be associated with reduced risk of developing hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). We aimed to investigate the association between aspirin use and HCC risk in CHB patients with or without cirrhosis.

Methods: We identified 329,635 adult patients with CHB who underwent health examinations from 2007 through 2017, using the Korean National Health Insurance Service database. Patients who received aspirin for 90 or more consecutive days (n=20,200) and patients who never received antiplatelet therapy (n=309,435) were identified. We generated propensity score-matched cohort to balance baseline characteristics between aspirin users and nonusers. The risk of HCC development was estimated, accounting for death as a competing

event.

Results: In overall population, propensity score matching analysis generated 19,003 pairs with a median follow-up period of 6.7 years. The cumulative HCC incidence among aspirin users was significantly lower than that among nonusers of aspirin (P<0.0001; panel A). Aspirin use showed a significant association with lower risk of HCC (adjusted hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.78–0.92; P<0.0001). Among patients without cirrhosis (16,507 pairs), aspirin users had significantly lower cumulative incidence of HCC (P<0.0001; panel B) and adjusted HR of 0.87 for HCC (95% CI, 0.79–0.95; P=0.002) compared to aspirin nonusers. However, among patients with cirrhosis (2,479 pairs), the cumulative HCC incidence did not differ significantly between aspirin users and nonusers (P=0.51; panel C) and the association between aspirin therapy and HCC risk was not evident (adjusted HR, 1.0; 95% CI, 0.85–1.18; P=0.99). Cirrhosis had a significant effect on the association between use of aspirin and HCC risk (P<0.0001 for interaction).



Conclusions: In this Korean nationwide cohort study of patients with CHB, aspirin therapy was associated with reduced risk of HCC. Cirrhosis had a substantial effect on this association.

Keywords: Hepatocellular Carcinoma, Chronic Hepatitis B, Cirrhosis, Aspirin

3. HBV

O-12

Switching from Tenofovir Disoproxil Fumarate (TDF) to Tenofovir Alafenamide (TAF) in Virally Suppressed Chronic Hepatitis B (CHB) Patients with Moderate or Severe Renal Impairment, or in End-Stage Renal Disease (ESRD) Patients on Hemodialysis (HD): Week 2

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Aims: TAF, a novel tenofovir prodrug, has demonstrated noninferior efficacy to TDF with superior bone and renal safety in virally suppressed CHB patients with eGFR (by Cockcroft-Gault; $eGFR_{CG}$) ³50 mL/min when switched from TDF. The efficacy and safety of virally suppressed patients on TDF with renal impairment who were switched to TAF were evaluated in this Phase 2 study.

Methods: CHB patients with renal impairment taking TDF for ³48 weeks and virally suppressed for ³6 months with HBV DNA <20 IU/mL at screening were enrolled into 2 cohorts: 1) moderate-severe renal impairment ($eGFR_{CG}$ 15 to <60mL/min) and 2) ESRD ($eGFR_{CG}$ <15 mL/min) patients on chronic HD. All patients were switched to TAF 25 mg QD for 96 weeks. Co-primary endpoints were proportion with HBV DNA <20 IU/mL and graded adverse events (AEs)/lab abnormalities at Week 24.

Results: 93 patients (Mod-severe impairment 78; ESRD 15) were enrolled from 26 sites in 8 countries. Median age was 65 years, 74% male, 77% Asian, 83% HBeAg-negative, up to 60% had low BMD at hip and/or spine, and 60% and 24% had a history of HTN and/or diabetes, respectively. Key efficacy/safety results at Week 24 are summarized in the Table. All patients on treatment at Week 24 maintained HBV DNA <20 IU/mL and a high proportion had normal ALT levels. Relative to baseline levels, switching to TAF from TDF resulted in increases in hip/spine BMD, decreases in bone turnover markers, as well as increases in $eGFR_{CG}$ and decreases in renal tubular markers. TAF was well tolerated with few having Grade 3 or 4 AEs (8%) and no discontinuations due to AEs.

Conclusions: In renally-impaired CHB patients, including ESRD patients on HD, viral suppression was well maintained and the bone and renal safety were improved 24 weeks after switching

from TDF to TAF.

Table. Efficacy and safety results at Week 24 in virally suppressed CHB patients with moderate or severe renal impairment or ESRD on HD when switched to TAF from TDF

n/N (%) or median (Q1, Q3)	Moderate-Severe RI[a]	ESRD on HD[b]
	n=78	n=15
Efficacy		
HBV DNA <20 IU/mL	76/78 (97)[c]	15/15 (100)
ALT normal (2018 AASLD criteria)	68/78 (87)	14/15 (93)
ALT normalization (2018 AASLD criteria)	2/5 (40)	NA[d]
HBsAg loss	0/78 (0)	0/15 (0)
HBeAg loss	0/13 (0)	0/3 (0)
qHBsAg, log_{10} change (IU/mL)	-0.02 (-0.08, 0.02)	-0.04 (-0.12, -0.01)
Bone parameters		
Hip BMD, % change	+0.48 (-0.96, 1.34)	+0.46 (-0.92, 1.60)
Spine BMD, % change	+1.29 (-0.50, 2.84)	+1.34 (-1.25, 2.34)
CTX, % change, (ng/mL)[d]	-14.8 (-29.3, 4.3)	-0.7 (-25.7, 27.5)
P1NP, % change, (ng/mL)[e]	-11.9 (-20.1, 6.9)	-22.4 (-39.1, 22.6)
Renal parameters		
Serum creatinine, mg/dL	0 (-0.08, 0.14)	-
Serum phosphorus, mg/dL	+0.1 (-0.2, 0.4)	+0.4 (-0.6, 2.4)
$eGFR_{CG}$, mL/min	+0.6 (-3.6, 3.6)	-
RBP/Cr, % change, µg/g[f]	-44.5 (-66.5, 3.9)	NA
β2MG/Cr, % change, µg/g[g]	-40.2 (-76.9, 41.4)	NA

HBV DNA, HBeAg loss, and ALT assessments are all missing equals failure
[a]Moderate-severe renal impairment: $eGFR_{CG}$ 15 - <60 mL/min
[b]ESRD: $eGFR_{CG}$ < 15 mL/min on hemodialysis
[c]Two patients discontinued study drug early (withdrew consent) with last available HBV DNA <20 IU/mL
[d]All ALT values were <ULN at baseline
[e]Serum C-type collagen sequence (bone resorption marker); [f]Serum procollagen type 1 N-terminal propeptide (bone formation marker)
[g]Urine retinol binding protein/creatinine (tubular marker); [h]Urine beta-2 microglobulin/creatinine (tubular marker).
Abbreviations: $eGFR_{CG}$, estimated creatinine clearance (Cockcroft-Gault method); ESRD, end-stage renal disease; BMD, bone mineral density by DXA scan); NA, not applicable

Keywords: TAF, ESRD, CHB, HD

O-13

Switching from Tenofovir Disoproxil Fumarate (TDF) or Other Oral Antiviral Therapy (OAV) to Tenofovir Alafenamide (TAF) in Virally Suppressed CHB Patients with Hepatic Impairment

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Aims: TAF, a novel tenofovir (TFV) prodrug, has greater plasma stability, more targeted delivery of TFV to hepatocytes, and reduced circulating levels of TFV compared to TDF. We evaluated efficacy and safety when virally suppressed CHB (Chronic Hepatitis B) patients with hepatic impairment were switched to TAF.

Methods: In this Phase 2 study (NCT03180619) CHB patients with a ChildTurcottePugh (CTP) score of ³7 and £12 at screening (or past history of CTP ³7 and any score £12 at screening) who were taking TDF and/or other OAVs for ³48 weeks, with HBV DNA <LLOQ for ³24 weeks and <20 IU/mL at screening were eligible. All patients were switched to TAF 25 mg QD and treated for 96 weeks. The co-primary endpoints were proportion with HBV DNA <20 IU/mL and graded adverse events (AEs)/lab abnormalities at Week 24.

Results: 31 patients were enrolled at 18 sites in 7 countries. At baseline, 19 (61%), 9 (29%) and 3 (10%) were CTP Class A, B, or C, respectively. Median age was 57 y (19% ³65 y), 68% male, 81% Asian, 90% HBeAg-negative, median fibrotest score 0.81, and median $eGFR_{CG}$ 98 mL/min; up to 48% had low BMD at hip and/or spine, and 68% had prior TDF exposure. Key efficacy/safety results at Week 24 are summarized in the Table. All patients had HBV DNA <20 IU/mL and a high proportion had normal ALT. Switching to TAF resulted in increases in hip/spine BMD, decreases in bone turnover markers, an increase in $eGFR_{CG}$ with decreases in tubular markers. TAF was well tolerated with few having Grade 3 or 4 AEs (2 patients) and no discontinuations for and AE.

Table. Efficacy and Safety Results at Week 24

n/N (%), or median (Q1, Q3)	TAF (N=31)
Efficacy	
HBV DNA <20 IU/mL[a]	31 (100)
ALT normal (2018 AASLD criteria)[b,c]	25 (81)
ALT normalization (2018 AASLD criteria)[d]	6/10 (60)
HBeAg loss[e]	0/3
HBsAg loss	0/30
qHBsAg, log_{10} change (IU/mL)	-0.02 (-0.10, 0.02)
Bone safety	

Hip BMD, % change	+0.64 (-0.844, 1.511)
Spine BMD, % change	+1.53 (-0.180, 3.091)
CTX, % change (ng/mL)[f]	-12.8 (-26, 22.4)
P1NP, % change (ng/mL)[g]	-11.9 (-19.8, 33.01)
Renal safety	
sCr, mg/dL	0.0 (-0.08, 0.04)
PO_4, mg/dL	0.0 (-0.2, 0.2)
$eGFR_{CG,}$ mL/min	+3.0 (-4.2, 10.2)
RBP/Cr, % change[h]	-10.9 (-38.1, 51.2)
β2MG/Cr, % change[i]	-21.3 (-57.8, 34.9)

[a]HBV DNA results are missing=failure. [b]ALT normal is the proportion with ALT ≤ULN at Week 48, regardless of baseline ALT level; [c]ULN 35 U/L males, 25 U/L females; [d]Patients with ALT >ULN at baseline; [e]HBeAg-positive at baseline. [f]Serum C-type collagen sequence (bone resorption marker); [g]Serum procollagen type 1 N-terminal propeptide (bone formation marker); [h]Urine retinol binding protein/creatinine (tubular marker); [i]Urine beta-2 microglobulin/creatinine (tubular marker).
BMD, bone mineral density by DXA scan; sCr, serum creatinine; PO_4, serum phosphorus; $eGFR_{CG}$, estimated creatinine clearance (Cockcroft-Gault method)

Conclusions: In CHB patients with hepatic impairment switched to TAF from TDF or other OAVs, viral suppression was well maintained and improved bone and renal safety was seen at Week 24.

Keywords: TAF, Hepatic impairment, CHB, Vemlidy

O-14

48-Week Safety and Efficacy of Switching to Tenofovir Alafenamide (TAF) from Tenofovir Disoproxil Fumarate (TDF) in Asian Patients with TDF Risk Factors (RF)

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Aims: In a recent Phase 3 study (Study 4018) in HBV patients suppressed on TDF treatment, switching to TAF demonstrated noninferior efficacy to continued TDF with superior bone and renal safety at Week 48. This study aims assess the safety and efficacy of switching to TAF from TDF in patients of Asian descent with risk factors for TDF toxicity as per current EASL and AASLD guidelines.

Methods: Virally suppressed patients (HBV DNA <20 IU/mL at screening) on TDF were randomized (1:1) to switch to TAF or continue TDF for 48 weeks in a double-blind fashion. Viral suppression and changes in bone (BMD by DXA) and renal (creatinine clearance [$eGFR_{CG}$]) parameters were assessed over 48 weeks.

Results: Among the 400 Asian patients enrolled, 288 (72%) had at least 1 TDF RF. At Week 48, similar proportions with ≥1 RF had HBV-DNA <20IU/mL (TAF 97%; TDF 97%) and normal ALT by 2018 AASLD criteria (TAF 76%; TDF 73%). TAF subjects with ≥1 RF had increases in $eGFR_{CG}$ compared to decreases on TDF [median (Q1, Q3) change; TAF: +2.6 (-2.01, 7.34); TDF: -2.7 (-7.56, +15.79); P<0.0001)]. Among patients with ≥1 RF, improvements were seen in BMD for TAF vs. continued declines in TDF patients at both spine (P<0.0001) and hip (P<0.0001).

Conclusions: Virally suppressed Asian patients with CHB and risk factors for TDF who switched to TAF showed improved bone and renal safety while efficacy was well-maintained.

Keywords: TAF, CHB, Switching, Vemlidy

O-15

Impact of Treatment with Tenofovir Alafenamide (TAF) or Tenofovir Disoproxil Fumarate (TDF) on Hepatocellular Carcinoma (HCC) Incidence in Patients with Chronic Hepatitis B (CHB)

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Aims: Potent antiviral treatment can reduce HCC incidence in CHB patients. TAF has shown antiviral efficacy similar to TDF, with higher rates of ALT normalization and no resistance in Phase 3 studies. We evaluated the impact of TAF or TDF on HCC in the ongoing Phase 3 studies.

Methods: HBeAg-positive (n=1039) and –negative (n=593) patients with HBV DNA≥20,000 IU/mL and ALT >60 U/L (males) or >38 U/L (females) were recruited from 190 sites in 20 countries and randomized (2:1) to TAF or TDF. HCC was assessed at 6-monthly intervals by hepatic ultrasonography introduced after Week 96 and throughout by local standards of care. The standardized incidence ratio (SIR) for HCC was calculated for observed cases relative to predicted risk using the REACH-B model.

Results: Through 5 years of follow-up, HCC occurred in 21 patients (1.0% [11/1,093] with TAF, 1.9% [10/539] with TDF). Median (Q1, Q3) time to HCC onset was 104 (55, 191) weeks. At baseline, relative to those without HCC, patients with HCC were more likely to be older (median age 53 vs 39y; *P*<0.001), male (90% vs 65%; *P*=0.014), and cirrhotic (FibroTest ³0.75; 33% vs 9%; *P*<0.001). The overall SIR was significantly reduced with TAF or TDF (SIR 0.42, 95% CI 0.27-0.64). HCC incidence was significantly reduced in noncirrhotic patients (SIR 0.37, 95% CI 0.22 to 0.63), and in patients receiving TAF (SIR 0.35, 95% CI 0.19-0.62). Lack of ALT normalization at Week 24 (HR 6.90; *P*=0.011), cirrhosis (HR 4.18; *P*=0.006), baseline HBsAg level (HR 0.53; *P*=0.006), and baseline hypertension (HR 5.55; *P*<0.001) were significant predictors of HCC development by multivariable analysis.

Conclusions: In CHB patients receiving TAF or TDF, the incidence of HCC was reduced comparing with expected HCC incidence from REACH-B model. In patients treated with TAF, a significant reduction in SIR was seen, whereas those treated with TDF showed a trend toward a reduction.

Keywords: TAF, HCC, Vemlidy, Liver cancer

O-16

Treatment with Nucleos(t)ide Analogues from HBeAg-Positive Hepatitis Phase is Associated with Lower Risk of Hepatocellular Carcinoma Development than from HBeAg-Negative Hepatitis Phase: A Multicenter Study Involving 10,390 Patients

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Aims: Recent studies indicate that the integration of hepatitis B virus (HBV) into host genome, which may directly develop hepatocellular carcinoma (HCC), occurs during HBV e antigen (HBeAg)-positive phase of chronic hepatitis B (CHB). However, it remains still unclear that an early antiviral treatment from HBeAg-positive hepatitis phase can reduce the risk of HCC more profoundly than antivirals from HBeAg-negative hepatitis. This study aimed to investigate the association between HBeAg-positivity and HCC risk in CHB patients who achieved viral suppression using nucleos(t)ide analogues (NAs).

Methods: We performed a multicenter study involving 10,390 CHB patients who achieved viral suppression (HBV DNA <2,000 IU/mL) using tenofovir or entecavir from 6 hospitals in Korea from January 2008 to December 2018. The primary endpoint was development of HCC. Death or liver transplantation before HCC development were considered as competing risk events. Index date was set at the first time of viral suppression in each patient. We draw Kaplan-Meier (KM) curves before and after balancing baseline characteristics by inverse probability of treatment weighting (IPTW) according to HBeAg status. Cox regression analyses were performed to find independent predictors of HCC. Analyses were performed in the entire study population, as well as in the two subgroups stratified by the presence of liver cirrhosis (LC).

Results: Of the 10,390 patients (median age, 50.9 years; male, 53.7%), 5,094 were HBeAg-positive and 5,296 were HBeAg-negative. During 4.8 years of median follow-up, 1,040 patients (10%) developed HCC: 423 (8.3%) were HBeAg-positive and 617 (11.7%) were HBeAg-negative (modified log-rank test *P*<0.001; Figure 1A). After adjusting baseline characteristics such as age and presence of LC using IPTW analysis, however, HBeAg status was not associated with HCC risk (modified log-rank test *P*=0.93; Figure 1A). In the non-LC subgroup (n=5,957), HBeAg-positive patients showed a lower rate of HCC development than HBeAg-negative patients before and after IPTW adjustment (both modified log-rank *P*<0.001; Figure 1B). In the LC subgroup (n=4,433), however, HBeAg-positive patients showed a higher rate of HCC development than HBeAg-negative patients before and after IPTW adjustment (modified log-rank *P*=0.004 for unadjusted KM curves; modified log-rank *P*=0.009 for adjusted KM curves; Figure 1C). In a multivariable

analysis of the entire population, HBeAg-positivity was not an independent predictor of HCC (adjusted hazard ratio [aHR], 0.95; 95% confidence interval [CI], 0.84–1.08; *P*=0.50) after adjusting variables such as age and presence of LC. In the non-LC subgroup, however, HBeAg-positivity was associated with a significantly lower risk of HCC (aHR, 0.54; 95% CI, 0.42–0.70; *P*<0.001). In contrast, in the LC subgroup, HBeAg-positivity was associated with a higher risk of HCC (aHR, 1.20; 95% CI, 1.04–1.39; *P*=0.02).

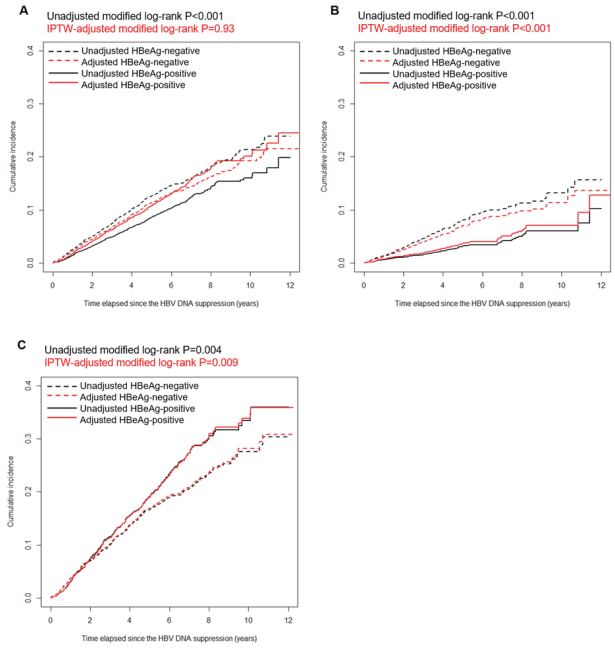

Figure 1. IPTW-adjusted and unadjusted Kaplan-Meier curves of hepatocellular carcinoma development adjusting competing risk of death or liver transplantation in the entire population (A), in the subgroup of patients without liver cirrhosis (B), and in the subgroup of patients with liver cirrhosis (C). IPTW, inverse probability of treatment weighting (IPTW).

Conclusions: HBeAg status was not an independent predictor of HCC development in the overall CHB patients. In non-cirrhotic CHB patients, however, an earlier treatment with NAs from HBeAg-positive hepatitis phase is associated with a lower risk of HCC occurrence than from HBeAg-negative hepatitis phase. This result supports that an earlier antiviral treatment from HBeAg-positive CHB patients without LC might reduce the risk of HCC more profoundly.

Keywords: Liver cancer, Hepatitis B virus, DNA, Cumulative incidence

O-17

Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients Receiving Entecavir or Tenofovir Treatment Showing Maintained Virological Response

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Aims: Observational studies suggested tenofovir may have favorable efficacy for the prevention of (HCC) development compared to entecavir. However, mechanism of both drugs is suppression of hepatitis B virus (HBV) replication and whether class effect exist despite same mechanism of action remains controversial, and data from randomized controlled trial are lacking. As a results, whether change in therapy is required for those who shows good virological response to entecavir treatment in order to further reduce HCC risk remains unknown.

Methods: A retrospective cohort of 1,336 treatment-naïve chronic HBV mono-infected adults patients without malignancy or organ transplantation at baseline who started entecavir or tenofovir treatment between June 2012 to December 2015, and showed maintained virological response during follow-up were analyzed. Primary outcome was comparison of entecavir and tenofovir on incident HCC during follow-up.

Results: During a median 4.4 years of follow-up (range: 1.0-7.4 years) after achieving virological response, 99 patients developed HCC. The 5-years cumulative HCC incidence rate was 7.3% and 6.3% for entecavir and tenofovir group, with similar risk of HCC between two groups (adjusted hazard ratio: 0.82; 95% confidence interval 0.52 to 1.28; *P*=0.39). The risk of HCC was similar in in propensity score-matched cohort (entecavir = 570; tenfovir =570; hazard ratio 1.02; 95% confidence interval 0.68 to 1.52; *P*=0.94). In subgroup analysis, HCC risk was similar between two drugs in both patients with and without cirrhosis.

Conclusions: In patients who showed good virological response, we observed no difference in the risk of HCC between two drugs. This observation suggest class effect may not exist and imply entecavir is equally effective as tenofovir for the prevention of HCC among those with good virological response.

Keywords: Entecavir, Tenofovir, Risk of HCC, Chronic hepatitis B

4. HCV, COVID

O-18

Clinical Characteristics and Treatment Outcome in Patients with HIV/HCV Coinfection in Korea

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Aims: Because of very low incidence of HIV/HCV coinfection in Korea, little is known about HIV/HCV coinfected patients in Korea. The aim of this study was to investigate the clinical characteristics and treatment outcome in these patients.
Methods: We performed a retrospective cohort study of all HCV monoinfected and HIV/HCV coinfected patients treated with antiviral agents between January 2009 and March 2020.
Results: We enrolled 235 patients with HCV monoinfection and 23 with HIV/HCV coinfection. Patients with HIV/HCV coinfection were younger (HCV vs HIV/HCV: 56.8±11.6 years vs 40.7±10.1 years, *P*<0.001) and had a higher proportion of men (HCV vs HIV/HCV: 54.0% (127/235) vs 91.3% (21/23), *P*<0.001) than those with HCV monoinfection. Patients with HCV monoinfection had more genotype 1b and 2 (HCV vs HIV/HCV: 94.9% (223/235) vs 60.9% (14/23), *P*<0.001), whereas genotype 1a and 3 was more frequent in those with HIV/HCV coinfection (HCV vs HIV/HCV: 4.7% (11/235) vs 39.1% (9/23), *P*<0.001). FIB-4 level was significantly lower in the patients with HIV/HCV coinfection than those with HCV monoinfection (HCV vs HIV/HCV: 3.70±3.32 vs 1.68±1.10, *P*<0.001). Rates of sustained viral response after 24 weeks (SVR24) in patients treated with pegylated interferon based therapy showed a tendency to be higher in the HCV monoinfection group (67.6% (75/111)) than the HIV/HCV coinfection group (50.0% (7/14)) but did not differ significantly (*P*=0.192). SVR12 in patients treated with direct acting agents (DAA) did not differ significantly between both group (HCV vs HIV/HCV: 95.2% (99/104) vs 90.9% (10/11), *P*=0.461).
Conclusions: In Korea, patients with HIV/HCV coinfection who received antiviral treatment were younger, more male, and had less advanced fibrosis than those with HCV monoinfection. HIV/HCV coinfected patients showed excellent SVR for DAA treatment, as did HCV monoinfected patients.
Keywords: Hepatitis C virus, Human immunodeficiency virus, Coinfection, Clinical Characteristics

O-19

Sofosbuvir/Ledipasvir in the Treatment of Chronic Hepatitis C – A Subgroup Analysis from A Nationwide Real-World HCV Registry Program (TACR) in Taiwan

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Aims: TASL HCV Registry (TACR) is a nationwide registry program organized and supervised by Taiwan Association for the Study of the Liver (TASL), which aims to setup the database and biobank of patients with chronic hepatitis C (CHC) in Taiwan. The present study aimed to evaluate the treatment outcome of sofosbuvir (SOF)/ledipasvir (LDV) in Taiwanese CHC patients in TACR.
Methods: By May 2020, 19 tertiary hospitals, 23 community hospitals and one primary care clinic join the TACR program. The baseline characteristics, prior liver and non-liver related medical history, DAA regimens, laboratory results, treatment course and outcome were recorded. The primary objective was sustained virological response, defined as undetectable HCV RNA 3 months after end-of-treatment (SVR12).
Results: A total of 4742 SOF/LDV± ribavirin treated CHC patients with available SVR12 data from 39 sites were enrolled in the current analysis. The mean age was 61.3 years, and female accounted for 54.8% of the population. The dominant viral genotypes were GT1b (52.6%) and GT2 (35.6%). 1354 (28.6%) patients had liver cirrhosis, including 156 (3.3%) with liver decompensation, 552 (11.6%) had preexisting hepatocellular carcinoma (HCC) before DAAs treatment and 413 (8.7%) had hepatitis B virus dual infections. The overall SVR12 rate was 98.5%, with 98.5%, 98.2%, 99.7% and 98.6% in treatment-naïve non-cirrhotics, treatment-naïve cirrhotics, treatment-experienced non-cirrhotics and treatment-experienced cirrhotics patients, respectively. While patients were stratified by HCV genotype, the SVR12 was 98.5%, 98.4% and 98.5% among those with GT1, GT2 and GT6 infection, respectively. The strongest factor independent associated with treatment failure was DAA adherence < 60% (odds ratio [OR]/95% confidence intervals [CI]: 125.4/25.7-612.4, *P*<0.0001), followed by

active HCC (OR/CI: 6.20/2.57-14.97, *P*<0.0001), HIV co-infection (OR/CI: 3.01/1.14-7.92, *P*=0.026), and male gender (OR/CI: 1.85/1.09-3.13, *P*=0.023). The eGFR decreased significantly at the end of treatment (EOT) (89.3 ml/min/1.73 m^2 vs. 93.2 ml/min/1.73m^2, *P*<0.001) and remained stable 3 months after EOT (89.3 ml/min/1.73m^2). However, the decreased eGFR was observed only in patients whose baseline eGFR $\geq$ 90 ml/min/1.73m^2. Instead, patients with chronic kidney diseases whose pretreatment eGFR < 60 ml/min/1.73 m^2 had improved eGFR after SOF/LDV.

Conclusions: SOF/LDV is highly effective in treating CHC patients in real-world setting of Taiwan. The satisfactory result could be explicitly generalized to patients with different viral genotypes and liver disease severities.

Keywords: HCV, DAA, REAL WORLD, SOFOSBUVIR/LEDIPASVIR

O-20

Safety and Efficacy Analysis of Direct Antiviral Agents in Patients with Chronic Hepatitis C and Chronic Kidney Diseases in Real Clinical Practice: Multicenter Cohort Study

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Aims: To evaluate the efficacy and safety of direct antiviral agents (DAAs) available in chronic kidney disease (CKD) patients with chronic hepatitis C (HCV) in Korea.

Methods: In a retrospective, multicenter study involving 8 medical institutions, 362 patients were enrolled from 2015 to 2019. The efficacy and safety of DAAs including glecaprevir/pibrentasvir, sofosubvir/ribavirin, ledipasvir/sofosbuvir, and daclatasvir/asunaprevir were analyzed for patients according to CKD stage. We evaluated sustained virologic response at week 12 after treatment (SVR12) as primary endpoint. The efficacy and adverse events were also evaluated according to CKD stage.

Results: Among 362 patients, 308 patients completed DAA treatment and follow-up period after end of treatment. The subjects comprised 87 patients (62 with CKD stage 3 and 25 with CKD stage 4-5), of whom 22 were undergoing hemodialysis. HCV patients with CKD stage 1 and 2 (eGFR>60) showed SVR12 of 98.1% and 95.5% respectively. SVR12 of CKD stage 3 and 4-5 (eGFR<60) patients was 91.9% and 88% respectively. All patients undergoing hemodialysis achieved SVR12 (90.9%). Treatment failure and cessation of DAAs was 2.7% (3/110) and 0% in stage 1, 2.6% (3/113) and 1.7% (2/113) in stage 2; 1.6% (1/62) and 6.4% (4/62) in stage 3 ; 4% (1/25) and 8% (2/25) in stage 4-5.

Conclusions: DAAs shows favorable SVR12 and safety with CKD patients (eGFR<60) with HCV compared with patients with eGFR>60. The efficacy and safety of DAAs may be related with duration of treatment and concomitant medications. Therefore, it is important to select adequate regimens of DAAs and to treat CKD patients with HCV properly.

Keywords: Direct antiviral agents, Chronic hepatitis C, Chronic kidney dieseases

O-21

Epidemiological and Clinical Characteristics of Hepatitis C Virus Infection among the People Who Have Ever Injected Drugs in South Korea: A Prospective Multicenter Cohort Study from 2007 to 2019

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Aims: Intravenous drug use is a major risk factor for hepatitis C virus (HCV) infection. The aim of this study is to investigate the epidemiological and clinical characteristics of HCV infection among people who inject drugs (PWID) in South Korea.

Methods: We used data from the Korea HCV cohort in which patients with hepatitis C were prospectively enrolled from 2007 to 2019 at seven tertiary centers, and clinical data and results of questionnaire surveys focused on lifetime risk factors related to HCV infection were comparatively analyzed based on the self-reported history of injection drug use.

Results: Among 2,971 patients with HCV infection (mean age 57.2, male 50.9%), 170 (6.7%) had experienced intravenous drug use (PWID group): They showed a younger age (50.4±8.4 vs. 57.9±13.3 years) and a higher proportion of male (81.8% vs 48.7%) than non-PWID group. There were several differences between PWID and non-PWID in terms of residence region and exposure rate of other risk factors related to HCV infection. The proportion of genotype 1 infection was significantly higher in PWID (66.5%) than non-PWID group (50.9%). Treatment rate was higher in PWID group in pre-direct antiviral agents (DAA) era in Korea (2007 to 2014), however, it was comparable in DAA era (2015 to 2019) than non-PWID group. The sustained virological response in PWID group were not different from that in non-PWID group.

Conclusions: PWID are a minority in the whole HCV infected

people in Korea until 2019. They have different epidemiological features from non-PWID group, however, treatment rates and outcomes are not different. Therefore, active screening and treatment should be offered to the PWID in Korea.

Keywords: Hepatitis C, Cohort, People who inject drugs, Treatment

O-22

Fibrosis-4 Index as Predictor of COVID-19 Mortality in Hospitalized Patients of the Daegu and Gyeongsangbuk-do Area, Korea

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Aims: This study was performed to evaluate risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) receiving respiratory support.

Methods: This retrospective multicenter cohort study was undertaken in the Daegu and Gyeongsangbuk-do area, South Korea. The clinical and laboratory features of patients with COVID-19 receiving respiratory support were analyzed to ascertain the risk factors for mortality.

Results: Of the1005 patients with a confirmed diagnosis of COVID-19, 289 (28.8%) received respiratory support and of these, 70 patients (24.2%) died. In multivariate analysis, high fibrosis-4 index (HR 2.784; 95% CI 1.691–4.585; *P*<0.001), low lymphocyte count (HR 0.480; 95% CI 0.271–0.852; *P*=0.012), diabetes (HR 1.917; 95% CI 1.181–3.111; *P*=0.009), and systemic inflammatory response syndrome (HR 1.714; 95% CI 1.048–2.802; *P*=0.032) were found to be independent risk factors for mortality in patients with COVID-19 receiving respiratory support. Regardless of respiratory support, fibrosis-4 index was found to be a robust predictive marker for mortality in patients with COVID-19 (*P*<0.001). A number of risk factors were also significantly related to survival in patients with COVID-19 regardless of respiratory support (*P*<0.001).

Conclusions: Fibrosis-4 index is a useful predictive marker for mortality in COVID-19 patients regardless of its severity.

Keywords: Coronavirus, COVID-19, Risk factors, Fibrosis, Mortality, Survival

5. NAFLD

O-23

Non-Alcoholic Fatty Liver Is Associated with Incidence of Dementia: A National Health Cohort Study in Korea

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Aims: Fatty liver disease and dementia are emerging health problems in many countries. Hepatic steatosis is a feature of abnormal fat metabolism in the body. Fat dysregulation in the brain might also increase risk for dementia. The aim of this study was to investigate whether hepatic steatosis is associated with development of dementia in the middle-aged population.

Methods: A nationwide population-based cohort study was conducted using customized data from the National Health Insurance Service of Korea. We identified subjects (40 to 69 years) who conducted two or more health examinations between 2004 and 2007, who were free of chronic viral hepatitis, alcoholic liver disease, cirrhosis, cancers, stroke, and dementia. Fatty liver was defined using hepatis steatosis index (HSI) > 36. Control was defined when all HSIs were less than 30 between 2004 and 2007. Dementia was identified using disease classification codes (F00, F01, F02, F03, G30, G31, or G32) and prescription data of an antidementia drug. Enrolled subjects (n=3,811,942) were observed until 2017 and incidence of dementia was evaluated according to fatty liver.

Results: Among the control group (all HSI < 30, n=651,481), dementia was identified in 37,182 persons (5.4%) during follow-up (2007 – 2017). Among subjects with all HSI > 36 (n=439,654), dementia was identified in 36,093 persons (7.59%, *P*<0.0001). After adjusting for sex, age, liver enzymes, body mass index, smoking status, diabetes, hypertension, cholesterol, and disability, the multivariate analysis showed non-alcoholic fatty liver (any HSI > 36) was significantly associated with incidence of dementia (adjusted HR 1.08; 95% CI 1.06–1.10). In subgroup analysis, dementia was not associated with improved fatty liver (initial HSI > 36, last HSI < 30), (adjusted HR 1.05; 95% CI 0.99–1.11). However, aggravated fatty liver (initial HSI < 30, last HSI > 36) was significantly associated with dementia (adjusted HR 1.10; 95% CI 1.03–1.17). Sustained fatty liver (all HSI > 36) was also associated with dementia (adjusted HR 1.03; 95% CI 1.01–1.16).

Conclusions: Non-alcoholic fatty liver is associated with development of dementia in middle-aged Korean population.

Keywords: Fatty liver, Dementia, Steatosis index

O-24

Relationship between Dynamics of Non-Invasive Assessment of Non-Alcoholic Fatty Liver Disease and Incident Diabetes Mellitus

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Aims: This study evaluated the association between the pattern of changes in NAFLD over time and the risk of incident DM.
Methods: A total of 3,047 subjects with no underlying DM were followed from 2001 until 2016 in the Anseong and Ansan cohorts. NAFLD status was determined by the hepatic steatosis index (HSI) biennially. Subjects were clustered into 7 groups according to pattern of HIS, BMI and HOMA-IR (Reference value [RV]: HSI ≥36, BMI ≥25 kg/m^2 and HOMA-IR ≥2.5, respectively); Group 1) all below RV (reference group) 2) All above RV, 3) above RV only once in the middle, 4) below RV only in the middle, 5) above RV at the beginning, but below RV in the last, 6) below RV at the beginning, but at the end exceeded RV, and 7) repeated below and above RV from the beginning to the end.
Results: In HSI groups, the risk of DM was higher in Group 2 (hazard ratio [HR] 2.710; 95% confidence interval [CI] 1.650–4.451; *P*<0.001), Group 3 (HR 1.559; 95% CI 1.053–2.308; *P*=0.027) and Group 7 (HR 2.062; 95% CI 1.384–3.073; *P*<0.001) compared to reference group. The pattern of change in BMI was not significantly correlated with the risk of DM. All groups of HOMA-IR except Group 5 showed a significantly higher risk of DM than reference group. Group 2 showed the highest risk (HR 8.998; 95% CI 5.111–15.842; *P*<0.001) followed by Group 6 (HR 5.118, 95% CI 3.664-7.574, *P*<0.001). Predicting ability for DM was powerful in the order of HOMA-IR, HSI, and BMI (Harrell' C = 0.6941, 0.6333 and 0.5913, respectively).
Conclusions: HSI, BMI and HOMA-IR values change dynamically during 14-year follow-up period. NAFLD is more useful in predicting incident DM rather than BMI considering changes over time.
Keywords: Non-alcoholic Fatty Liver Disease, Diabetes Mellitus

O-25

The Severity of Liver Fibrosis Predicts Poor Cardiovascular Outcomes in Patients with Type 2 Diabetes

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Aims: Cardiovascular disease (CVD) is the principal cause of death in patients with type 2 diabetes (T2D). We explored whether liver fibrosis predicted the risk of CVD in patients with T2D.
Methods: A total of 1,604 patients who had commenced oral anti-diabetic drugs to treat newly diagnosed T2D between 2006 and 2010 were recruited. The fibrotic burden was assessed using fibrosis-4 index (FIB-4) and non-alcoholic fatty liver disease fibrosis score (NFS). The predicted CVD risk was calculated using the 10-year Atherosclerotic cardiovascular disease risk prediction model from the 2013 ACC/AHA guideline.
Results: Non-alcoholic fatty liver disease was identified in 920 (57.4%) patients. During the follow-up period (median 80.1 [interquartile range 40.2-115.2] months), CVD developed in 199 (12.4%) patients. CVD occurred more frequently in older patients, and was associated with hypertension, metabolic syndrome, lower platelet counts, lower aspartate and alanine aminotransferase levels, lower total cholesterol levels, lower HbA1c levels, higher homeostatic model assessment of insulin resistance, higher FIB-4, higher NFS, and higher predicted CVD risk (all *P*<0.05). Of these, FIB-4 (hazard ratio [HR]=1.259), NFS (HR=1.390), and hypertension (HR=2.613) independently predicted the increased risk of CVD (all *P*<0.05). The cumulative incidence of CVD was significantly different among groups stratified by liver fibrotic burden (all *P*<0.05 by log-rank test). The 10-year observed and predicted CVD risk rates were significantly different among groups stratified by the CVD risk (all *P*<0.001), and increased significantly as the degree of liver fibrosis increased (all *P*<0.05).
Conclusions: The severity of liver fibrosis independently predicted CVD in patients with T2D. Thus, assessment of liver fibrosis might allow physicians to optimize the timing of appropriate preventative or diagnostic cardiovascular interventions in such patients.
Keywords: Type 2 diabetes, Cardiovascular disease, Liver fibrosis, Non-alcoholic fatty liver disease

O-26

MR-Based Non-Alcoholic Steato Hepatitis (MASH) Score in Patients with Non-Alcoholic Fatty Liver Disease

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Aims: As prevalence of NAFLD accounts for up to 30% of the general population worldwide, non-invasive evaluation of disease severity of NAFLD and non-invasive diagnosis of NASH are important issues. The objective of this prospective cross-sectional study was to develop a diagnostic scoring system that

could improve the accuracy of NASH diagnosis by combining multiparametric MR and clinical indicators.

Methods: This study included 130 patients who were diagnosed NAFLD by liver biopsy from October 2016 to July 2019. All patients were examined for medical history, laboratory tests, and multiparametric MR consisting of MRI proton density fat fraction, MR spectroscopy, T1 mapping, and MR elastography (MRE). Scoring model was developed using logistic regression. Internal validation was performed using bootstrapping.

Results: NASH patients were older (59 years vs. 46 years, *P*<0.001) and had lower BMI (28.23 kg/m^2 vs. 31.19 kg/m^2, *P*=0.032) than nonalcoholic fatty liver (NAFL) patients. NASH group showed higher prevalence of diabetes/impaired fasting glucose, hypertension, and dyslipidemia. Four categorical variables and 19 continuous variables were evaluated for NASH diagnostic model. Diabetes/IFG and hypertension among categorical variables and age, BMI, hemoglobin, platelet count, T1 mapping, and MRE among continuous variables met the criterion of P-value ≤ 0.1. Variable interactions were identified between BMI and hemoglobin, between platelet count and diabetes/IFG, and between platelet count and MRE. Finally, equation for MR-based NASH (MASH) score was obtained using four demographic factors, two laboratory variables, and two MRI parameters (Figure 1). MASH score showed satisfactory accuracy for NASH diagnosis (C-statistics: 0.892; 95% CI: 0.834-0.950; *P*<0.001). When MASH score of 0.73 was set as a cut-off for NASH diagnosis, its sensitivity was 0.67 and its specificity was 0.90 (PPV = 0.89, 47/53). When MASH score of 0.37 was set as a cut-off for NASH exclusion, its sensitivity was 0.90 and its specificity was 0.78 (NPV = 0.87, 47/54). Only 17% (22/130) of patients were located in the gray zone (Table 1). Internal validation using 1000 bootstrapping also showed satisfactory accuracy for NASH diagnosis (C-statistics: 0.909; 95% CI: 0.855-0.964; *P*<0.001).

MASH score = -17.655 + 0.01*(Age, years) + 0.576*(BMI, kg/m^2) + 5.003*(Diabetes/IFG, no=0, yes=1) + 0.439*(Hypertension, no=0, yes=1) + 1.406*(Hemoglobin, g/dL) - 0.044*(platelet count, 10^3/μL) - 1.238*(MRE, kPa) + 0.008*(T1 mapping, ms) - 0.056*(BMI)*(Hemoglobin, g/dL) - 0.023*(Diabetes/IFG, no=0, yes=1)*(platelet count, 10^3/μL) + 0.013*(platelet count, 10^3/μL)*(MRE, kPa)

Figure 1. Equation for the MASH score.

Table 1. Diagnostic performance of MASH score for NASH diagnosis

	Exclusion cut-off	Gray zone	Diagnostic cut-off
MASH score	≤0.37	0.37< MASH score< 0.73	≥0.73
Number of patients	55 (42%)	22 (17%)	53 (41%)
Number of non-NASH patients	54		77
Number of NASH patients	76		53
Sensitivity	0.90		0.67
Specificity	0.78		0.90
PPV	0.83		0.89
NPV	0.87		0.70

Conclusions: MASH score is a novel non-invasive biomarker for the diagnosis of NASH in patients with NAFLD. Further external validation is required for its clinical application.

Keywords: NASH, MRI, Score

O-27

Sequential Combination of FIB-4 Followed by M2BPGi Enhanced Diagnostic Performance for Advanced Hepatic Fibrosis in an Average Risk Population

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Aims: The fibrosis-4 (FIB-4) index is the most widely used estimated formula to screen for advanced hepatic fibrosis; however, it has a considerable intermediate zone. Here, we propose an algorithm to reduce the intermediate zone and improve the diagnostic performance of screening for advanced liver fibrosis by incorporating Mac-2-binding protein glycan isomer (M2BPGi) into a FIB-4 based screening strategy in an average risk group.

Methods: Four-hundred eighty-eight healthy and chronic liver disease subjects were analyzed using a 1:1 propensity score matched for age and sex. Advanced liver fibrosis (≥F3) was defined by magnetic resonance elastography (MRE, ≥3.6 kPa). Classification tree analysis was employed to improve diagnostic performance using a combination of the FIB-4 index and M2BPGi.

Results: The median serum M2BPGi levels of healthy subjects, patients without advanced fibrosis, and those with the condition were 0.48, 0.94, and 2.93, respectively. The area under the receiver operating characteristic (AUROC) curve of M2BPGi (0.918) for advanced fibrosis was the highest compared to those of the FIB-4 index (0.887), APRI (0.873), and AST/ALT ratio (0.794). When M2BPGi was incorporated following the FIB-4 index, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 87.1%, 82.5%, 54.0%, and 96.4%, respectively Moreover, 74.3% (133/179) of cases in the intermediate zone of the FIB-4 index avoided unnecessary referrals.

Conclusions: Two-step pathway (FIB-4 followed by M2BPGi) could reduce unnecessary referrals and/or liver biopsies in an average-risk population.

Keywords: Mac-2-binding protein, Cirrhosis, Magnetic resonance elastography

O-28

Machine Learning Model to Predict Risk of Cardiovascular Disease among Non-Alcoholic Fatty Liver Disease Patients: Results from Two Nationwide Long-Term Follow Up Studies

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Aims: There have been emerging evidences on increased cardiovascular disease (CVD) risk among non-alcoholic fatty liver (NAFLD) patients. Improved method to risk-stratify and predict CVD risk among NAFLD patients is a significant unmet need in clinical field. The aim of this study was to develop and externally validate a machine learning (ML) model to predict 7 year- risk of CVD among NAFLD patients using nationally representative long-term follow up studies in Korea.

Methods: We used data from the Korean health examinee (HEXA) study (baseline: 2004-2013, follow up: 2012-2017, n= 173290), and CAVAS study ((baseline: 2005-2011, follow up: 2007-2016, n=28337) to develop, and externally validate ML prediction model, respectively. After exclusion of participants with excessive alcohol ingestion, baseline CVD history, and no data on CVD in follow up study, total of 24539 NAFLD patients from HEXA study, and 9563 NAFLD patients from CAVAS study who were free of CVD at baseline were finally enrolled. NAFLD was defined by Hepatic Steatosis Index over 36, and CVD included myocardial infarction and cerebrovascular attack history. For training and test sets for ML algorithm, 5- fold cross validation was done using HEXA study data. ML algorithms included support vector machine, random forest, artificial neural network, XGBoost, and ensemble methods. Area under receive operating curves (AUROC) of each methods were compared using 5- fold cross validated HEXA data and externally validated CAVAS data.

Results: During follow up period, incidental 491 cases of CVD cases from HEXA study (306918 person-years of follow up), and 199 cases of CVD cases from CAVAS study (72678 person-year of follow up) occurred. Among ML models, Ensemble methods showed best function with statistical significance (P<0.001). ML model of Ensemble method for prediction of 7-year risk of CVD risk among NAFLD patients from 5- fold cross validation of HEXA study data yielded AUC of 0.86 (95% confidence interval (CI):0.80-0.90) using lifestyle factors (diet, physical activity, smoking and alcohol), anthropometric indices, laboratory data, presence of liver fibrosis, and medical history. Externally validated using CAVAS study, ML model of Ensemble method for prediction of CVD risk among NAFLD patients yielded AUCs of 0.81 (95% CI:0.79-0.85).

Conclusions: ML based prediction model for CVD risk among NAFLD patients could be used to identify at risk CVD among NAFLD patients and enable physicians to close follow up based on patient level estimation through ML algorithm.

Keywords: Machine learning, Prediction, Non-alcoholic fatty liver disease, Cardiovascular disease

6. Liver Cirrhosis

O-29

Changing Trends of Cirrhosis in South Korea from 2008 to 2017 : Alcohol Became the Most Important Etiology

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Aims: Chronic hepatitis B has occupied the largest portion for liver cirrhosis in South Korea but clinical implications have been changing since introduction of antiviral agents and nationwide vaccination for hepatitis B virus. On the other hands, alcoholic liver cirrhosis is still not well controlled and has shown increasing trends. We aimed to investigate the change in etiology and severity of cirrhotic patients in Korea.

Methods: Ten years (2008-2017) of 16,888 medical records from 9,768 cirrhotic patients in six tertiary hospitals in South Korea were retrospectively reviewed.

Results: The most common etiologies were hepatitis B and alcohol with decreasing tendency in hepatitis B (Exp(B)=0.975, P<0.001) and increasing tendency in alcohol (Exp(B)=1.013, P=0.003). Cirrhosis due to non-alcoholic steatohepatitis, autoimmune hepatitis, primary biliary cholangitis and primary sclerosing cholangitis showed increase during 10 year period (P<0.001). Although proportions of patients with treatment increased from 45.7% to 61.1% (P<0.001), Child-Pugh score and prevalence of decompensation showed no change during 10 years. Among complications, incidence of varix bleeding, severe ascites and hepatic encephalopathy and spontaneous bacterial peritonitis reduced significantly from 12.3% to 7.7%, 7.8% to 4.1%, 1.0% to 0.5% and 1.9% to 1.1%, respectively (P<0.01). In sub-group analysis, patients group with hepatitis B showed improving Child-Pugh score (B=-0.025, P<0.001) and decreasing rates of decompensated liver cirrhosis (Exp(B)=0.977, P=0.016), however patients group with alcohol showed larger portions of Child-Pugh C (Exp(B)=1.031, P=0.005) and higher MELD score (B=0.081, P=0.005) during 10 year period.

Conclusions: Etiology of liver cirrhosis is changing with decrease in hepatitis B while increase in alcohol. With effort of vaccination and anti-viral agents, hepatitis B group is showing improved results, however alcohol group is still presenting dis-

mal liver functions and outcomes. Future national policies and systematic approaches to enhance the course of alcoholic hepatitis is indispensable.

Keywords: Liver Cirrhosis, Epidemiology, Mortality, Decompensation

O-30

The Prediction of Liver Decompensation Using Hepatic Collagen Deposition Assessed by Computer-Assisted Image Analysis with Masson-Trichrome Stain

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Aims: METAVIR staging classifies structural deformation caused by hepatic fibrosis semi-quantitatively. However, there could be disagreement of fibrosis staging by METAVIR among pathologists. Quantification of fibrosis using computer-assisted image analysis can offer relative objective information for liver fibrosis. We measured hepatic fibrosis quantitatively using collagen proportionate area (CPA) and assessed its impact on predicting the development of liver decompensation (which was defined as the presence of ascites, variceal bleeding and hepatic encephalopathy).

Methods: During January 2010 to June 2018, we assessed 582 patients who got liver biopsy and computer assisted image analysis (ZEN 2.3 lite software by ZEISS) were available. Clinical and laboratory data were collected at baseline and at the time of the last follow-up or progression to liver decompensation (LD). Forty-two patients with acute hepatitis who had no underlying chronic liver disease were excluded.

Results: The mean age was 45.3±13.7 years, and most common etiology of liver disease was chronic hepatitis B (28.6%) and followed by fatty liver disease (26.9%). Median follow-up duration was 37 months during which 28 out of 540 patients experienced LD. Mean analyzed dimension of collagen was 5653362±2423925 μm^2 and included portal tract was 8.9±3.9. Mean CPA was 8.91±7.10%. A positive correlation between CPA and liver fibrosis stage was observed (r=0.553, *P*<0.001) (Figure 1). Albumin at baseline (HR: 0.257, 95% CI: 0.094-0.701, *P*=0.008), CPA (HR: 1.107 per 1% increase, 95% CI: 1.059-1.157, *P*<0.001), presence of diabetes mellitus (HR: 4.315, 95% CI: 1.063-17.510, *P*=0.041), and presence of alcoholic hepatitis (reference : chronic hepatitis B) (HR : 5.811, CI : 1.351-24.987, *P*=0.018) were independent predictors of liver decompensation on multivariate Cox-regression analysis. The concordance indices of CPA and METAVIR stage for progression to LD were 0.803±0.044 and 0.758±0.041, respectively, without significant difference. When dividing patients with calculating cut-point with maximally selected rank difference, higher CPA (≥16.6%) predicts LD better than lower CPA (Log-rank test: *P*<0.001) (Figure 2).

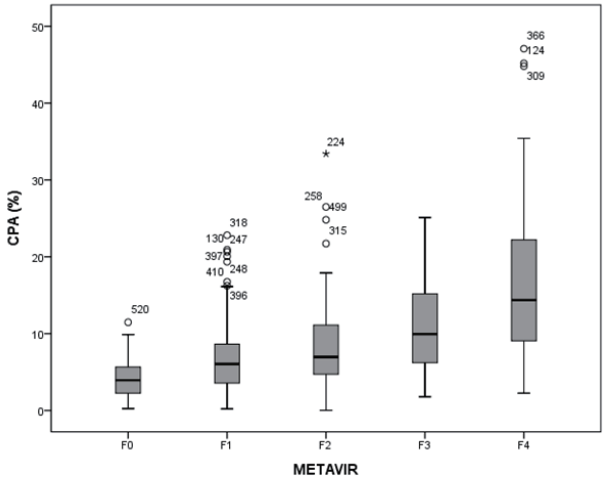

Figure 1. Correlation between fibrosis stage and CPA

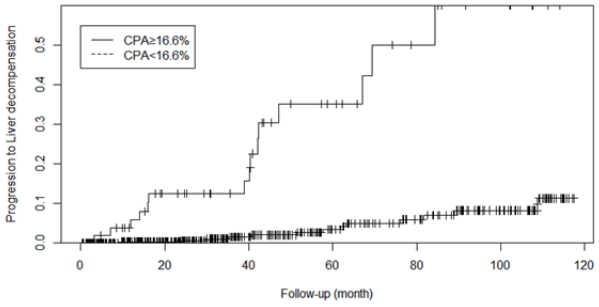

Figure 2. Kaplan Meier curve for predicting liver decompensation

Conclusions: The CPA correlates very well with the METAVIR stage of liver fibrosis and also is an independent predictor of clinical outcomes in liver disease. It is expected to be useful quantitative determination of liver fibrosis and prognosis.

Keywords: Trichrome, CPA, Collagen proportionate area, Liver fibrosis

O-31

Longitudinal Outcomes of Application of Non-Selective Beta-Blockers in Portal Hypertension with Real-Life Multicenter Data

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Aims: This study investigated the effect of non-selective ß-blockers (NSBB) in real-life situations and whether low-dose NSBB is beneficial compared to maximally tolerated doses.
Methods: Study participant of 890 were divided into two groups: primary prophylaxis (PP) and secondary prophylaxis (SP); 595 in the PP group (NSBB = 370, non-NSBB = 225) and 291 in the SP group (NSBB = 217, non-NSBB = 74). The NSBB group was sub-divided into 2 groups: low-dose (≤ 80 mg) and high-dose (>80 mg). Hepatic venous pressure gradient (HVPG) measurement was performed before NSBB treatment in the majority of patients (n=803).
Results: In the PP group, 272 patients received NSBB only, while 98 patients received NSBB plus endoscopic band ligation (EBL) (low-dose NSBB, n=170; high-dose NSBB, n=200). The NSBB group showed similar survival rates to the non-NSBB group. However, NSBB was partially effective for patients who had clinically significant portal hypertension (CSPH, HVPG ≥10 mmHg: hazard ratio [HR], 0.63; *P*=0.02) or CTP class B/C (HR, 0.59; *P*=0.01). The low-dose NSBB had significant reductions in the risk of mortality compared with the non-NSBB (HVPG ≥10 mmHg: HR, 0.55; *P*=0.02 and CTP class B/C: HR, 0.52; *P*=0.01), but effect size was weaker in the high-dose NSBB. In the SP group, 217 received NSBB plus EBL (low-dose NSBB, n=87; high-dose NSBB, n=130). NSBB prolonged survival regardless of the severity of portal hypertension (adjusted HR, 0.56; *P*<0.001). The low-dose NSBB had a greater benefit with a 58% risk reduction in mortality compared to a 39% risk reduction in mortality in the high-dose NSBB.
Conclusions: NSBB therapy was partially associated with longer survival in patients of the PP group with CSPH. In the SP group, NSBB therapy improved survival, and relatively low-dose NSBB had a greater benefit than standard-titrated high-dose NSBB.
Keywords: Nonselective ß-blockers, Liver cirrhosis, Survival

O-32

H6C Score as a Novel Prognostic Model in Cirrhotic Patients with Low Model for End-Stage Liver Disease (MELD) Scores

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Aims: We aimed to derive a model to discriminate cirrhotic patients with poor prognosis even if the Model for End Stage Liver Disease (MELD) score is low.
Methods: This study enrolled 700 cirrhotic patients with MELD score of less than 20 who underwent hepatic vein pressure gradient (HVPG) measurement. A novel model using HVPG to predict overall survival was derived and specified as the H6C score. Internal and external validations were conducted with the derivation and validation cohorts.
Results: The H6C score using the HVPG and Child-Pugh scores was developed on the basis of a multivariate Cox regression analysis. The H6C score showed great predictive power for overall survival with a time-dependent AUC of 0.733, which was superior to that of a MELD of 0.602. In patients with viral etiology, the performance of the H6C score was much improved with a time-dependent AUC of 0.850 and was consistently superior to that of the MELD (0.748). Patients with an H6C score below 45 demonstrated an excellent overall survival with a 5-year survival rate of 91.5%. Whereas patients with an H6C score above 64 showed a dismal prognosis with a 5-year survival rate of 51.1%. The performance of the H6C score was further verified to be excellent in the validation cohort.
Conclusions: This new model using the HVPG provides better predictive power than the MELD in cirrhotic patients, especially with viral etiology. In patients with H6C above 64, it would be wise to consider early liver transplantation in order to positively impact long-term survival, even when these patients have a low MELD score.
Keywords: H6C score, HVPG, Prognostic model, Liver cirrhosis

O-33

Does Non-Invasive Assessment of Portal Hypertension Using Magnetic Resonance Elastography Predict Clinically Relevant Changes in the Hepatic Venous Pressure Gradient?

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Aims: Hepatic venous pressure gradient (HVPG) measurement is a validated method, which accurately evaluates changes in portal hypertension (PH). Magnetic resonance elastography (MRE) is a well-established method for liver fibrosis staging. We investigated the correlation between MRE-assessed stiffness of the

liver and spleen and HVPG values. Furthermore, we evaluated whether MRE values reflected changes in PH after the administration of ß-blockers.

Methods: From January 2018 to September 2019, we enrolled 37 consecutive patients with cirrhosis requiring prophylactic treatment of esophageal varices according to the Baveno VI criteria were prospectively included. At enrollment, patients were initiated on carvedilol starting at a dose of 6.25 mg/day, which was up-titrated to 12.5 mg/day. Patients underwent HVPG measurement and multifrequency MRE at baseline and 6 weeks.

Results: The median HVPG and MELD score of the patients was 15.0 mmHg (Interquartile range [IQR], 11.5–20.5) and 11.4 (IQR, 8.5–13.9), respectively. Median baseline values of MRE-assessed liver and spleen stiffness were 5.92 kPa (IQR, 4.89–7.10) and 8.38 kPa (IQR, 7.38–9.43), respectively. Multiple linear regression analysis revealed a significant correlation between HVPG and MRE-assessed liver stiffness (γ =0.485, *P*=0.004), but not MRE-assessed spleen stiffness (γ =-0.065, *P*=0.708). Median 6-week changes in MRE-assessed liver stiffness (Δliver), spleen stiffness (Δspleen) and HVPG (ΔHVPG) were -0.4 kPa, -0.13 kPa, and -1.5 mmHg, respectively. Overall, neither MRE-assessed Δliver (γ =0.311, *P*=0.170) nor MRE-assessed Δspleen (γ =-0.135, *P*=0.559) was correlated with ΔHVPG. However, using the categorized stage of HVPG, MRE-assessed Δliver significantly correlated with ΔHVPG in patients with low-HVPG ≤16 mmHg (γ =0.575, *P*=0.040), though not in patients with high-HVPG >16 mmHg (γ =-0.048, *P*=0.909).

Conclusions: MR parameters related to liver stiffness provide excellent accuracy for diagnosing PH, and reflect changes in HVPG following administration of ß blockers for less severe PH.

Keywords: Portal hypertension, Magnetic resonance elastography, Hepatic venous pressure gradient

O-34

Real-World Efficacy of M2BPGi on Diagnosing Liver Fibrosis in Chronic Hepatitis Patients

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Aims: Mac-2 binding protein glycosylation isomer (M2BPGi) is a novel non-invasive marker for liver fibrosis, but still needs more validation. We aimed to compare the diagnostic efficacy of M2BPGi with transient elastography (TE), FIB-4, and APRI.

Methods: This retrospective study included chronic hepatitis patients who underwent M2BPGi and TE for evaluation of liver fibrosis.

Results: A total of 302 patients were included: non alcoholic fatty liver disease 135 (44.7%), fatty liver 76 (25.2%), alcoholic hepatitis 61 (20.2%). M2BPGi levels were well correlated with TE levels (r=0.715). Clinically significant liver cirrhosis (LC) was observed in 37 (12.3%) patients. Using cut-off 1.0 and 3.0 the AUROC of M2BPGi for predicting clinical liver cirrhosis was 0.839, which was comparable with TE, FIB-4 and APRI, 0.921, 0.918 and 0.818, respectively. The sensitivity and specificity for predicting clinical LC were 97.3% and 86.8% for TE alone, however positive predictive value (PPV) was only 50.7%. Adding TE with M2BPGi increased the PPV to 80.8%.

Conclusions: A novel fibrosis marker M2BPGi well correlates with TE and other non-invasive markers, and M2BPGi can improve the diagnostic probability of TE.

Keywords: Liver fibrosis, Chronic hepatitis, Non-invasive marker, M2BPGi

7. Alcoholic Liver Disease/Autoimmune Liver Disease/Drug and Toxic Injury/Genetic

O-35

Microbiome Restoration after Rifaximin Treatment in Patients with Severe Alcoholic Hepatitis

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Aims: Severe alcoholic hepatitis (SAH) is the most aggressive form of alcohol-related liver disease with high mortality. The gut microbiome is an emerging therapeutic target in alcohol-related liver disease. We aimed to investigate the fecal microbiome composition in patients with SAH and determine microbiome recovery after rifaximin treatment in gut bacteria (BTs) and bacteria derived-extracellular vesicles (EVs).

Methods: A total of 24 patients with SAH and 24 healthy controls were prospectively enrolled. Additional fecal samples were collected after 4 weeks in 8 patients with SAH who received the rifaximin treatment. Metagenomic profiling was assessed using 16S ribosomal RNA amplicon sequencing.

Results: Fecal microbiomes of patients with SAH had lower a-diversity and higher ß-diversity than those of healthy controls in both BT and EV. Metagenomic profiling demonstrated Ba-

cilli, Lactobacillales, and Veillonella were significantly increased in BT of patients with SAH and Veillonella, Veillonella parvula group, and Lactobacillales were significantly increased in EV of patients with SAH. Eubacterium_g23, Oscillibacter, and Clostridiales decreased in BT of patients with SAH and Eubacterium_g23, Oscillibacter, and Christensenellaceae decreased in EV of patients with SAH. After rifaximin treatment, 17 taxa in BT and 23 taxa in EV were significantly restored in patients with SAH. In common, Veillonella and Veillonella parvula group increased in patients with SAH and decreased after rifaximin treatment, and Prevotella and Prevotellaceae decreased in patients with SAH and increased after rifaximin treatment.

Conclusions: In an analysis of fecal microbiomes of patients with SAH, we demonstrated SAH related dysbiosis and improvement after rifaximin. These taxa are likely to be a candidate for the therapeutic target for the treatment of SAH.

Keywords: Microbiome, Severe alcoholic hepatitis, Rifaximin, Extracellular vesicle

O-36

Intrahepatic Infiltration of Activated CD8+ T Cells and Macrophages Is Associated with the Severity of Liver Injury in Drug-Induced Liver Injury: Implications in Steroid Therapy

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Aims: Drug-induced liver injury (DILI) is caused by the interplay between drugs, their metabolites and host immune response. The aim of this study is to investigate the phenotypes of the infiltrating immune cells in DILI and the role of steroid treatment in DILI.

Methods: From January 2017 to February 2020, 41 consecutive patients with DILI who underwent liver biopsy were enrolled prospectively in this study. Diagnosis of DILI was based on patient medication history after exclusion of the other etiologies. Liver biopsy was performed, and immunohistochemical stain and multicolor fluorescence-activated cell sorting (FACS) analysis were done with the biopsy specimen. Experienced pathologist confirmed the pathologic and immunohistochemical findings.

Results: Median RUCAM score was 9 (5-14). Patients with positive for anti-nuclear antibody, smooth muscle antibody, and liver-kidney microsomal antibody were 28 (70%), 3 (7.5%), and 0, respectively. The number of intrahepatic T cells (CD3+ cells) showed positive correlation with serum levels of total bilirubin, AST, ALT, and model for end-stage liver disease (MELD) score (r=0.353, 0.353, 0.381, and 0.352, respectively, $P<0.05$). The number of intrahepatic macrophages (CD68+ cells), also showed positive correlation with serum levels of total bilirubin, AST, ALT, and MELD score (r=0.441, 0.508, 0.505, and 0.404, respectively, $P<0.05$). The frequency of activated CD8+ T cells (CD38+HLA-DR+) among the liver-infiltrating CD8+ T cells in DILI livers, was significantly higher than that in healthy livers ($P<0.01$). Importantly, the percentage of CD38+HLA-DR+ cells among intrahepatic CD8+ T cells in DILI livers showed positive correlation with ALT (r=0.593, $P=0.04$). Thirty patients (73.2%) were treated with steroid. Among them, 22 patients (78.6%) showed more than 50% of reduction of ALT level after 1 week of steroid treatment and 2 patients progressed to hepatic failure, but recovered after steroid treatment.

Conclusions: In conclusion, we found the positive correlation between the number of intrahepatic macrophages, T cells, CD8+ T cells and activated CD8+ T cells infiltrations and the degree of liver injury in patients with DILI. We suggest that T cells and macrophage play critical roles in DILI. Therefore, steroid can be a treatment option for patient with DILI. This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (2020R1A2C3011569). This study was also supported by the Research Fund from Eunpyeong St. Mary's Hospital.

Keywords: Drug induced liver injury, T cell, Macrophage, Steroid

O-37

Incidence and Pattern of Liver Injury during Anti-Hypertensive Therapy with Angiotensin-II Receptor Blockers in Korean Patients

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Aims: Angiotensin type II receptor blockers (ARB) is one of the most used drugs, but there were several reports about the concern of fimasartan-induced liver injury in Korea. This study was conducted to assess the likelihood of hepatic impairment and to elucidate the pattern of ARB-induced liver injury in Korean patients.

Methods: Patients who had started fimasartan (n=4,286), losartan (n=7,105) or candesartan (n=3,301) were retrieved from clinical data warehouse of Seoul National University Bundang Hospital. Patients who treated <5 days, with baseline alanine aminotransferase (ALT) level > x3 UNL, or had underlying liver disease except fatty liver were excluded. All patients who showed ALT levels > x5 UNL during the medication were assessed according to Roussel Uclaf Causality Assessment Meth-

od (RUCAM).

Results: In fimasartan group, 13 (0.3%) showed ALT > x5 UNL. Eight (61.5%) were females and median age was 69.8 years old. The peak ALT level was median 304 IU/L (range 209-2394) after median 109 days (range 6 – 716) of fimasartan treatment, and 11 (84.6%) had improved within 30 days after drug withdrawal. Of 74 (1.04%) showed ALT > x5 UNL during losartan treatment, 26 (35.1%) were females and median age was 68.7 years old. The peak ALT level was median 302 IU/L (range 202-2182) after median 401 days (range 5-1902) of treatment. In candesartan group, 25 (0.9%) showed ALT > x5 UNL during treatment. Seventeen (68%) were females and median age was 71.5 years old. The peak ALT level was median 335IU/L (range 203-2300) after median 382.2 (range 10-1571) days.

Conclusions: Although fimasartan showed significantly lower incidence of hepatotoxicity compared with other ARB, some severe fimasartan-induced hepatitis has been found, and it tended to develop earlier than losartan or candesartan therapy in Korean patients. Further evaluation is needed to define risk factors of ARB-induced liver injury.

Keywords: ARB, DILI, Hepatitis

O-38

Aspects of Primary Biliary Cholangitis Diagnosis and Treatment Response in a Single Institutional Experience

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Aims: Primary biliary cholangitis is an autoimmune liver disease that is common among middle-aged women, and the small bile ducts are lost by non-purulent cholecystitis and can gradually progress to cholestasis, liver fibrosis, and cirrhosis. For a type of autoimmune disease, Anti Mitochondrial Antibody(AMA) is found in about 90-95% of patients. However, the incidence is relatively low, and furthermore, studies on the evaluation of treatment response in Korea are very rare. This study was designed to analyze the patterns and treatment trends of patients diagnosed with PBC in a single institution.

Methods: From 2010 to 2020, the medical records of Korea Univ. Ansan Hospital were investigated and 95 patients suspected or diagnosed as PBC have been checked to analyze 92 patients, excluding those with missing records or insufficient diagnosis. Among these patients, the response rate of UDCA treatment was evaluated in 67 patients who were followed up for more than one year. For diagnosis and evaluation of treatment response refer to 2018 AASLD PBC Practice Guidance. The treatment response was based on the normalization of ALP at the first year of treatment. In the serum test, the Anti Mitochondrial Antibody (AMA) test was performed using the Fluorescent antibody test.

Results: A total of 95 patients had an mean age of 56 years, of which 87 were female and 8 were male, with a sex ratio of 10.9: 1. At the time of diagnosis, 33 patients (34.7%) had cirrhosis and 48 patients (50.5%) had auto-immune related comorbidities. The most common was thyroid disease (13 patients, hypothyroidism), and Sicca syndrome, Raynaud disease, Behcet's disease, SLE, and so on. Symptoms usually complained of itching and pruritis. but most were asymptomatic. In serologic examination, 92 AMA positive PBC (96.8%), and the other 3 showed negative findings in gp210 or sp100, but the diagnosis was progressed by clinical pathological findings. In further studies with stored samples, gp210 and sp100 were positive in 33% and 15%, respectively. In addition, PBC / AIH overlap was diagnosed in 13 patients (13.7%) on serological histological examination. Eight patients (11.9%) showed insufficient treatment response in 67 patients following follow-up of UDCA for more than one year, especially positive (33%) in gp210 and Ro-52 antibodies and with autoimmune hepatitis(AIH). More than half the patients with insufficient treatment response showed PBC / AIH overlap feature.

Conclusions: PBC patients are often accompanied by systemic autoimmune disease at the time of diagnosis, and some patients are accompanied by AIH when diagnosed, and they often do not reach a sufficient response within 1 year of treatment with UDCA. In addition, antibody diagnostics other than AMA may be helpful in predicting treatment response during diagnosis of these patients.

Keywords: Primary biliary cholangitis, Diagnosis, Treatment

O-39

Initial Experience of High-Volume Plasma Exchange In Patients with Acute Liver Failure

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Aims: High-volume plasma exchange (HVP) defined as exchange of 8-12 or 15% of ideal body weight with fresh frozen plasma has shown promising results in improving survival of patients with acute liver failure (ALF). However, real-life clinical evidences are still limited. The aim of this study was to report our initial experience of using HVP as a bridge treatment in patients with ALF.

Methods: We retrospectively reviewed 32 consecutive patients who were enlisted for liver transplantation (LT) due to ALF between 2013 and 2020 at Samsung Medical Center in Korea. HVP was initiated in patients with ALF since May 2016 at our

institution.

Results: During study period, 16 Patients received HVP. After HVP, coagulopathy (prothrombin time, INR, 4.46 [2.32-6.02] vs. 1.48 [1.33-1.76], *P*<0.05), total bilirubin (22.6 [9.1-26.4] vs. 8.9 [5.6-11.3], *P*<0.05), ALT (506 [341-1963] vs. 120 [88-315], *P*<0.05), and ammonia level (130.6 [123.7-143.8] vs 98.2 [84.2-116.5], *P*=0.033) were improved. Improvement in hepatic encephalopathy grade was observed in four patients, including three case of spontaneous recovery. The overall survival was better in patients who received HVP than that in patients who did not receive HVP (survival rate: 93.8% vs. 68.8% at 30 days) without overlap in survival curve between the two groups, although the difference between the two was statistically marginal (*P*=0.068). Among 18 patients with high SOFA score (≥13), the overall survival was significantly better for those who received HVP than those did not (90.9% vs. 28.6%, *P*=0.003).

Conclusions: Initial clinical experience with HVP suggests that HVP can be a viable option to improve outcome for patients presenting with ALF, especially for those with high SOFA score.

Keywords: High-volume plasma exchange, Acute liver failure, Bridge therapy

O-40

PKHD1 Gene Mutations and Clinical Manifestations in Korean Children with Caroli Syndrome and Autosomal Recessive Polycystic Kidney Disease

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Aims: Caroli syndrome(CS) is defined as congenital hepatic fibrosis combined the dilatation of intrahepatic bile duct (IHD) and is often associated with autosomal recessive polycystic kidney disease (ARPKD). The main causative gene of ARPKD is PKHD1 located on chromosome 6p21 encoding for fibrocystin/polyductin. We investigated mutation spectrums and clinical features in Korean patients with PKHD1 mutations.

Methods: Genetic analysis using next generation sequencing was performed in the pediatric patients diagnosed with CS accompanied by ARPKD. Clinical manifestations were collected by the review of medical records.

Results: Compound heterozygous PKHD1 mutations were found in 6 patients. The median age at initial diagnosis was 1.85 years. Six patients had 11 different PKHD1 mutations including 10 novel mutations. They were 5 truncating mutations (3 nonsense, 1 splicing, and 1 frameshift) and 6 missense mutations. One novel nonsense mutation (p.Trp2280*) was detected in two patients. Mutations were found to be widely distributed throughout the gene without evidence of hot spot. A patient with two truncating mutations showed severe liver disease, while a patient with both missense mutations showed relatively mild clinical phenotype of both liver and kidney. All patients had progressive renal insufficiency and 2 reached to chronic kidney disease stage 4. CS and Caroli disease were found in 5 patients and 1 patient, respectively. Imaging findings showed cystic dilatation of IHD and common bile duct in 4 of 6 (67%) patients. Congenital hepatic fibrosis was proven by liver biopsy in 3 patients. None received a kidney or liver transplant.

Conclusions: Mutation analysis of PKHD1 is useful for the molecular diagnosis of Caroli syndrome and ARPKD before performing invasive liver biopsy. This is the first report of PKHD1 mutations in Korean patients with Caroli syndrome and ARPKD, and mutation hot spot was not found.

Keywords: Caroli syndrome, Congenital hepatic fibrosis, Autosomal recessive polycystic kidney disease, PKHD1

8. Liver Cancer, Basic

O-41

NOX4 Knockdown Promotes Tumorigenesis Arising from Fibrotic Background Liver by Inducing M2-Macropahges in Tumor Microenvironment

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Aims: Hepatocellular carcinoma (HCC) commonly arise in cirrhotic liver, therefore there are close relationship between hepatic fibrosis and HCC carcinogenesis. Reactive oxygen species (ROS) mainly produced by NADPH oxidase (NOX) 4 contributes to hepatic fibrogenesis. In contrast, NOX4 plays a tumor suppressive role in HCC development. We aimed to investigate how NOX4 affects the HCC tumor microenvironment (TME) in fibrotic background liver.

Methods: HCC in fibrotic background liver were induced using diethylnitrosamine (DEN) and carbon tetrachloride (CCl_4) injections in Wild-type (WT) and NOX4 knockout (NOX4KO) mice. Tumor and non-tumor tissue were analyzed by histology, immunohistochemistry, quantitative RT-PCR. The expression of M1 and M2 macrophage were evaluated by CD68 and CD206, respectively. After short-term DEN plus CCl_4 treatment in WT and NOX4KO mice, the phenotype of macrophage were analysed by fluorescence-activated cell sorting (FACS) analysis. Transient knockdown of NOX4 in HCC cell lines were used to determine the effect of NOX4 on cell proliferation *in vitro*.

Results: At 30 weeks after DEN plus CCl_4 treatment, NOX4KO mice showed less hepatic fibrosis, but more tumor development and higher cell proliferation index compared to WT mice. The pro-inflammatory cytokine such as IL-6 and TNF-α mRNA were upregulated in both tumor and nontumor tissue in

NOX4KO mice than in WT mice. TGF-ß mRNA expression was lower in nontumor but higher in tumor tissue in NOX4KO mice compared to WT mice. The expression of CD206, a marker for M2-macrophage was significantly higher in NOX4KO mice than WT mice in both long-term and short-term DEN plus CCl_4 treatment animal model. NOX4 knockdown using NOX4-siRNA increased HCC cell proliferation *in vitro*.

Conclusions: Deficiency of NOX4 induces M2-macrophage in tumor microenvironment resulting in increased tumorigenesis in DEN plus CCl_4 model. These finding has novel insight on the mechanism of NOX4-mediated tumor suppression in HCC arising from fibrotic background liver.

Keywords: Hepatic fibrosis, Liver cancer, NADPH Oxidase 4, Macrophage, Tumor microenvironment

O-42

Highly Sensitive Circulating Cell-free DNA (cfDNA) Detection Using Polydopamine-Silica Hybrids Allows Early Diagnosis of Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is frequently diagnosed at the advanced stage, delaying the timely treatment. Therefore, the early detection of HCC can reduce the mortality of a cancer by inhibiting its progression in earlier stage. Herein, we designed a non-invasive, low cost liquid biopsy platform based on the analysis of circulating cell-free DNA (cfDNA) for the early diagnosis of HCC. cfDNA is extracted by the polydopamine (PDA)-silica (SiO_2) hybrids, which synergistically interact with different part of nucleotide, allowing more accurate sensing of cfDNA. We evaluated the diagnostic capability of our cfDNA testing platform for detecting early stage HCC.

Methods: PDA-SiO_2 hybrids were coated on the alginate beads, in order to enhance the cfDNA adsorption. The beads were directly applied on human plasma samples after treating with proteinase K and lysis buffer. Plasma cfDNA concentrations were quantified using NanoDrop 1000 (Thermo Scientific). Total 209 individuals were enrolled in this study including 99 patients with HCC, 50 patients with liver cirrhosis, 30 patients with alcoholic liver disease, and 30 healthy individuals, respectively.

Results: Average cfDNA concentration was significantly higher for HCC patients compared to both healthy donors and other types of liver disease patients, including alcoholic liver disease and liver cirrhosis (1.68 ± 1.2 ng/μL vs. 0.16 ± 0.17 ng/μL, 0.41 ± 0.28 ng/μL, and 0.59 ± 0.49 ng/μL, respectively; $P<0.0001$). Other serum biomarkers such as ALT, AST, ALP, total protein level, and platelet concentration did not show significant difference between the cancer patients and at least one of the control groups. Obviously, alpha-fetoprotein (AFP) was the only serum protein that demonstrated high diagnostic capability for HCC patients, exhibiting 655.2 ± 3,181.3 ng/mL, 9.7 ± 19.9 ng/mL, 11.4 ± 32.4 ng/mL, and 3.4 ± 1.9 ng/mL for the patients with cancer, alcoholic liver disease, liver cirrhosis, and non-diseased, respectively ($P<0.0001$). We further conducted receiver operating characteristic (ROC) curve analysis and confirmed that cfDNA concentration has superior diagnostic capability by showing high level of area under the ROC curve (AUC-ROC) (0.896, 95% CI: 0.855-0.937; $P<0.0001$) than that of serum AFP level (0.770, 95% CI: 0.705-0.835; $P<0.0001$). Interestingly, when combining these two markers together by adding normalized serum AFP levels and plasma cfDNA concentrations, the AUC-ROC value has increased up to 0.907 (95% CI: 0.867-0.947; $P<0.0001$), showing the best HCC diagnostic ability.

Conclusions: We have demonstrated that cfDNA has higher diagnostic functionality to differentiate patients with HCC from other types of liver diseases, compared to other conventional serum biomarkers. When analyzed together with AFP, the diagnostic capability could be further enhanced, showing both higher sensitivity and specificity than either of cfDNA or serum AFP. Therefore, our cfDNA-based diagnosis platform enables patients to receive appropriate curative therapy at the earlier stage of the tumor.

Keywords: Cell-free DNA, Hepatocelluar carcinoma, Liver cirrhosis, Hepatitis

O-43

Validation of a Disintegrin and Metalloproteinase 9 (ADAM9) as a Prognostic Biomarker for Hepatocellular Carcinoma Patients Using 'The Cancer Genome Atlas (TCGA)' Database

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Aims: A disintegrin and metalloproteinase 9 (ADAM9) is an important mediator of invasion and metastasis of hepatocellular carcinoma (HCC). Previous reports suggest that ADAM9 may serve as a biomarker to predict treatment response in HCC

systemic treatment. Also, in our previous study, we found that decreased expression of serum ADAM9 mRNA was significantly associated with the clinical response to nivolumab therapy. To support our earlier findings, this time we investigated the role of ADAM9 as prognostic biomarker for HCC patients using "the Cancer Genome Atlas (TCGA)" database of National Human Genome Research Institute and National Cancer Institute.

Methods: We downloaded transcriptomic, survival and clinical data of HCC patients (indexed as LIHC) from Xena TCGA database hub (https://xenabrowser.net). The transcriptomic data includes 370 patients and was generated by University of North Carolina TCGA genome characterization center. The survival data includes information of overall survival. For statistical evaluation, t-test, Pearson's correlation, Cox-regression, and log rank analyses were performed. All of statistical analyses with TCGA dataset were performed with Python (Version 2.7.10) and R-studio (Version 1.1.456).

Results: To evaluate effect of ADAM9 expression on HCC prognosis, we performed in-silico analyses with 370 HCC patients from TCGA database. Kaplan-Meier plot revealed that the higher expression group than a median value of ADAM9 expression had significantly poorer overall survival rate (Log-rank test P=3.9 x 10^{-4}). In addition, ADAM9 was significantly upregulated in primary tumor tissues of HCC (n=370) compared with adjacent normal liver tissues (n=50) (t-test P=4.6 x 10^{-6}). Unlike ADAM9, other ADAM family genes, including ADAM10 and ADAM17, did not differ in their expression levels between HCC tumor tissues and adjacent normal liver tissues, and neither showed significant correlation with survival analysis. Also, the ADAM9 expression was tested for its correlation with expression of immune checkpoint molecules in HCC patients (n=370) from TCGA database. ADAM9 expression was positively correlated with of programmed cell death 1 (PD-1), T cell immunoglobulin- and mucin-domain-containing molecule 3 (TIM-3) and B and T lymphocyte attenuator (BTLA). TIM-3 had the strongest positive correlation with ADAM9 (Correlation coefficient r = 0.37 and P=1.3 x 10^{-13}).

Conclusions: Using the TCGA database, we found that higher expression of ADAM9 in HCC tumor tissues is associated with poor survival of HCC patients. Therefore, ADAM9 has a potential as a biomarker predicting HCC prognosis, and its influence on tumor microenvironment and prognosis of human HCC patients should be investigated in future studies.

Keywords: ADAM9, ADAM10, ADAM17, HCC, PD-1, TIM-3

O-44

SREBP2 Activation Drives Drug Resistance through Promotion of Cholesterol Biosynthesis-Driven Sonic Hedgehog Signaling (SHH) Pathway in Hepatocellular Carcinoma

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Aims: Acquired drug resistance is a hurdle for effective treatment for hepatocellular carcinoma (HCC) patients. We have established sorafenib-resistant HCC patient-derived xenografts and found that cholesterol biosynthesis was most significantly upregulated in sorafenib-resistant PDTX cells with enhanced cholesterol deposition. This observation is similarly observed in lenvatinib-resistant HCC xenografts. This, together with an observation that SREBP2-mediated cholesterol biosynthesis was activated in enriched liver CSC populations, prompt us to investigate the role of SREBP2-mediated cholesterol biosynthesis in regulation of drug resistance of HCC via augmentation of liver CSCs.

Methods: We evaluated the clinic-pathological relevance of SREBP2 and its correlation with sorafenib resistance in HCC samples by immunohistochemistry. CRISPR activation and knockdown approaches were performed to characterize the functional roles of SREBP2 in regulating liver CSCs. Pathways mediating the phenotypic alterations was identified through RNA sequencing analysis. The combinatorial effect of Simvastatin and sorafenib was tested using patient-derived tumour xenograft (PDTX) model.

Results: We found that SREBP2-mediated cholesterol biosynthesis was found to critically involve in regulation of liver CSCs, including self-renewal, cell invasiveness and tumorigenicity, and bears clinical significance. Strikingly, this process is a crucial determinant for drug resistance in HCC cells, and correlated with sorafenib resistance in sorafenib-treated HCC patients. Exogenous cholesterol also exerted the similar effect on cancer stemness, drug resistance, and expansion of HCC organoids. Sorafenib/lenvatinib induced nuclear translocation of SREBP2 from endoplasmic reticulum, resulting in activation of cholesterol biosynthesis-driven sonic hedgehog signaling (SHH) pathway. Simvastatin, a FDA-approved cholesterol lowering drug, sensitized the effects to sorafenib/lenvatinib via hampering liver CSC populations. Using PDTX model, we found that simvastatin at the clinically equivalent dose (40 mg) not only suppressed HCC tumor growth but also sensitized the effect to sorafenib.

Conclusions: We reveal a previously unrecognized link between SREBP2-mediated cholesterol biosynthesis and cancer stemness that modulates acquired drug resistance of cancer cells.

Keywords: Cholesterol, SREBP2, Drug Resistance, Hepatocellular Carcinoma, Sonic Hedgehog Signaling

O-45

Telomerase Reverse Transcriptase Gene Alterations and Disease-Promoting Properties of Hepatocellular Carcinoma

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Aims: Telomerase reverse transcriptase (TERT) was recently identified as a gatekeeper driver gene with a fundamental role in multi-step hepatocarcinogenesis. This study aimed to investigate the tumor-promoting effects of TERT interaction gene set and genomic alterations in hepatocellular carcinoma (HCC).
Methods: A total of 239 biopsy-proven HCC samples were analyzed for the study. Protein-protein interaction (PPI) networks through the STRING database were performed to establish a set of interacting genes with TERT. The expression of the selected gene set, TERT, and telomere length were examined by qRT-PCR. TERT promoter mutations were assessed using Sanger sequencing. Integration of hepatitis B virus (HBV) was examined using the NGS-based probe capture assay. The data were correlated with outcomes of HCC patients.
Results: The PPI networks identified eight key TERT-interaction gene sets, such as CCT5, TUBA1B, mTOR, RPS6KB1, AKT1, WHAZ, YWHAQ, and TERT. Among these, TERT was the most significant differentially expressed gene, with its significantly higher expression in the tumor than non-tumor tissues. The high expression of TERT was correlated with tumor size and HCC stage progression. TERT expression and telomere lengths were positively correlated in patients with HBV-HCC invading portal vein. Together with telomere length, the presence of C228T, the hot spot mutation in the TERT promoter, as well as HBV integration resulted in a higher expression of TERT, with enhanced expression with the presence of both TERT promoter mutation and HBV integration. Patients with high TERT expression had significantly higher rates of recurrence and worse progression-free survival than those with low TERT expression.
Conclusions: TERT gene alterations and expression are involved in hepatocarcinogenesis and the clinical outcomes of HCC, in terms of the development, recurrence, and disease progression. TERT pathway might serve as a potential therapeutic target for HCC.
Keywords: Liver cancer, Telomere, Genetics, Biomarker

9. Liver Cancer, Clinical

O-46

Long-term Outcomes of Percutaneous Radiofrequency Ablation as First-Line Therapy of Hepatocellular Carcinoma in Milan Criteria

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Aims: Radiofrequency ablation (RFA) has been performed for treatment of early stage hepatocellular carcinoma (HCC). Many studies have confirmed the safety and efficacy of RFA for HCC with excellent long-term prognosis. The aim of this study is to analyze long-term outcomes of RFA for early stage HCC as an initial therapy at a single center.
Methods: Percutaneous RFA as first-line therapy was applied to 1,097 patients (male: 821, median age: 61 years) diagnosed with HCC within the Milan criteria from January 2001 to December 2019 (Fig.1). Overall and recurrence-free survivals were estimated by Kaplan–meier method and prognostic factors affecting those survivals were analyzed using Cox proportional hazards model. Fig.1. Flowchart of study inclusion. Flowchart summarizing the included patients who were treated by radifrequency ablation (RFA) as a first-line treatment in this study.

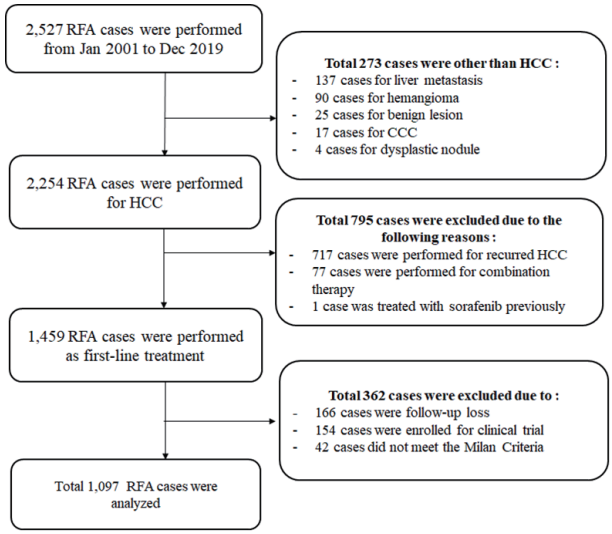

Figure 1. Flowchart of study inclusion. Flowchart summarizing the included patients who were treated by radifrequency ablation (RFA) as a first-line treatment in this study.

Results: Liver function of the patients was either Child-Pugh class A (n=982), B (n=108), or C (n=7). Cumulative overall survival rates at 1-, 5-, 10-, and 15-years were 96.1%, 65.8%, 41.6%, and 30.8%, respectively. Cumulative recurrence-free survival rates at 1-, 5-, 10-, and 15-years were 79.7%, 36.4%, 24.9%, and 18.5%, respectively. Prognostic factors for overall survival were age (> 61 years, Hazard ratio, HR=2.025; 95% Confidence interval, CI=1.662–2.468), cirrhosis (HR=1.422; 95% CI=1.145–1.766), tumor size (HR=1.358; 95% CI=1.122–1.642), and Child-Pugh class (HR=2.893; 95% CI=2.281–3.669). Prognostic factors for recurrence-free survival were age (> 61 years, HR=1.561; 95% CI=1.336–1.825), a-fetoprotein (>20 ng/mL, HR=1.407; 95% CI=1.200–1.650), tumor size (HR=1.329; 95% CI=1.140–1.550), Child-Pugh class (HR=1.935; 95% CI=1.556–2.408), and tumor location (surface location, HR=0.817; 95% CI=0.700–0.953).
Conclusions: The long-term outcomes of RFA showed good results in treating HCC within the Milan criteria as first-line

treatment. RFA was an effective and safe method treating early stage HCC.

Keywords: Hepatocellular Carcinoma, Radiofrequency Ablation, Survival, Recurrence

O-47

The Complementary Role of Serum Alpha-Fetoprotein Estimation in Evaluating and Predicting Response to Nivolumab in Patients with Hepatocellular Carcinoma

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Aims: Serum alpha-fetoprotein (AFP) level has been found to be a useful marker for predicting responsiveness to locoregional or systemic therapies in patients with hepatocellular carcinoma (HCC). We aimed to evaluate whether changes in serum AFP could accurately reflect response and predict prognosis in nivolumab-treated patients with the disease.

Methods: In this study, a total of 84 HCC patients who had baseline serum AFP of ≥20 ng/mL and received an over 8-week course of nivolumab treatment between 2017 and 2019 were included. We defined 'response to therapy' as a result assessed at 8 weeks after nivolumab. Radiological response was evaluated by the RECIST criteria with CT images; and serological response was based on AFP changes from baseline (decrease and increase by 20% or 50%). Prognostic effect of AFP response was evaluated by overall survival analysis.

Results: Baseline characteristics of 84 patients were as follows: 68 Child-Pugh class A, 1 treatment-naïve, 33 portal invasion, 73 distant metastasis, 81 BCLC stage C, and 66 serum AFP ≥200 ng/ml. AFP response defined as >20% (n=6) or >50% (n=5) reduction in the value was agreed upon objective responses by RECIST (complete or partial response; n=7) in 86% and 71%, respectively. There were also agreements in 93% and 85%, respectively between progressive disease on CT scans (n=55) and serological progression by >20% (n=51) or >50% (n=47) increase in AFP level. After 8 weeks of treatment, responders and progressors determined by a cut-off of 20% for AFP change independently predicted overall survival of patients (adjusted hazard ratios, 0.39 and 2.95, respectively), as did those by RECIST (0.24 and 4.56, respectively; Ps<0.05).

Conclusions: Serological response criteria using 20% changes in serum AFP had good performance in predicting clinical outcomes in patients with AFP-producing HCC receiving nivolumab. Serial AFP measurement could be useful particularly for non-measurable infiltrative HCC in the relevant setting.

Keywords: Nivolumab, Hepatocellular carcinoma, Serum alpha-fetoprotein, Treatment response

O-48

Comparison of Dexamethasone and Celecoxib for Prophylaxis for Transarterial Chemoembolization

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Aims: Transarterial Chemoembolization(TACE) is one of the most frequently used treatment method for hepatocellular carcinoma(HCC). The prevalence of Post-embolization syndrome(PES) has been reported till 90%, but its significance has been ignored. The mechanism of PES has not been elucidated yet, but it is thought to be an inflammatory reaction due to ischemic and necrotic changes of the tumor and normal tissue according to the procedure. Recently, studies using steroids and non-steroidal anti-inflammatory drugs have been published to prevent PES. However, its stability and practical application are not yet known. In this study, we compared the effect of COX-2 inhibitor on the low-dose dexamethasone pretreatment and the effect of high-dose dexamethasone on the prevention of PES and its stabilities.

Methods: This prospective, randomized trial was conducted in a single center from May 2019 to December 2019. A total of 69 patients with HCC were enrolled. After randomization, 37 patients were assigned to the COX-2 inhibitor group and the other 32 to the dexamethasone group. The dexamethasone group received intravenous dexamethasone 15 mg and ramosetron 0.3 mg on the first day, and intravenous injection of dexamethasone 5 mg and oral ramosetron 0.1 mg on the second, and third day. In the COX-2 inhibitor group, Celecoxib 200 mg was administered the night before the procedure, and the dose was administered for 3 days after the procedure at 12-hour intervals (total 6 times). In addition, 5 mg of dexamethasone and 0.3 mg of ramosetron were administered intravenously before procedure, and on the second, third day oral ramosetron 0.1 mg.

Results: The incidences of PES were 72.97% in the COX-2 inhibitor group and 43.75% in the dexamethasone group (*P*=0.023). Mean hospitalization times after TACE were 4.10 days 7.29 in the COX-2 inhibitor group and 2.62 days 1.51 in the dexamethasone group (*P*=0.21). Underlying stage of HCC, re-admission rate and treatment response showed no statistical differences between two groups.

Conclusions: This study demonstrates that the prophylactic administration of high-dose dexamethasone before TACE is better to prevent PES than COX-2 inhibitor without significant complication.

Keywords: Hepatocellular carcinoma, Transarterial chemoembolization, Post-embolization syndrome, Dexamethasone, COX-2 inhibitor

O-49

Yttrium-90 Radioembolization Might Have Better Efficacy in Overall Survival in Patients with Hepatocellular Carcinoma Compared with Conventional Chemoembolization: A Propensity Score-Matched Study

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Aims: Locoregional therapies, such as yttrium-90 (Y-90) radioembolization (RE) and conventional chemoembolization (CE) can effectively control localized hepatocellular carcinoma (HCC) in patients who are not amenable to curative resection. However, it has not yet been fully established which modality is more effective. The aim of this study was to compare effectiveness of RE and CE as the first treatment of HCC.

Methods: We retrospectively reviewed data of patients who received RE or CE as the first treatment of HCC at Seoul National University Hospital from March 2012 to December 2017. A propensity score matching was performed to reduce selection bias. Overall survival (OS), progression-free survival (PFS), and intrahepatic PFS were compared.

Results: A total of 138 patients who were initially treated with RE (n=54) or CE (n=84) was included in this study and baseline characteristics was well-balanced between the two groups. Of 138 patients, median age was 59 and median follow-up period was 22.5 months. RE showed better overall survival than CE (hazard ratio [HR]=0.30, 95% confidence interval [CI]=0.10–0.90, log-rank *P*=0.02) and tended toward better intrahepatic PFS than CE (HR=0.52, 95% CI=0.25–1.09, log-rank *P*=0.08). However, progression-free survival was not significantly different between the two groups (HR=0.67, 95% CI=0.39–1.16, log-rank *P*=0.15). In multivariable analysis, RE was an independent prognositc factor for overall survival (adjusted HR=0.31, 95% CI=0.11–0.92, *P*=0.04).

Conclusions: RE might be more effective as the initial treatment than CE in patients with HCC.

Keywords: Liver cancer, SIRT, TACE

O-50

Radiofrequency Ablation versus Stereotactic Body Radiation Therapy for Small (≤ 3 cm), Inoperable Hepatocellular Carcinoma: A Comparison Retrospective Analysis

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Aims: To compare the outcomes of radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT) in contemporary patients with small (≤3 cm), inoperable hepatocellular carcinoma (HCC).

Methods: A total of 266 patients (307 lesions) treated with RFA (n=179, 210 lesions) or SBRT (n=87, 97 lesions) were retrospectively reviewed. Baseline characteristics, local control rates (LCR), intrahepatic recurrence-free survival (IHRFS), and overall survival (OS) rates were compared between the two groups. Inverse probability of treatment weighting (IPTW) was used to adjust for imbalances in baseline characteristics between the two groups.

Results: Tumors treated with SBRT were more frequently located in the hepatic dome, subcapsular area, or gallbladder fossa (*P*=.003) and perivascular areas (*P*=.023) than those treated with RFA. Patients treated with SBRT had higher numbers of prior treatment (*P*<.001). The median follow-up period was 50.3 months (range, 0.6–58.8). The 4-year LCR did not significantly differ between the RFA and SBRT groups (92.7% vs. 95.0%, *P*=.533). Perivascular location was the only significant prognostic factor for LCR in univariate and multivariate analyses (HR = 4.855; 95% CI, 1.873–12.585; *P*=.001). The 4-year IHRFS rates were not significantly different between the RFA and SBRT groups (36.7% vs. 27.6%, *P*=.107). The 4-year OS rates after RFA and SBRT were 78.1% and 64.1%, respectively (*P*=.011). LCR, IHRFS, and OS were not significantly different between the two groups in both multivariate Cox proportional hazards model and IPTW-adjusted analysis.

Conclusions: Although the unadjusted OS was significantly higher in RFA than that in SBRT, the two treatment modalities showed comparable rates of LCR and IHRFS. SBRT seems to be a viable alternative treatment modality for small HCCs that are not suitable for RFA due to tumor location.

Keywords: Hepatocellular carcinoma, Radiofrequency ablation, Stereotactic body radiation therapy, Local control rate, Survival rate

10. Liver Cancer, Clinical

O-51

Association with Body Mass Index and Risk of Hepatocellular Carcinoma According Liver Disorder Status

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Aims: Body mass index (BMI) is known to be associated with higher risk of hepatocellular carcinoma (HCC) in the general population. However, the association between BMI and risk of HCC in patients with various liver disease is not well understood.
Methods: We used data from National Health Insurance Service (NHIS) that provides compulsory health insurance coverage and national health screening for all citizens in the Republic of Korea. Hazard ratios (HRs) were calculated using Cox regression models to examine associations between body mass index (BMI) and risk of HCC. We included 15016551 adults (aged 18-99 years) who underwent health examinations between 2003 and 2006, in the NHIS database. Participants were classified into six groups according to the liver diseases; liver cirrhosis (LC), hepatitis B or C virus infection (HBVHCV), other liver disease (O-LD), unidentified liver disease with alanine aminotransferase (ALT) ≥40 or aspartate aminotransferase (AST) ≥40 (ALT40), no known liver diseases with 20≤ALT<40 or 20≤AST<40 IU/ml (ALT2040), and ALT<20 and AST<20 (ALT20).
Results: During mean 13.7 years of follow-up. HCC occurred in 71570 individuals. In total population, BMI had a non-linear association with HCC. In BMI above 25 kg/m², BMI was positively associated with risk of HCC regardless of liver disorder. In the multivariable adjusted analysis, the HR per 5 kg/m² increase in BMI above 25 kg/m² was 1.48 (95% CI 1.44–1.52) in total population, 1.11 (95% CI 1.00–1.23) in LC, 1.12 (95% CI 1.44–1.52) in HBVHCV, 1.32 (95% CI 1.22–1.44) in O-LD, 1.07 (95% CI 1.03–1.12) in ALT40, 1.47 (95% CI 1.38–1.57) in ALT2040, 1.67 (95% CI 1.32–2.09) in ALT20. In the subgroup analysis for the HCC high-risk group, the HR of HCC (95% CI) for a 5 kg/m^2 increase in BMI was 1.21 in HBV-LC (1.01–1.46), 1.13 in other LC (1.08–1.19) and 1.15 in HBV without LC (1.04–1.27), 1.14 in HCV without LC (0.92 –1.40) and 1.05 in HCV-LC (0.64–1.74). Associations between BMI and risk of HCC in HBV (HR; 1.46 vs 1.05), HCV (HR; 1.30 vs 0.92) and LC (HR; 1.28 vs 1.02) patients were stronger in female than in male.
Conclusions: Our study showed that BMI was positively associated with risk of HCC regardless of liver disorder in BMI above 25 kg/m². As the severity of liver disease weakened, the association between increased BMI and HCC became stronger. In patients with HBV, HCV, and LC, the harmful effects of higher BMI on HCC risk was stronger in women than in men.
Keywords: Body mass index, Hepatocellular carcinoma, Liver disease, Risk factor

O-52

The ALPs Score Based on AFP, AFP-L3, and PIVKA-II Improves Diagnostic Performance for Hepatocellular Carcinoma

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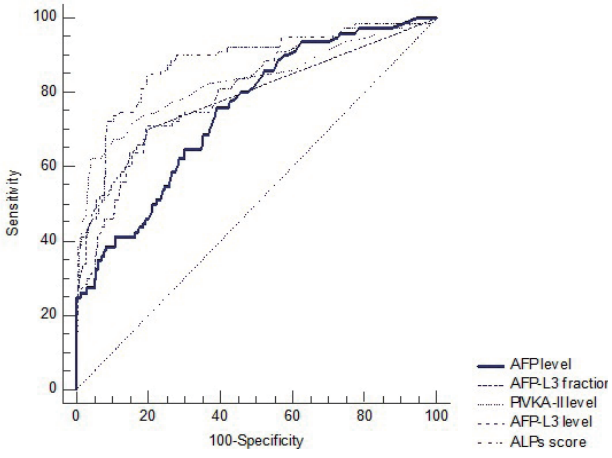
Aims: We investigated the diagnostic performance of alpha-fetoprotein (AFP), AFP-L3, protein induced by vitamin K absence or antagonist-II (PIVKA-II) and their combination in diagnosis of hepatocellular carcinoma (HCC).
Methods: Patients who were referred from primary clinic to Korea University Medical Center for newly detected liver mass or elevated serum AFP level were considered to be eligible. Serum AFP, AFP-L3, and PIVKA-II levels were measured at the time of first visit.
Results: In total, 622 patients were included for analysis. In these patients, 355 patients (57.1%) had chronic liver disease and 208 patients (33.4%) had liver cirrhosis. HCC was diagnosed in 160 patients (25.7%). Area under the receiver operating characteristics (AUROCs) of serum AFP level, AFP-L3 fraction, AFP-L3 level and PIVKA-II level for the diagnosis of HCC were 0.775, 0.792, 0.814, and 0.834, respectively. To develop a novel diagnostic model, all included patients were classified into two groups with a 1:1 ratio under the stratification by presence or absence of HCC, training and validation sets. Using the results of binary regression analysis in training cohort using AFP-L3 and PIVKA-II levels, we calculated ALPs (AFP, AFP-L3 fraction, and PIVKA-II) score with the formula as follows: ALPs score = 3.8 × [serum AFP level (ng/mL) × AFP-L3 fraction (%) × 0.01] + 0.2 × PIVKA-II level (mAU/mL). The AUROC of ALPs score for the diagnosis of HCC was 0.878, which was significantly higher than those of serum AFP level (P<0.001), AFP-L3 fraction (P<0.001), PIVKA-II level (P=0.036), and AFP-L3 level (P=0.006) (Fig. 1). The optimal cutoff value of ALPs score was 5.3 (sensitivity, 85.0%, specificity 80.1%, PPV 59.6%, and NPV 93.9%). Similar results were also shown in validation cohort.



Conclusions: ALPs score calculated using serum AFP level, AFP-L3 fraction, and serum PIVKA-II level showed improved accuracy in diagnosis of HCC.
Keywords: AFP-L3, PIVKA-II, Tumor marker, Hepatocellular carcinoma

O-53

Efficacy and Safety of Lenvatinib as a Salvage Therapy for Transarterial Treatment of Unresectable Hepatocellular Carcinoma: A Real-World Experience in an Endemic Area of Hepatitis B Virus Infection

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Aims: In unresectable hepatocellular carcinoma (HCC), patients who are refractory to transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy (HAIC) have been considered suitable for multikinase inhibitor treatment, and sorafenib has traditionally been used as a salvage treatment option. Recently, lenvatinib was demonstrated to be non-inferior to sorafenib in a phase 3 randomized controlled trial. In this study, we aimed to investigate the efficacy and safety of lenvatinib as a salvage treatment for HCC after transarterial treatment.

Methods: Between January 2019 and March 2020, all patients with confirmed intermediate-to-advanced HCC who were administered lenvatinib treatment after transarterial treatment in five Korean centers were retrospectively analyzed. We used overall survival (OS), progression free survival (PFS), objective response rate (ORR) and disease control rate (DCR) to evaluate efficacy of the treatment. Clinical parameters and outcomes after the introduction of lenvatinib were assessed.

Results: We enrolled 38 unresectable HCC patients treated with lenvatinib after transarterial treatment. At the time of treatment initiation, 6 and 32 patients were classified as BCLC stage B and C, respectively. For the liver reserve, patients were classified as Child–Pugh class A (30 patients) or B (8 patients). Previous treatment included TACE for 35 patients, HAIC for 10 patients, and both TACE and HAIC for 7 patients. The median OS and PFS was 5.9 months (range, 0.7–13.2 months) and 3.9 months (range, 0.1–9.6 months), respectively. Sixteen among 38 patients were administered a 12-mg daily dose and 22 were administered an 8-mg daily dose. During the treatment, 10 of 38 (26.3%) patients had hand-foot syndrome (HFS); only 3 patients had grade 3 toxicity HFS. Among the patients, 6 (15.8%) had proteinuria and only one patient suffered grade 2 proteinuria while others had grade 1. In a best response evaluation, 5 patients exhibited a partial response (13.2%) and 12 patients had achieved stable disease (31.6%) according to the mRECIST criteria. Patients in the disease-controlled state (CR+PR+SD) showed superior OS (P=0.006) and PFS (P=0.003) to those with PD. Tumor size less than 5 cm was also associated with longer PFS (P=0.045). There was no statistically significant difference between OS and the number of prior transarterial treatments.

Conclusions: Lenvatinib treatment is safe and efficacious after the failure of transarterial treatments in unresectable HCC. Change of treatment modality from loco-regional treatment to lenvatinib before the deterioration of liver function may achieve better survival outcomes in advanced HCC.
Keywords: HCC, Lenvatinib, TACE

O-54

Differential Responses to Nivolumab in Multiple Tumours in Patients with Hepatocellular Carcinoma: Real-Life Experiences in an Endemic Area of Hepatitis B-Virus Infection

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Aims: Real-world results of nivolumab monotherapy against HCC are lacking in the hepatitis B virus (HBV)-endemic, Asia-Pacific regions. Moreover, heterogeneous responses to immune checkpoint inhibitors have rarely been described in advanced HCC. The aim of this study is to evaluate the efficacy and safety of nivolumab monotherapy in a real-world setting in 33 Korean patients with unresectable HCC.

Methods: Data was collected between October 2016 and November 2019 from 33 consecutive patients treated at three university-affiliated hospitals in Korea. Among the enrolled patients,

31 patients were enrolled between February 2018 and November 2019. Clinical parameters and outcome were assessed.

Results: In our cohort, twenty-nine patients (88%) showed HBsAg positivity. At the time of nivolumab initiation, 4 among 33 patients (12%) were classified as Barcelona Clinic Liver Cancer (BCLC)-B stage and 29 (88%) as BCLC-C stage, respectively. Prior sorafenib treatment was given to 31 (94%) patients, and 13 (39%) received prior regorafenib treatment. For the liver reserve, patients were classified as Child–Pugh class A (79%) and B (21%), respectively. Grade 3 toxicities occurred in one patient, who developed pneumonitis after 5 cycles of nivolumab treatment. Best overall responses were complete response in 2 patients out of the 33 enrolled patients (6%), partial response in 4 patients (12%) and stable disease in 4 patients (12%). With 29 patients having images for the response evaluation, the objective response rate was 21.4%. The median overall survival (OS) of the cohort was 26.4 weeks (range 2.3-175.1). Achieving objective responses, pre-treatment small tumours (maximal diameter less than 5 cm) and favourable liver function as assessed by Albumin–Bilirubin grade were significant factors for the favourable OS. Interestingly, differential responses to nivolumab among multiple tumours in a single patient were noted in 6 patients (18%). In these patients, small metastatic tumours were regressed, although their larger tumours did not respond to nivolumab monotherapy.

Conclusions: In summary, nivolumab treatment seems clinically efficacious in treating unresectable HCC in an endemic area of HBV infection. Further prospective evaluation is required to overcome the heterogeneous efficacy of nivolumab monotherapy according to the baseline tumour burden.

Keywords: Hepatocellular carcinoma, Nivolumab, Treatment response, Tumor size

O-55

Infiltrative Type HCC Has Prognostic Impact in Patients with Hepatocellular Carcinoma: Comparison of Modified AJCC Staging System versus Latest AJCC Staging System

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Aims: The American Joint Committee on Cancer (AJCC) 8th edition staging manual introduced several significant changes to the staging system for hepatocellular carcinoma (HCC). However, the revised staging system still does not consider tumor gross morphology when staging, which is considered to be an important predictive factor of survival in HCC patients as previously reported. Firstly, we aimed to compare the diagnostic efficacy of 8th edition of AJCC staging system to 7th edition. Secondly we evaluated the impact of infiltrative type HCC and propose new staging system to improve the diagnostic efficacy of current staging system.

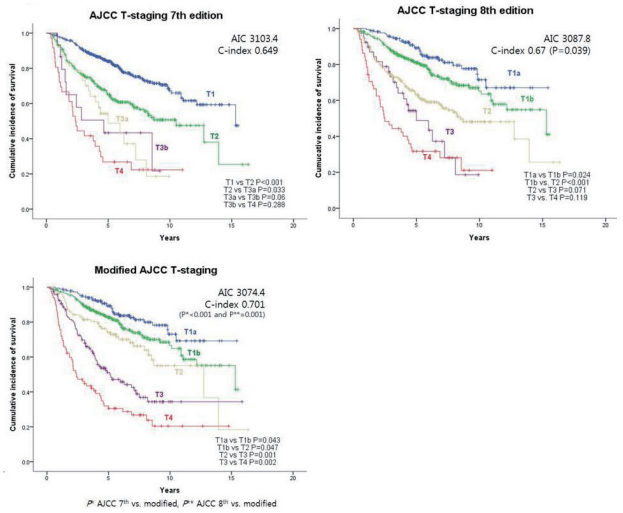

Figure 1.

Table 1.

AJCC T-staging 7th edition		AJCC T-staging 8th edition		Modified AJCC T-staging
T1	Solitary tumor without VI	Solitary tumor ≤2 cm	T1a	Solitary tumor ≤2cm or Multifocal tumors ≤2cm
		Solitary tumor >2 cm without VI	T1b	Solitary tumor >2 cm without VI
T2	Solitary tumor with VI or Multifocal tumors, none >5 cm	Solitary tumor >2 cm with VI or Multifocal tumors, none >5 cm	T2	Solitary tumor >2-4cm with VI or Multifocal tumors >2-4cm
T3a	Multifocal tumors at least one of which is >5 cm	Multifocal tumors at least one of which is >5 cm	T3	Solitary tumor >4cm with VI or Multifocal tumors >4cm
T3b	Solitary tumor or multifocal tumors of any size involving a major branch of the portal vein or hepatic vein			
T4	Tumor with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum	Solitary tumor or multifocal tumors of any size involving a major branch of the PV or HV or tumors with direct invasion of adjacent organs other than the GB or with perforation of the visceral peritoneum	T4	Solitary tumor or multifocal tumors of any size involving a major branch of the PV or HV or tumors with direct invasion of adjacent organs other than the GB or with perforation of the visceral peritoneum or **Large infiltrative type**

Methods: We retrospectively reviewed database of 992 patients with pathologically confirmed HCC between year 2004 and 2016 from three institutes. The infiltrative type HCC was defined as a mass with foci varying in size which fuse to form a larger foci without a distinct margin or a mass with a permeative appearance which blends into the background of the cirrhotic liver with an indistinct margin. Overall survival analysis (OS) were performed using Kaplan-Meier method and compared using log-rank tests. The Harrell concordance index (c index) and Akaike information criterion (AIC) were calculated to compare prognostic powers.
Results: A total of 774 patients who had undergone hepatic resection were available for the analysis. The cohort was comprised of T1 (55.6%), T2 (32.8%), T3a (5%), T3b (4.7%) and T4 (1.9%) stages according to AJCC 7th staging system while T1a (21.4%), T1b (37%), T2 (30%), T3 (5%) T4 (6.6%) stages according to AJCC 8th staging system (Fig. 1). The OS did not differ between the advanced stages (T3a vs T3b; T3b vs T4 in AJCC 7th edition similarly between T2 vs T3; T3 vs T4 in 8th edition). Among all patients, 56 patients had infiltrative type HCC and OS analysis was performed after reclassifying the infiltrative type HCC separately. The OS of the patients with infiltrative type HCC was similar to OS of T4. After excluding infiltrative type HCC, sub-analysis was performed according to tumor sizes (≤2cm, >2-4cm, >4cm) for single and multiple tumors respectively as survival rate did not differ between the stages as shown above. Since the OS rate differed significantly among tumors with different sizes, we modified the T-stages as shown in Table 1. The modified AJCC T-staging system efficiently stratified patients according to survival as shown in Fig.1. Furthermore, modified staging system showed highest diagnostic performance followed by AJCC 8th edition and AJCC 7th edition (AIC 3074.4 vs 3087.8 vs 3103.4 and C-index 0.701 vs 0.67 vs 0.65, all P<0.01).
Conclusions: The AJCC 8th T-staging system showed improved prognostic efficacy compared to 7th edition. However, modified AJCC staging system presented finer stratification of patients compared to previous staging systems by reclassifying sizes within single or multiple tumors and reassigning infiltrative type HCC to T4. The AJCC staging system requires surgical specimen for analysis and this study includes a large number of patients who undergone hepatectomy which is believed to have clinical impact with further validation in other cohorts.
Keywords: Modified AJCC staging system, Hepatocellular carcinoma, Diagnostic performance, C-index

O-56

Comparison of the Effects of Ultrasound Alone and Ultrasound, Computed Tomography, and Magnetic Resonance Imaging Combination on Surveillance in High-Risk Patients with Hepatocellular Carcinoma

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Aims: Many guidelines suggest ultrasonography at six-month intervals for patients at high risk for hepatocellular carcinoma (HCC). Nevertheless, surveillance is often performed by combining ultrasound with computed tomography (CT) and magnetic resonance imaging (MRI). This study analyzed the differences in clinical outcomes depending on whether the patients had imaging tests other than ultrasound as a surveillance test.
Methods: Patients diagnosed with chronic hepatitis B or cirrhosis at Seoul National University Hospital from 2010 to 2014 were included. Patients diagnosed with other cancers or with surveillance intervals shorter or longer than 6±1 month were excluded. Patients were divided into 2 groups: those who only had ultrasound scans (USG group) and those who had a combination of ultrasound, CT, and MRI. (combination group). Propensity score matching was applied to adjust the difference in baseline characteristics between the two groups. The difference of HCC detection, liver-related mortality and all-cause mortality between the two groups was analyzed by the Cox proportional hazards model. The difference in the stages at HCC diagnosis between the two groups was compared using Fisher's exact test.
Results: From a total of 4,779 patients, we obtained a propensity score matched cohort of 794 patients. The combination group showed a higher risk of HCC detection than the USG group. (adjusted hazard ratio [aHR] 2.07; 95% confidence interval [CI] 1.21–3.54) The combination group showed more very early stages at the time of HCC diagnosis based on the Barcelona Clinic Liver Cancer staging system. (Fisher's exact test P=0.03). Liver-related mortality (aHR 2.00; 95% CI 0.53–7.56) and all-cause mortality (aHR 1.06; 95% CI 0.49–2.26) were not significantly different between the two groups.
Conclusions: Combining ultrasound, CT, and MRI as a surveillance test may detect HCC in earlier stages.
Keywords: Hepatocellular Carcinoma, Surveillance, Ultrasound, Computed Tomography, Magnetic Resonance Imaging, Stage

11. Liver Cancer Surgery

O-57

Prognostic Accuracy of the ADV Score Following Resection of Hepatocellular Carcinoma with Portal Vein Tumor Thrombosis

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Aims: We assessed the prognostic accuracy of ADV score (a-fetoprotein [AFP]-des-γ-carboxyprothrombin [DCP]-tumor volume [TV] score) following resection of hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT).
Methods: This was a retrospective observational study. This study included 147 patients who underwent hepatic resection for HCC with PVTT. They were followed up for ≥66 months or until patient death.
Results: The grades of PVTT were Vp1 in 121 (14.3%), Vp2 in 41 (27.9%), Vp3 in 71 (48.3%), and Vp4 in14 (9.5%) cases. Preoperative HCC treatment was performed in 48 (32.7%) patients. R0 and R1 resections were performed in 119 (81.0%) and 28 (19.0%) cases, respectively. The 5-year tumor recurrence, HCC-specific survival and post-recurrence survival rates were 79.2%, 43.5% and 25.4%, respectively. Neither PVTT grade nor history of preoperative HCC treatment was a significant prognostic indicator. Stratification in accordance with ADV scores of 1log- and 3log-intervals resulted in high prognostic accuracy in predicting tumor recurrence and patient survival. Following cluster analysis, the cutoff for ADV score was determined at 9log and was more prognostically significant in terms of tumor recurrence and patient survival than surgical curability or microvascular invasion. Further comparisons revealed that prognostic prediction with an ADV score cutoff at 9log was more accurate than that using the Eastern Hepatobiliary Surgery Hospital-PVTT score.
Conclusions: ADV score is an integrated surrogate biomarker for post-resection prognosis in HCC with PVTT. Our prognostic prediction model using ADV scores provides reliable post-resection prognosis for patients with various grades of these tumors.
Keywords: Resection, Recurrence, Microvascular invasion, Tumor biology

O-58

Prognostic Values of Tumor Burden-Adjusted Levels of AFP and PIVKA-II in Patients with Hepatocellular Carcinoma

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Aims: Alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) are important serum biomarkers for the diagnosis and prognosis of hepatocellular carcinoma (HCC). However, little is known about the expected levels of AFP or PIVKA-II according to the tumor burden. Moreover, the prognostic values of the discrepancy between the actual and expected levels of AFP or PIVKA-II have not been reported. We aimed to determine the expected levels of AFP or PIVKA-II according to tumor burden and evaluate the clinical impact of the difference between the actual and expected levels of AFP or PIVKA-II on prognosis of HCC.
Methods: We included 2,716 patients with newly diagnosed HCC who had a solitary tumor without vascular invasion ($T_1N_0M_0$) utilizing a nationwide population-based cancer registry between 2008 and 2014 in Korea. The expected levels of AFP or PIVKA-II according to the maximal tumor diameters were calculated using linear regression models. We divided the patients into 4 groups according to the difference between the actual and expected levels of AFP or PIVKA-II: both lower than expected (L), AFP-higher and PIVKA-II-lower than expected (AH), AFP-lower and PIVKA-II-higher than expected (PH), both higher than expected (H). The overall survival (OS) of the groups was compared by Log-rank test. Hazard ratios (HRs) of group AH, PH, and H were determined using Cox proportional hazards regression analysis (reference: group L).
Results: There were significant correlations between the maximal tumor diameter and $\log_{10}$-transformed AFP (Pearson's r=0.20, P<0.001) or PIVKA-II (Pearson's r=0.62, P<0.001). Among the 4 groups, the survival rate of group L was the lowest and that of group H was the highest (Log-rank P<0.001; Figure 1). In a post-hoc analysis for the Log-rank test, the survival rate of group AH was comparable with that of group L (P=66), whereas the survival rate of group PH or H was significantly higher than that of group L (both P<0.001). Notably, group PH showed a significantly lower survival rate than group AH (P<0.001). In a multivariable analysis, the adjusted HRs (95% confidence interval) of group AH, PH, and H were 1.18 (0.99–1.41), 1.43 (1.21–1.68), and 1.86 (1.58–2.20), respectively.

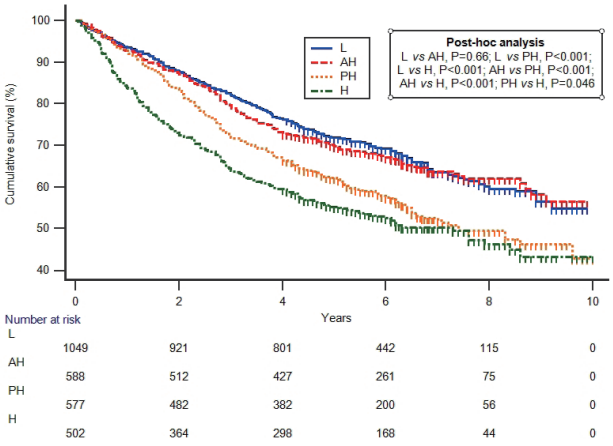

Figure 1. Kaplan-Meier curves according to the difference between the actual and expected levels of AFP and PIVKA-II.
AFP, Alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.
L: actual values of both AFP and PIVKA-II were lower than expected values; AH: actual values of AFP were higher than expected values, but actual values of PIVKA-II were lower than expected values; PH, actual values of AFP were lower than expected values, but actual values of PIVKA-II were higher than expected values, H, actual values of both AFP and PIVKA-II were higher than expected values.

Conclusions: The levels of AFP and PIVKA-II were significantly correlated with the tumor burden in patients with HCC. The difference between the actual and expected levels of AFP and PIVKA-II showed a significant impact on prognosis of HCC.

Keywords: Tumor marker, Tumor burden, Liver cancer, Overall survival

O-59

Risk Factors, Patterns and Long-Term Prognosis of Early and Late Recurrence in Patients with Hepatitis B Virus-Associated Hepatocellular Carcinoma

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Aims: Survival after liver resection of hepatocellular carcinoma (HCC) remains poor due to a high incidence of recurrence. We sought to investigate risk factors, patterns, and long-term prognosis among patients with early and late recurrence after liver resection for hepatitis B virus (HBV)-associated HCC.

Methods: Data of consecutive patients undergoing curative resection for HBV-associated HCC were analyzed. According to the time to recurrence after surgery, recurrence was divided into early (≤ 2 years) and late recurrence (> 2 years). Characteristics, patterns of initial recurrence and post-recurrence survival (PRS) were compared between patients with early and late recurrence. Risk factors of early and late recurrence, and predictors of PRS were identified by univariable and multivariable Cox-regression analyses.

Results: mong 894 patients, 322 (36.0%) and 282 (31.5%) developed early and late recurrence, respectively. On multivariable analyses preoperative HBV-DNA>104 copies/ml was associated with both early and late recurrence, while postoperative no/irregular antiviral therapy was associated with late recurrence. Compared with patients with late recurrence, patients with early recurrence had a lower proportion of intrahepatic only recurrence (72.0% vs. 91.1%, *P*<0.001), as well as a lower chance of receiving potentially-curative treatments for recurrence (33.9% vs. 50.7%, *P*<0.001) and a worse median PRS (19.1 vs. 37.5 months, *P*<0.001). Multivariable analysis demonstrated that early recurrence was independently associated with worse PRS (HR 1.361, 95%CI 1.094-1.692, *P*=0.006).

Conclusions: Although risk factors associated with early recurrence and late recurrence were different, a high preoperative HBV-DNA load was an independent hepatitis-related risk for both early and late recurrence. Early recurrence was associated with

O-60

Consensus Molecular Subtypes Reflecting Distinct Clinical Phenotypes of Hepatocellular Carcinoma: Deciphering Resectable Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is a heterogeneous disease with therapeutic resistance even in the early stage. Current genomic subtyping systems reflect the heterogeneity of HCC, but its clinical use is hampered by discrepancies among different studies.

Methods: By integrating 15 previously established genomic signatures for HCC subtypes, we identified five clinically and molecularly distinct consensus subtypes using transcriptomic data from 8 HCC cohorts with 1754 patients (Discovery set; n=1006, Validation set; n=748).

Results: We demonstrated five consensus subtypes of HCC showing distinct molecular and clinical features regarding STM, CIN, IMH, BCM, and DLP subtypes. Briefly, STM (STeM) is characterized by high stem cell features, vascular invasion, and sensitivity to sorafenib. CIN (Chromosome INstable) has moderate stem cell features, but high genomic instability and low immune activity. IMH (IMmune High) is characterized by high immune activity predicting possible responders for immunotherapies. BCM (Beta-Catenin with Male high predominance) is characterized by prominent beta-catenin activation, low miRNA expression, and hypomethylation. DLP (Differentiated and Low Proliferation) is differentiated with high HNF4A activity. Lastly, we developed and validated a robust predictor of integrated consensus subtype with subtype-specific serum biomarkers using integrative genomic and statistical analysis.

Conclusions: Consensus subtypes of HCC from the comprehensive genomic analysis showed distinct biological and clinical phenotypes, including different dependency for oncogenic pathways and discriminated therapeutic efficacy. Based on the clinical relevance of consensus subtypes for current available therapeutic options in terms of molecular target therapies and immunotherapies, our findings may provide the foundation for rationalized biomarker-based clinical trials for resectable HCC.

O-61

Application of Self-Assembly Peptides Targeting the Mitochondria as a Novel Treatment for Sorafenib-Resistant Hepatocellular Carcinoma Cells

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Aims: Currently, there is no appropriate treatment option for patients with sorafenib-resistant hepatocellular carcinoma (HCC). Meanwhile, pronounced anticancer activities of newly-developed mitochondria-accumulating self-assembly peptides (Mito-FF) have been demonstrated. This study intended to determine the anticancer effects of Mito-FF against sorafenib-resistant HCC cells.

Methods: To generate sorafenib-resistant cultures, Huh7 HCC cells were grown *in vitro* using increasing doses of sorafenib (0.5 μmol/L initially and increasing up to 15 μmol/L) for a total of 8 months. Anticancer effects of Mito-FF against sorafenib-resistant Huh7 (Huh7-R) cells were determined using flow cytometry, cell viability testing, western blot analysis, and MitoSOX staining.

Results: Mito-FF led to the significant reduction of cell viability as well as the increase of apoptosis in Huh7-R cells. Relatively higher populations of apoptotic cell populations were observed in Huh7-R cells following Mito-FF treatment compared to sorafenib ($P<0.05$). Compared to sorafenib, Mito-FF led to the generation of relatively higher amounts of mitochondrial ROS as well as the greater reduction in the expression of antioxidant enzymes ($P<0.05$). Addition of an ROS inhibitor (N-acetyl-L-cysteine) significantly reduced the expression of poly-ADP ribose polymerase (an apoptotic marker) in the Mito-FF treated Huh7-R cells ($P<0.05$).

Conclusions: Mito-FF was found to significantly promote cell apoptosis while inhibiting cell proliferation of Huh7-R cells. Mito-FF also reduces the expression of antioxidant enzymes while significantly increasing mitochondrial ROS in Huh7-R cells. The pro-apoptotic effect of Mito-FFs for Huh7-R cells is possibly caused by their up-regulation of mitochondrial ROS, which is caused by the destruction of the mitochondria of HCC cells.

12. Biliary and Pancreatic Disease

O-62

Prognostic Implication of Biliary Intraepithelial Neoplasia-3 in Bile Duct Resection Margin for Patients with Resected Perihilar Cholangiocarcinoma

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Aims: In surgery for perihilar cholangiocarcinoma (PHCC), it is still controversial as to whether additional resection of the bile duct is needed on biliary intraepithelial neoplasia-3 (BilIN-3) margin.

Methods: Patients who underwent surgery for PHCC with curative intent between 2001 and 2015 were stratified by resection margin, and were analyzed comparing the clinical outcomes.

Results: Of the 306 study participants, 217 patients had negative margins (R0), 18 patients had BilIN-3, and 71 patients had positive margins (R1). The median overall survival of each group was 36.0 months in R0 group, 41.0 months in BilIN-3 group, and 25.0 months in R1 group while overall survival rates at 5 years were 34.5% in the R0 group, 44.4% in the BilIN-3 group, and 21.0% in R1 group. The median disease-free survival was 15.0 months in R0 group, 16.5 months in BilIN-3 group, and 12.0 months in R1 group. In the BilIN-3 group who had recurrence, 8 out of 9 patients had locoregional recurrence.

Conclusions: Even if the BilIN-3 group has the potential to transform into malignancy, the survival and recurrence outcomes were comparable with R0 group, which suggests no additional resection is needed when maximal bile duct margin is BilIN-3 during PHCC surgery.

Keywords: Perihilar cholangiocarcinoma, Margins of excision, Biliary intraepithelial neoplasia-3

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Impact of Latrogenic Biliary Injury during Laparoscopic Cholecystectomy on Surgeon's Mental Distress A Nationwide Survey from China

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Aims: Iatrogenic biliary injury (IBI) following laparoscopic cholecystectomy (LC) is the most common and recognized iatrogenic complications. Little is known whether LC-IBI would lead to surgeon's mental distress. This study reports the incidence of surgeon's mental distress who have caused LC-IBI and risk factors of surgeon's severe mental distress (SMD).
Methods: A cross-sectional survey in the form of electronic questionnaire was conducted among Chinese general surgeons who have caused LC-IBI. The six collected clinical features relating to mental distress included: 1) feeling burnout, anxiety, or depression, 2) avoiding performing LC, 3) having physical reactions when recalling the incidence, 4) having the urge to quit surgery, 5) taking psychiatric medications, and 6) seeking professional psychological counseling. Univariable and multivariable analyses were performed to identify risk factors of SMD, which was defined as meeting ≥3 of the above-mentioned clinical features.
Results: Among 1,466 surveyed surgeons, 1,236(84.3%) experienced mental distress following LC-IBI, and nearly half (49.7%, 614/1236) had SMD. Multivariable analyses demonstrated that surgeons from non-university affiliated hospitals (OR:1.873), patients who required multiple repair operations (OR:4.075), patients who required hepaticojejunostomy/partial hepatectomy (OR:1.859), existing lawsuit litigation (OR:10.491), existing violent doctor-patient conflicts (OR:4.995), needing surgeons' personal compensation (OR:2.531), and additional administrative punishment by hospitals (OR:2.324) were independent risk factors of surgeon's SMD.
Conclusions: Four out of five surgeons experienced mental distress following LC-IBI, and nearly half had SMD. Several independent risk factors of SMD were identified, which could help to make strategies to improve mental well-being of these surgeons.

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Comparison of Perioperative and Postoperative Long-Term Quality of Life after Total Pancreatectomy

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Aims: Quality of Life (QoL) is widely known to be poor after total pancreatectomy. This study was designed to evaluate the short-term and long-term consequences of endocrine and exocrine insufficiency and their associated effects on QoL and nutritional status.
Methods: Prospective data was collected from patients who underwent total pancreatectomy at Seoul National University Hospital during an interval of 4 years and followed up for at least 1 year. QoL, and nutritional status were assessed by administering validated questionnaires (EORTC QLQ C-30, PAN26, GIQLI, MNA), preoperatively and 3, 12 months postoperatively.
Results: A total of 30 patients were eligible for the study. 3 months after receiving total pancreatectomy, the global heath score (GHS) showed no significant difference (preoperatively 57.2 vs. 3 months postoperatively 68.3; *P*=0.119). By the 1st postoperative year, the GHS still showed no significant difference (preoperatively 57 vs. 1 year postoperatively 52.4; *P*=0.2) and there was no significant differences in most of the QoL categories. However, poor physical function (79.2 vs. 67.6; *P*=0.01), digestive difficulties (14.9 vs. 36.9; *P*=0.03) and altered bowel habits (9.2 vs. 25.6; *P*=0.03) continued even 1 year after surgery.
Conclusions: The overall QoL score after total pancreatectomy was comparable to the preoperative QoL score. Some symptoms after total pancreatectomy significantly worsen after 3 months postoperatively, but then improve to a comparable level 1 year after surgery. Because some symptoms persist even after time has passed, supportive management is needed for total pancreatectomy patients, including nutritional support with pancreatic enzyme replacement and education for diabetes and diet.

O-65

Precision Strategies for Multifocal Intrahepatic Cholangiocarcinoma: Integrative Analysis for Comprehensive Genomic Profiling of Multiple

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Aims: Intrahepatic cholangiocarcinoma (IHC) is the second most common primary liver cancer. There is no clinical consensus for the management of multiple tumors in the intrahepatic cholangiocarcinoma. The aim of this study is to evaluate the spatio-temporal evolutions of multiple tumors that belong to the same patients and provide the clinically relevant evidence for precision therapeutic strategies in the intrahepatic cholangiocarcinoma.
Methods: A total of 34 tumors from nine patients were analyzed by next-generation sequencing using custom-designed targeted gene panel with the deep targeted platform. Single nucleotide variants with indel aberration, somatic mutations, and copy number alterations were obtained from bioinformatics computational analysis.
Results: All multiple tumors in each patient showed the signifi-

cant similarity of somatic mutation with indel pattern and copy number alteration. The analysis for spatio-temporal evolution using clustering cancer evolutionary trees revealed that 8 out of 9 patients have multiple tumors from genetically same clonal origin even in different anatomical locations of the liver. We identified shared driver mutations in each patient such as BAP1, IDH1, and BRAF. The only patient not having shared non-synonymous somatic mutation showed a significantly concordant pattern of copy number alteration in multiple tumors.

Conclusions: Genomic profiles were concordant among all tumors in each patient, suggesting a common progenitor cell origin regardless of the location in the liver. Most of the patients were identified to share the actionable genetic alteration commonly in multiple tumors. Our results support the development of molecular-targeted therapeutic strategies in multifocal intrahepatic cholangiocarcinoma.

O-66

Should Patient's Age Be Considered When Performing Pancreaticoduodenectomy for Periampullary Cancer?: National Database Analysis in South Korea

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Aims: The incidence of periampullary cancer in the elderly is increasing. Safety and oncologic effectiveness of pancreaticoduodenectomy (PD) in elderly patients is still controversial.

Methods: From 2002 to 2016, patients with periampullary cancer were evaluated. Customized health information data provided by the National Health Insurance Corporation (NHIS-2018-1-157) were used for analysis. Chronological changes in the incidence of periampullary cancer and long-term survival outcomes were estimated according to patients' age.

Results: A total of 148,080 patients were found to have periampullary cancer. Chronologically, the incidence of periampullary cancer increased, and the proportion of elderly patients with periampullary cancer prominently increased (about 2.1 times in patients in their 70s and about 4.7 times in those aged over 80 years). The number of patients with Pylorus preserving pancreaticoduodenectomy(PPPD) in their 70s (about 5.6 times, $P<0.001$) and over 80 years of age (about 8.9 times, $P<0.001$) was much higher than the number of patients aged below 50 years (about 1.7 times) and in their 60s (about 2.5 times). Long-term survival was different according to diagnosis ($P<0.001$). However, it was observed that age was a factor attenuating the survival of patients with resected periampullary cancers ($P<0.001$).

Conclusions: The incidence of periampullary cancer is increasing in the elderly. Therefore, PD can be considered. However, age was found to attenuate the long-term survival outcome of patients with resected periampullary cancer. The present data can be helpful in the decision-making process for elderly patients with periampullary cancer.

O-67

Histone Deacetylase 8 Inhibition Alleviates Cholestatic Liver Injury and Fibrosis

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Aims: Cholestasis is a pathological condition of blockage of bile flow that results in hepatotoxicity, inflammation, and fibrosis. Recent studies have shown that histone deacetylases (HDACs) are involved in the progression of fibrosis in various organs, but the role of HDAC8 on liver fibrosis has never been explored. In this study, we hypothesized that HDAC8 inhibition could protect against liver fibrosis.

Methods: To address this hypothesis, we newly synthesized a selective HDAC8 inhibitor SPA3014 which is composed of vinyl disulfide-sulfoxide core and evaluated its therapeutic efficacy against cholestatic liver injury and fibrosis in bile duct ligated (BDL) mice.

Results: We observed the increase in hepatic HDAC8 protein levels in mice with BDL and patients with cholestatic liver disease. BDL mice pretreated with SPA3014 had a reduced liver damage and fibrosis, based on gross examination, histopathologic findings and biochemical analyses than vehicle-treated mice. Studies with LX-2 human hepatic stellate cells showed that SPA3014 exerted its protective effects by the inhibition of TGF-ß/MAPK signaling pathway.

Conclusions: All of these results suggest that HDAC8 inhibition could be a new therapeutic strategy for treatment of cholestatic liver injury.

Keywords: HDAC8, Liver fibrosis, Drug therapy, Cholestasis

O-68

Filamin-A Expression Predicts Recurrence of Mass-Forming Cholangiocarcinoma after Hepatectomy

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Aims: Recurrence of mass-forming cholangiocarcinoma (MFCCC) after hepatectomy is very high. A predictive marker of recurrence capable of personalizing follow-up and developing new targeted therapy would be beneficial. The overexpression of Filamin-A (FlnA), a cytoskeleton protein with scaffolding properties, has recently been associated with cell signalling, migration and adhesion in different tumors. The aim of this study was to test the expression of FlnA in a cohort of patients operated for MFCCC.

Methods: A retrospective cohort of patients who underwent hepatic resection for MFCCC at Humanitas Clinical and Research Center between January 2004 and December 2018 was analyzed. FlnA expression was measured by calculating its intensity score at immunohistochemistry on paraffin-embedded tumor tissue sections for each patient. Such expression was then correlated with prognostic parameter of disease-free survival (DFS) by using survival analyses.

Results: A total of 82 patients were considered. Median DFS in patients with low expression of FlnA was significantly increased in comparison with patients with high expression of FlnA (27 months vs. 10 months). Similarly, 5-year DFS was 30.8% vs. 10.9% (*P*=0.008). At the multivariate analysis number of tumor (HR=2.18; CI95% 1.98-3-21; *P*=0.004), tumor grade (HR=2.81; CI95% 1.77-5.12; *P*=0.001) and high expression of FlnA (HR=1.81; CI95% 0.98-2.31; *P*=.0.005) were found to be independently associated with worse DFS.

Conclusions: FlnA expression is associated with higher risk of recurrence of MFCCC after hepatectomy. This finding provides important insights that would help physicians to personalize follow-up strategies and develop targeted therapy.

O-69

Three Thousand Consecutive Pancreaticoduodenectomies in Tertiary Cancer Center: Retrospective Observational Study

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Aims: To evaluate clinicopathological features and chronologic changes of postoperative outcomes in patients undergoing pancreaticoduodenectomy (PD).

Methods: We retrospectively reviewed 2,668 cases of PD performed at Samsung Medical Center in Seoul, Korea for 14 years from January 2005 to December 2018. To identify clinicopathologic features, periampullary diseases were classified into 4 locations of pancreas, bile duct, ampulla and duodenum. The chronologic changes in postoperative outcomes were compared between subdivided periods of 1st period (between 2005 and 2011) and 2nd period (between 2012 and 2018). In order to obtain at least 2 years of follow-up data for survival analysis, 2nd period was set between 2012 and 2016.

Results: 1,098 and 1,570 cases were performed in 1st and 2nd periods, respectively. Most of PD were performed on diseases of pancreas, followed by bile duct, ampulla, and duodenum. Benign cases accounted for about 15% of entire cases. When analyzing chronologic changes of postoperative outcomes in entire cases, we identified complication rate was significantly lower, and hospital stay was significantly shorter in 2nd period. The postoperative pancreatic fistula did not significantly differ between two period groups. In survival analysis of cancers of each location, survival rates were significantly higher in 2nd period than in 1st period.

Conclusions: PD has been increasingly being performed to more patients. It was confirmed the incidence of postoperative complications was reduced and survival was improved in our study. Although we cannot conclude PD is sole factor in improving survival, development of PD will lead to therapeutic improvement in periampullary diseases.

13. Surgery, Technical Issues

O-70

Ten Years Outcomes of Right Anterior Sectionectomy for Liver Disease: A Single-Center Experience with 415 Patients

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Aims: Right anterior sectionectomy (RAS) for hepatic disease is technically difficult and performed infrequently, so there is an insufficient reports about this surgery. We describe here the clinicopathologic and oncologic outcomes of right anterior segmentectomy in 415 patients.

Methods: Patients treated with RAS at department of hepato-biliary and pancreatic surgery, Asan Medical Center, Seoul, South Korea between January 2008 and December 2017 were retrospectively reviewed.
Results: All patients underwent RAS with alternative Glissonean pedicle clamp and Kelly clamp-crushing method for liver transection. Mean operative time was 165 minutes and transection time was 28 minutes. The incidence of major morbidity (≥grade III) occurred in 28 cases(6.7%). Bile leakage occurred in 63 patients (15.1%) but no patient needed reopration(grade C). Post hepatectomy liver failure grade A occurred in 39 patients (9.4%), grade B occurred in 7 patients (1.7%) but there was no patient of PHLF grade C. There was no in-hospital mortality due to postoperative complication. The mean hospital stay was 13.3 days.The pathologic diagnosis were hepatocellular carcinoma (HCC; n=361, 87.0%), intrahepatic cholangiocarcionoma (IHCC; n=15, 3.6%), HCC and IHCC mixed type (n=17, 4.1%), colorectal cancer liver metastasis (n=12, 2.9%), and the other lesions (n=10, 2.4%). Mean tumor size was 3.8 cm. In hepatocellular carcinoma (HCC), 5 year overall survival(OS) rate was 78.3% and 10 year OS rate was 64.4%. Five year disease free survival(DFS) rate was 57.2%, 10 year DFS rate was 37.7%.
Conclusions: RAS showed acceptable procedure-related morbidity, mortality and appropriate oncologic outcomes for HCC.
Keywords: Right anterior sectionectomy, Hepatocellular carcinoma

O-71

Pure Laparoscopic Donor Hepatectomy for Living Donor Liver Transplantation Using Selective Liver Parenchymal Hanging Maneuver and Rubber Band Retraction Technique- Early Experience

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Aims: Most important concern in living donor liver transplantation is donor safety. At the same time, pure laparoscopic donor hepatectomy is being increasingly performed in experienced center although technical difficulties. The aim of this study was to introduce usefulness of selective liver parenchymal hanging maneuver and rubber band retraction technique for pure laparoscopic donor hepatectomy.
Methods: We retrospectively reviewed perioperative data from 19 patients who underwent pure laparoscopic donor hepatectomy. In all procedure, after mobilization of liver, liver parenchymal Transection plane was straightly exposed using rubber band retraction technique. silastic drain for hanging maneuver was pulled up behind the hepatic hilum for the selective liver parenchymal hanging maneuver. after parenchyma transaction was completed, graft side bile duct, hepatic artery and portal vein was divided. hepatic vein ligated and divided using endo GIA. Graft liver was procured via transverse suprapubic incision.
Results: The overall median operation time was 351 min (range 280-482 min), and the volume of blood loss was 412 mL (150-600 mL). The warm ischemic time was 10 min (7-17 min). A conversion to open procedure and more than grade III complication according to the Clavien-Dindo classification was not occurred.
Conclusions: selective liver parenchymal hanging maneuver and rubber band retraction technique is easy to apply and leads to successful pure laparoscopic procedure for donor hepatectomy. Our results demonstrate the safety and feasibility of this technique.

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A Novel Technique for Bile Duct Division during Laparoscopic Living Donor Heptectomy to Overcome Biliary Complication in Liver Transplantation Recipients: 'Cut and Clip' rather than 'Clip and Cut'

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Aims: This study was designed to analyze the clinical impact of our new bile duct division technique during laparoscopic living donor hepatectomy.
Methods: Laparoscopic donor hepatectomy performed by a single surgeon between December 2016 to August 2019 were included. The magnetic resonance cholangiopancreatography of the donors were reconstructed and the length of the common channel of the dividing intrahepatic duct was measured. Patients were divided into two groups based on the bile duct division technique of 'clip and cut' and 'cut and clip'. Outcome of bile duct division was categorized based on the graft and bile duct type and number of bile duct opening
Results: A total of 159 transplantations were included. There were more patients with bile duct division point within the common channel in the 'cut and clip' group (77.5% vs. 90.6%, *P*=0.039). While 'cut and clip' only showed a trend toward significance for better biliary stricture-free survival compared to 'clip and cut' (*P*=0.057), it showed significantly superior biliary stricture-free survival in cases with a common channel of intrahepatic ducts. (n=128, *P*=0.029) When cases were subdivided based on the length of the common channel, 'cut and clip' showed significantly superior outcome in donors with a common channel shorter than 10 millimeters (*P*=0.043) while the outcomes were similar in cases with 10 to 14.99 millimeters (*P*=0.236) and longer than 15 millimeters (*P*=1.000).
Conclusions: 'Cut and clip' technique during bile duct division of laparoscopic donor hepatectomy showed superior outcome in bile duct division and biliary stricture-free survival of the recipients.

O-73

Aggressive Approach for Preoperative Future Liver Augmentation with Special Focus on Local Tumor Control and In-Situ Immunization for Patient with Advanced HCC and Liver Cirrhosis

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Aims: Portal vein embolization(PVE) provokes cancer progression. Our aim was to develop method of future liver remnant(-FLR) augmentation that not only enable local tumor control but possible enable anticancer In Situ immunization during FLR regeneration.

Methods: 3 initially unresectable patients due to small FLR with advanced hepatocellular carcinoma(HCC) and liver cirrhosis were treated. Selective transarterial chemoembolization with doxorubicin 50mg and short term biodegradable starch microspheres(DSM-TACE), into tumor bearing liver to be resected, was simultaneously followed by PVE of latter. Upon completion of PVE selective intratumoral immunotherapy(HIT-IT) with atezolizumab 1200mg into restored after DSM-TACE tumor arterial feeders (for selective connection with PD-L1 ligands located on tumor cells but not on normal human tissues) was done. DSM-TACE and HIT-IT was repeated one more time in all patients after postzenith decrease of T-cytotoxic cells level in peripheral blood had started. Anticancer immune response was investigated by comparison of Initial histopathology specimen with specimen obtained just before second DSM-TACE+HIT IT and finaly with specimen of resected tumor bearing liver. Latter were analysed along with peripheral blood flow cytometry.

Results: Predominantly T and NK cells response was obtained. All patients had successfully underwent extended liver resection upon sufficient FLR regeneration. In all 3 cases we had achieved effective local tumor control via total or subtotal HCC necrosis, even more, in 1(33%) case planned amount of liver resection was decreased due to achieved tumor downsizing. There were no procedure related severe morbidity or Immune-related adverse events (irAEs). Also there were no postresectional liver failure.

Conclusions: Herein we had proposed new aggressive but safe method of FLR augmentation for patients with HCC and liver cirrhosis that could not only potentially preclude drop out of patients during anticipated prolonged waiting period of FLR augmentation but also possible improves long-term outcomes by means of tumor downsizing and HCC immunoscore conversion.

Keywords: HCC, PVE, In Situ Immunization

O-74

Safety of Barbed Suture Material for Wound Closure in Single Incisional Cholecystectomy

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Aims: Single incisional cholecystectomy is surgical methods that provide comparable results to standard laparoscopic cholecystectomy (LC). However, single incisional cholecystectomy has been accused for post-operative incisional hernia. The incidence of incisional hernia after single incisional cholecystectomy is reported at 2.2% to 2.4% in short-term follow-up studies and up to 10.9% in long-term follow-up. One of incisional hernia's risk factor is surgical technique failure during wound closure. This study evaluated the incidence of patients developing incisional hernia after single incisional cholecystectomy, and we hope to suggest a solution in overcoming incisional hernia arising out surgical technique failure by using barbed suture material during wound closure.

Methods: Total number of 984 patients underwent single incisional cholecystectomy between March 2014 and December 2019. During this period, there were 689 patients who underwent wound closure with non-barbed suture material (Monosyn◯R) and 295 patients with barbed suture material (StratafixTM). Both Patient groups were comparable in age, gender, BMI, ASA score and total operation.

Results: 2 patients (0.3%) developed an incisional hernia in non-barbed suture group and none in the barbed suture group. The incidence of incisional hernia was higher in the non-barbed suture group (0.3% versus 0%), but statistically insignificant. (P=1.00).

Conclusions: Our large volume study showed lower incidence of incisional hernia (0.3%) to comparing previous studies. Also, there was no incisional hernia patient in barbed suture group, although statistically insignificant, which means possibility of overcoming the surgical technique failure using barbed suture material. We hope to share our experience on safety and advantage of using barbed suture.

O-75

The Utility of Intercostal Port with the Left Lateral Position for Laparoscopic Liver Resection of Tumors in the Right Posterior Section

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Aims: This study aimed to evaluate the utility and safety of intercostal port with the left lateral position for laparoscopic partial resection of hepatic tumors in the right posterior section.

Methods: A total of 21 patients were included in this study. All surgical procedures were performed in the left lateral position. Intercostal port was inserted at the 8th to 10th intercostal space with inspecting the movement of diaphragm, not to penetrate the lung. Parenchymal transection was performed with the intermittent Pringle maneuver using the bulldog clamp. After transection, intercostal port was closed by an Endostitch device (Covidien, Mansfield, MA) concurrently with aspiration of intrapleural air for preventing pneumothorax. Perioperative characteristics were evaluated.
Results: The surgical indications were hepatocellular carcinoma in 14 patients and colorectal cancer liver metastasis in 4 patients. Median operation time was 190 minutes (100–355), and no patients received transfusion. Median tumor size was 2.1 cm (0.8–3.6), and R0 resection was achieved in all patients. In this cohort, pulmonary complications including pneumothorax did not occur, and only one patient experienced complication of Clavien–Dindo grade IIIA; irrelevant to the intercostal port. Median hospital stay was 6 days (5–37).
Conclusions: Laparoscopic liver resection using the intercostal port in the left decubitus position could be a safe and feasible approach for tumors in the posterior section without causing serious complications.

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GI Surgery

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Aims: The aim of this study was to determine the outcome of liver injuries managed operatively or non-operatively and predict factors affecting morbidity and mortality.
Methods: This was a retrospective study of 40 liver injuries managed in the department of Surgical Gastroenterology at College of Medical Sciences over a period of 2 years. The liver injury was classified in accordance with the American Association for the Surgery of Trauma liver injury scoring scale. Patients were divided into two groups those managed operatively or non-operatively and were compared in terms of demographic profile and outcome.
Results: Forty patients were analyzed. The mean age of the patients was 29.95years. Male predominance was seen with 72.5% of the cases. Road traffic accidents were the commonest mode of injury seen in 72.5% cases. The mean Revised Trauma Score (RTS) and Injury severity score (ISS) were 7.11and 22.58. The mean systolic BP, hospital stay and ICU stay were 93.80 mm of mercury, 11.55 days and 3.55 days respectively. Twenty six patients (65%) were initially managed non-operatively and 14 patients were managed operatively. Five patients had to be converted to operative management for hemodynamic instability. Mortality was 7.6% in patient undergoing non-operative management and 21.43% in patients managed operatively. Low systolic BP at presentation, low RTS score, high ISS score, high AST, ALT and prothrombin time were significantly associated with operative management and mortality.
Conclusions: Patients with hemodynamic instability, low RTS score, high ISS score, high liver enzymes have high likelihood of operative management.
Keywords: Liver injury, Non-operative management, Operative management, Revised trauma score

O-77

Technique of Robotic Repair of Postcholecystectomy Bile Duct Stricture

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Aims: Despite technical advancements, iatrogenic bile duct injury continues to be a major concern in open and laparoscopic cholecystectomy. Traditionally repair of postcholecystectomy biliary stricture by tension-free Roux-en-Y hepaticojejunostomy (RYHJ) is done through a large subcostal or midline incision. While laparoscopic RYHJ is feasible, it has many limitations. The use of the robotic platform for postcholecystectomy biliary stricture is scarcely described. The technique of robotic postcholecystectomy biliary stricture repair using DaVinci Xi Robotic Surgical System is described in this video
Methods: With the patient in a supine position, four 8mm robotic trocars 6-8cm apart are placed in a straight horizontal line at the level of the umbilicus. One 12 mm assistant trocar is placed 4 cm below umbilicus between arm 1 and 2. Before docking intraabdominal adhesiolysis is performed except perihepatic adhesions as it facilitates liver retraction. Key steps are the identification of the base of segment 4, preservation of left hepatic artery, lowering of the hilar plate, the opening of the left hepatic duct, identification of right anterior and posterior sectoral duct, preparation of roux limb and construction of RYHJ.
Results: Five patients (type II stricture(n=3), type III(n=2)) underwent robotic repair. The median (range) operative time, blood loss, and postoperative hospital stay were 280(260-300) min, 125(100-150)mL, and 5(4-7) days respectively. At a median follow-up of 12 months, all are asymptomatic with normal liver function tests.
Conclusions: Robotic postcholecystectomy biliary stricture repair is safe and feasible in expert hands. The long-term outcome needs to be evaluated in a larger series.

14. Liver Transplantation

O-78

Outcomes of Robotic Living Donor Right Hepatectomy from 52 Consecutive Cases: Comparison with Open and Laparoscopy-Assisted Donor Hepatectomy

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Aims: To investigate the feasibility and safety of an alternative robotic living-donor right hepatectomy (RLDRH) technique.Data for minimally invasive living-donor right hepatectomy, especially RLDRH, in a relatively large donor cohort have not been reported yet.

Methods: From March 2016 to March 2019, 52 liver donors underwent RLDRH. The clinical and perioperative outcomes of RLDRH were compared with those of conventional open donor right hepatectomy (CODRH; n=62) and laparoscopy-assisted donor right hepatectomy (LADRH; n=118). Donor satisfaction with cosmetic results was compared between RLDRH and LADRH using a body image questionnaire.

Results: Although RLDRH had a longer operative time (RLDRH, 493.6 min; CODRH, 404.4 min; LADRH, 355.9 min, P<0.001), its mean estimated blood loss was significantly lower (RLDRH, 109.8 mL; CODRH, 287.1 mL; LADRH, 265.5 mL; P<0.001). The postoperative complication rates were similar among the three groups (RLDRH, 23.1%; CODRH, 35.5%; LADRH, 28.0%; P=0.420). Regarding donor satisfaction, the body image and cosmetic appearance scores were significantly higher in RLDRH than in LADRH. There was no significant difference in hospital stay among the three groups (P=0.105). After propensity score matching, RLDRH showed a shorter hospital stay and similar complication rate than CODRH.

Conclusions: RLDRH resulted in a similar postoperative complication rate and shorter length of hospital stay compared with those of CODRH and provided better body image and cosmetic results compared with those of LADRH. RLDRH is feasible and can be safely performed by expert surgeons in both robotic systems and open hepatectomy.

O-79

Outcomes of Pediatric Liver Transplantation in Korea Using Two National Registries

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Aims: This retrospective study aimed to evaluate overall survival and the risk factors for mortality among Korean pediatric liver transplantation (LT) patients using data from two national registries: the Korean Network Organ Sharing (KONOS) of the Korea Centers for Disease Control and Prevention and the Korean Organ Transplantation Registry (KOTRY).

Methods: Prospectively collected data of 755 (333 male, 422 female) pediatric patients who underwent primary LT (KONOS, February 2000 to December 2015; KOTRY, May 2014 to December 2017) were retrospectively reviewed.

Results: The 1-, 5-, 10-, and 15-year survival rates were 90.6%, 86.7%, 85.8%, and 85.5%, respectively, in KONOS, and the 1-month, 3-month, 1-year, and 2-year survival rates were 92.1%, 89.4%, 89.4%, and 87.2%, respectively, in KOTRY. There was no significant difference in survival between the two registries. Multivariate analysis identified that body weight ≥6 kg (P<0.001), biliary atresia as underlying liver disease (P=0.001), and high-volume center (P<0.001) were associated with better survival according to the KONOS database, while hepatic artery complication (P<0.001) was associated with poorer overall survival rates according to the KOTRY database.

Conclusions: Long-term pediatric patient survival after LT was satisfactory in this Korean national registry analysis. However, children with risk factors for poor outcomes should be carefully managed after LT.

Keywords: Pediatric, Liver transplantation, Survival

O-80

Liver Stiffness Measurement and Outcome of Living Donor Liver Transplantation

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Aims: Liver stiffness measurement using transient elastography (Fibroscan) is non-invasive method for evaluating liver fibrosis which is preceding factor for cirrhosis and widely used. Liver stiffness measurement in liver transplant era is not-well known yet. The aim of this study is to evaluate the correlation between liver stiffness measurement and graft survival, patient survival, hepatocellular recurrence and acute rejection in living donor liver transplantation.

Methods: From January 1, 2014 to May 30, 2019, patients who received living donor liver transplantation and checked

by fibroscan either donor or recipient were included. Baseline characteristics and pre-operative donor LSM (liver stiffness measurement), recipient post 1-month and 1-year LSM was evaluated. Graft survival, patient survival, HCC recurrence and rejection was checked and analyzed with LSM values.

Results: Total 237 patients were included. 174 patients were with hepatitis B virus, and 63 were not. Donor LSM was checked in 233 patient, 1-month LSM in 206 patients and 1-year LSM in 62 patients. Each LSM did not affect graft survival significantly. Donor LSM increased patient death in univariate and multivariate analysis (RR=1.50, *P*=0.018, multivariate). Especially, donor LSM more than 5kPa has higher effect on patient death (HR=3.58, *P*=0.004, multivariate). Each LSM did not affect HCC recurrence significantly. Regarding TCMR (T-cell mediated rejection), 1-year LSM had increased the risk (HR=1.20, *P*=0.045, multivariate), especially when 1-year LSM value was more than 8kPa (HR=8.45, *P*=0.007, multivariate). This tendency was also shown with correlation between 1-year LSM (>8kPa) and TCMR which happened after 1 year (HR=9.93, *P*=0.048, multivariate). In hepatitis B virus patients, LSM looks like having more influence on patient death and TCMR at all times. Donor LSM more than 5kPa increased the risk of patient death (HR=4.5, *P*=0.001, multivariate), 1-year LSM more than 8kPa increased the risk of TCMR in all times (HR=38.7, *P*=0.009, multivariate) in patients with HBV.

Conclusions: Pre-operative donor LSM more than 5kPa had increased patient death noticeably. Recipient's 1-year LSM more than 8kPa had increased TCMR both at all times and 1 year after transplantation noticeably. This tendency had slightly bigger when patients were with hepatitis B virus.

Keywords: Liver transplantation, Fibroscan, Patient death, Rejection

O-81

Prognostic Impact of MELD Scores Greater than 40 in Deceased Donor Liver Transplant Recipients

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Aims: Since 2016, Korean liver organ allocation system has been based on model for end-stage liver disease (MELD). Some patients on waiting list progressed to MELDs >40 due to serious shortage of donor organs. This study investigated prognosis of deceased donor liver transplantation (DDLT) recipients with MELD scores >40.

Methods: Data from adult patients with MELD scores ≥31 who underwent DDLT between June 2016 and November 2019 were retrospectively evaluated. Patients were categorized according to Korean Network for Organ Sharing (KONOS) status 3, 2, or MELD-over-40.

Results: During the study period, 168 DDLT operations were performed in 160 patients with KONOS status 3 in 77 (48.1%), status 2 in 65 (40.6%) and MELD-over-40 in 18 (11.3%). Graft survival rates of primary DDLT were 84.0% at 1 year and 70.7% at 3 years. Overall patient survival was 85.2% at 1 year and 70.7% at 3 years. The 3-year patient survival was 74.4%, 75.7%, and 52.7% in KONOS status 3, status 2, and MELD-over-40 groups (*P*=0.19). Pretransplant ventilator support was associated with inferior patient survival outcomes (*P*=0.043), but pretransplant renal replacement therapy showed no prognostic significance. Retransplantation showed a significant prognostic difference (*P*<0.001). Multivariate analysis for overall patient survival showed that pretransplant ventilator support and retransplantation were significant prognostic factors, but MELD score >40 was not seen to be an independent risk factor.

Conclusions: This analysis revealed that very high MELD scores >40 appear to confer additional risk in patients with KONOS status 2 although it was not an independent prognostic factor.

Keywords: Deceased donor, Mortality, Waiting list, Ventilator

O-82

Effect of Statin Use on the Prognosis of Patients Who Underwent Liver Transplantation for Hepatocellular Carcinoma

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Aims: The protective effect of statin on the development of hepatocellular carcinoma (HCC) and survival has been demonstrated from previous observational studies in patients with chronic live disease. However, it is unclear whether statin use is associated with a risk reduction of HCC recurrence in patients who underwent liver transplantation (LT) for HCC.

Methods: Consecutive patients who underwent LT for HCC between January 1995 and December 2019 were enrolled. Patients who used statins for more than 30 days after the date of LT were defined as statin users. Patients were excluded when they were followed up for less than 3 months or HCC recurred within 2 months after LT. We used time-dependent Cox regression models to overcome immortal-time bias.

Results: A total of 430 patients were enrolled and 321 patients (74.7%) were statin non-users and 109 (25.3%) were statin

users. During a median follow-up of 64.9 months (range 3.1–267.5), 298 patients (69.3%) survived and 111 (25.8%) expired. The number of patients within the Milan criteria before LT was 356 out of 427 (83.4%). HCC recurred in 79 (18.4%) patients after a median 11.1 months (range 2.4–150.8) of LT. Statin use was associated with significantly lower risk of HCC recurrence after adjustment of age, sex, history of pre-treatment, trough concentration of calcineurin inhibitor, total cholesterol, AFP, Milan criteria and time-dependent covariates (DM, use of aspirin and metformin) (P=0.043, HR = 0.98, CI 0.95–1.00). Statin users also had a significantly higher overall survival and lower HCC-related mortality than statin non-users (P=0.003 and P=0.042 by Cox regression analysis, respectively). There was a dose-dependent relationship between statin use and HCC recurrence.

Conclusions: Statin use significantly reduced the risk of HCC recurrence and improved survival of patients who underwent LT for HCC.

Keywords: Statin, Liver transplantation, Hepatocellular carcinoma

O-83

Extended Living Liver Donor Criteria Focusing on Donor Safety in Living Donor Liver Transplatation

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Aims: Donor safety has been considered as primary focus of transplant programs that perform living donor liver transplantation (LDLT) and moreover, a major living donor complications seem to be avoidable through the strict selection criteria of living donor. Recently, conventional donor selection criteria has been modified to expand the donor pool in LDLT but the extended donor concept is not clearly defined yet. Herein, we describe our center's experience for extended donor criteria for LDLT focusing on donor safety.

Methods: We retrospectively reviewed the outcomes of 424 living donor right hepatectomy (LDRH) including 105 extended criteria donors who performed at our institution from January 2010 to June 2019. Extended Donor was defined with criteria as follows; 1) old donor (age >40 years) with remnant liver volume of <35%, 2) young donor (age ≤40 years) with remnant liver volume <29% and minimal fatty change (<15%), 3) young donor with mild hepatosteatosis (15%-30%) and remnant liver volume < 35%. The outcomes in extended living donors were compared with those in living donors under conventional criteria focusing on donor safety. Posthepatectomy liver failure (PHLF) was defined according to the International Study Group of Liver Surgery (ISGLS) criteria. We also included statistical analysis of risk factors that are related to PHLF.

Results: PHLF occurred in 43 donors (10.1%). Most cases were grade A except one case in conventional donor group (grade B) and PHLF did not occur more frequently in extended donor group. (7.6% vs. 11.0% P=0.32) and the incidence of major postoperative complications requiring any interventions did not differ between the 2 groups. Moreover, no difference in either posttransplant graft function or survival was apparent between the 2 groups. In multivariate logistic regression analyses, only the event for major complications (OR, 3.002; 95% CI, 1.042-8,649; P=0.042) was associated with PHLF but not related to extended criteria.

Conclusions: LDRH under our extended donor criteria could be performed to expand donor pools without adverse effects on donor safety.

Keywords: Extended criteria, Donor safety, Living liver donor, Liver transplantation

O-84

Indocyanine Green Near Infrared Fluorescence Cholangiogram during Pure Laparoscpic Living Donor Hepatectomy for Optimal Bile Duct Division

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Aims: Various methods to decrease biliary complications have been studied and determining the optimal bile duct division point is important to decrease complication. Recently, indocyanine green (ICG) near-infrared fluorescence cholangiography has been applied in laparoscopic donor hepatectomy. Because of its advantages in laparoscopic surgery, conventional cholangiography replaced by ICG fluorescence cholangiography in some institutions which have laparoscopic donor hepatectomy cases. We compared conventional cholangiography and ICG fluorescence cholangiography in determining optimal bile duct division point in pure laparoscopic donor hepatectomy.

Methods: From May 2016 to October 2019, 80 cases of pure laparoscopic donor hepatectomy has been performed by a single surgeon in Kyungpook national university hospital. Conventional cholangiography was used in 45 cases, ICG fluorescence cholangiography was used in 35 cases. We compared the outcomes of two groups in preoperative bile duct anomaly of donor, operative time and postoperative complications.

Results: In bile duct anomaly of donors, there were no differences between two groups because donor selection criteria was same. Operative time was much longer in conventional cholangiography group because the procedure itself was time consuming. In conventional cholangiography group, 1 case biliary complication occurred. Bile leakage from the cutting edge of the remnant right hepatic duct was identified, resolved by ERCP and ERBD insertion.

Conclusions: ICG fluorescence cholangiography is more easier and convenient method than conventional cholangiography to perform bile duct division and dissection and is helpful to determine optimal bile division point.

Poster Exhibition

Liver Failure, Acute

PE-001

Role of Wearable Technology on Chronic Liver Disease in Type 2 Diabetic Patients

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Aims: New wearable sensor networks together with smartphone applications are being examined and tested for their potential to monitor and manage chronic liver disease (CLD) in type 2 diabetic patients. To develop methods for analyzes and monitor of map the intersection(s) of hepatology data in relation to CLD via wearable technology (MI band and Yu band). To study effects of daily life routine activities on data by a wearable devices that can obtain real-time CLD data, help technologists understand medical aspects, and clinicians to understand technological processes them and provides assistance based on pre-determined specifications in CLD in type 2 diabetic patients in Agra city, India.

Methods: Total of 106 CLD with type 2 diabetes patients were taken as subject with an equal ratio of male and female. Wearable monitoring devices were put on the wrist of CLD patients for 30 days and a questionnaire was filled out by each patient. Both diabetes and cardiovascular disease in turn are known as important factors for developing CLD and aggravation toward once end-stage liverl disease. In all subjects, blood glucose was measured on daily basis with day to day data of their monitoring of step count (deep sleep, light sleep, wake up time), blood pressure, calorie burnt, insulin dose, motion time i.e. every time when your body was in motion, sleep monitoring, monitoring heart rate, cardiac arrhythmias to know daily routines and recording them for health purpose.

Results: Present results shown that both wearable device reading showed there was a normal heart rate, more calorie burnt with better control of sugar control and average good sleep count in more physically workout, include walking in CLD patients compared to less physically workout CLD patients, identified by professional physiotherapists. Both device reading showed that after changing lifestyle routine among less physically active CLD patients, their post- CLD events normalize with less requirement of medicine and insulin injection dose.

Conclusions: With this study we show that, by using, these wearable devices ensured online assistive feedback for CLD patients with type 2 diabetes is possible with their health awareness, exercising and motivate further studies.

Keywords: Chronic liver disease, Type 2 diabetes, Patients, Wearable technology

PE-002

Thermoneutral Housing Exacerbates Liver Fibrosis In Mice

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Aims: Thermoneutral condition has been had a significant impact on metabolic studies. The roles of brown adipose tissue (BAT) on metabolic disease including obesity or fatty liver is receiving increasing attention. Here, we investigated the impact of thermoneutral condition on hepatic fibrosis as well as the contribution of BAT on regulation liver fibrosis in mice.

Methods: In this study, we used carbon tetrachloride (CCl_4) induced liver fibrosis mouse model and hepatic stellate cells isolated from mice in order to checked fibrotic marker in mice livers housed under room temperature and thermoneutral condition for three weeks. We also compared the changes in the population of hepatic immune cells and the deposition of collagen in mice livers between two kinds of housing conditions. Furthermore, we investigated the effect of secreted factors from brown adipocytes-conditioned media on hepatic stellate cells (HSC) activation process.

Results: Serum levels of liver injury and the expression of *Col1a1, Acta2* and inflammatory cytokines were up-regulated in the liver of mice under thermoneutral condition compared to room temperature. Moreover, inactivation of BAT by thermoneutrality aggravated hepatic collagen deposition as well as promoted the activation of hepatic stellate cells during CCl_4-induced liver fibrogenesis. In consistent with these findings, we also found that the population of infiltrating liver immune cells and pro-inflammatory cytokine-producing T cells was significantly increased in thermoneutral housing mice livers. Treatment of brown adipocytes-conditioned media attenuated HSC activation through down-regulated expression of *a-SMA* at day 4, day 7 and day 10 cultured HSC.

Conclusions: These results suggest that BAT inactivation by thermoneutrality contributes to the activation of pro-inflammatory and pro-fibrotic pathways in CCl_4-induced liver fibrogenesis. Secreted factors released from BAT have potential roles on inhibiting HSC activation. Thus, BAT-liver axis may serve as a potential therapeutic target for liver fibrosis.

Keywords: Liver fibrosis, Hepatic stellate cells, Thermoneutral, Brown adipose tissue

PE-003

The Gate Keeper System in Accessing Health Services, Can It Prevent Cirrhosis Hepatitis Patient from Out of Pocket?

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Aims: In Indonesia, Cirrhosis Hepatitis is the 5th disease with the most social insurance claims after heart disease, stroke, kidney failure, and cancer. Hepatitis Cirrhosis case-control program is focused on preventing Mother to Child Transmission (PPIA) because 95% of hepatitis B transmission is vertical, ie from mothers who are positive for hepatitis B to the fetus. Thus, every baby (0-11 months old) is required to get a complete basic immunization consisting of 1 dose of Hepatitis B, 1 dose of BCG, 3 doses of DPT-HB-HiB, 4 doses of polio drops, and 1 dose of measles / MR. Program coverage reaches 90.61% in 2018 nationally. Nevertheless, the prevalence of hepatitis sufferers increased from 0.2% in 2013 to 0.4% in 2018, equivalent to 13.5 million sufferers dominated from remote provinces such as Papua Island and the Nusa Tenggara Islands. This number makes Indonesia the 3rd country in Asia with the most cases of chronic hepatitis B sufferers after China and India. This study aims to analyze and evaluate risk factors of national policy objectives implementation.

Methods: Using the juridical-empirical approach, this study analyzes whether Indonesia's health service practices conformity is in line with national policy objectives. In accordance with National Social Security and Law Number 11 of 2009 concerning Article 19 of Law concerning Social Welfare, the government is obliged to ensure equal health services access and facilities due to Universal Health Coverage including promotive, preventive, curative, and rehabilitative services by adhering to the cooperation principle (*gotong royong*).

Results: JKN aims to protect the citizens from financial risks through the Social Security Organizing Agency (BPJS) that will cover all types of diseases (Minister of Health Regulation 28/2014). Thus, the cost burden is allocated by the BPJS for curative Cirrhosis Hepatitis absorbs U $ 21.17 million in 2017 and U $ 14 million in 2018. Meanwhile, almost 784.3 thousand individuals each year fall into poverty as a result of hepatic health costs. However, the provisions on the National Formulary 2017 on drugs to reduce symptoms such as pegylated injection, adefovir dipropyl, entecavir, lamivudine, ribavirin, tenofovir, and telbivudine are limited in number and can only be accessed at level 1 facilities at hospitals that are difficult to access community in remote areas. Further, when performing surgery, it turns out there are costs that are not covered and eventually patients become difficult to pay for health care costs. Meanwhile, patients fall into poverty as a result of Cirrhosis Hepatitis health costs. The patient has to spend the cost of illness that is borne for life by 2.7 percent of total household consumption expenditure. This has an impact on reducing the quality of life of patients.

Conclusions: The government has not achieved the goal of eliminating Cirrhosis Hepatitis patients from "out of pocket" yet. The government needs to overcome the health policies overlapping and develop hospital formularies due to prevention and health promotion programs. Further, the national health insurance program needs to be allocated more effectively for the construction of the health infrastructure in remote areas to improve the patient's QoL.

Keywords: Social insurance, Gate-keeper system, Liver dysfunction, Juridical-empirical approach, Out of pocket, Quality of life

PE-004

Acute Liver Failure due to Disseminated Varicella Zoster Virus Infection

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Aims: Varicella zoster virus (VZV) can cause chicken pox and herpes zoster. VZV infection can result in life-threatening complications including hepatitis, pneumonitis and encephalitis, especially in immunocompromised patients. We report a case of varicella hepatitis and esophagitis in a healthy patient with a recent use of steroids.

Methods: A 54-year-old male with hypertension, presented to the emergency department with two days of abdominal pain. A week ago he was discharged from the department of ophthalmology. The following drugs were used during the hospital stay; Intravenous(IV) methylprednisolone for 4 days, oral prednisolone for 7 days, oral levofloxacin for 3 weeks, and IV flomoxef for 2 weeks. Laboratory studies showed leukocytosis and elevation of liver enzymes. We performed abdomen computerized tomography, which showed mild hepatomegaly with periportal edema. He was hospitalized for hepatitis. The morning after, we underwent upper gastrointestinal endoscopy due to sustained abdominal pain. Endoscopy showed white multiple punch-out-shaped ulceration (Figure 1). After 24 hours of hospitalization, diffuse maculopapular eruption on the whole body was noted (Figure 2).

Results: Considering the clinical situation, disseminated VZV infection with secondary bacterial infection was suspected, and IV acyclovir, VZV immunoglobulin, IV ceftriaxone was initiated. In addition, IV hydrocortisone was used upon the diagnosis of adrenal insufficiency. On day 2 of hospitalization, laboratory studies showed worsening liver enzyme elevations and coagulopathy. Within 48 hours of admission, the patient expired with multi-organ failure accompanied by hepatic failure. A few days after the patient's death, blood PCRs were positive with VZV and the biopsy showed multi-nucleated giant cells (Figures 3, 4). Liver biopsy was not performed due to the patient's rapid deterioration.

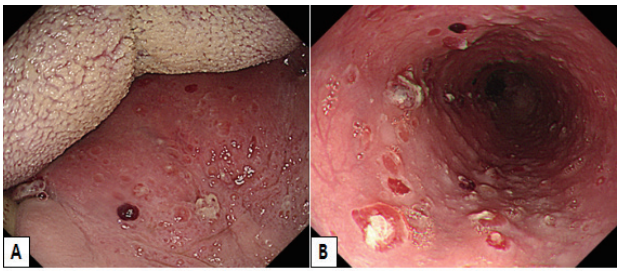

Figure 1. White multiple punch-out-shaped ulceration from the hard palate (A) to the entire esophagus (B).

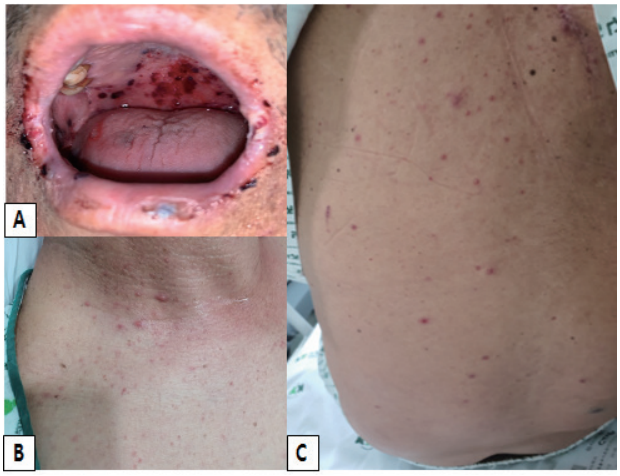

Figure 2. Diffuse maculopapular eruption with a few vesicles on whole body. (A, oral cavity; B, anterior neck; C, back)

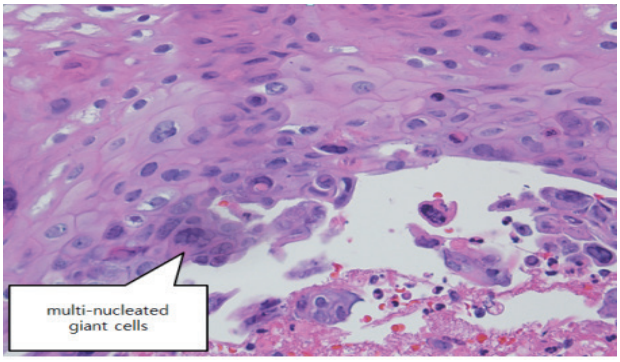

Figure 3. Biopsy of esophageal ulcer showing multi-nucleated giant cells (arrow).

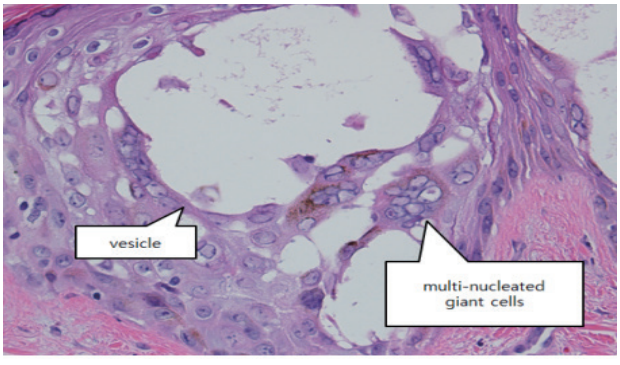

Figure 4. Biopsy of skin lesion showing vesicles and multi-nucleated giant cells (arrows).

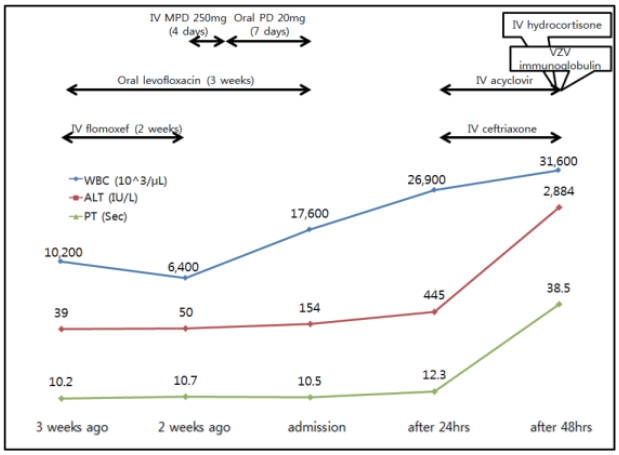

Figure 5. The patient's clinical course. MPD; methylprednisolone, PD; prednisolone.

Conclusions: This case is very unusual as there were no pre-existing factors such as an underlying immunocompromised state or advanced age. We should keep in mind that recent steroid use may increase the risk of fatal varicella.

Keywords: Varicella zoster virus, Fulminant hepatitis, Esophagitis, Steroid use

PE-005

Acute Liver Rejection Values of Doppler US Measurements in Pediatric Cases

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Aims: To prospectively evaluate accuracy and predictive values of Doppler ultrasonographic (US) measurement of portal blood velocity (PBV) and splenic pulsatility index (SPI) in diagnosis of clinically relevant acute rejection in pediatric patients with clinicobiochemical hepatic dysfunction after orthotopic liver transplantation (OLT).

Methods: Study was approved by the institutional review board, and protocol conformed to ethical guidelines of Declaration of Helsinki. Patient informed consent was obtained. In 8 patients with OLT (5 men, 3 women; mean age, 8 years; range, 6-16 years), PBV and SPI were measured at Doppler US within 48 hours before or after liver biopsy for clinically suspected acute rejection. Biopsy specimens were assigned scores according to Banff method, and rejection activity index (RAI) was calculated. RAI score of 4 or greater was considered clinically relevant acute rejection. Doppler US parameters were analyzed as absolute values and as percentage point changes with respect to values obtained at last examination before rejection was suspected.

Results: Clinically relevant acute rejection was diagnosed in nine patients. Median time from OLT until histologic diagnosis of acute rejection was 8 days (range, 5-20 days). Rejection was associated with a marked reduction in mean PBV (-43% +/- 5

[standard error of the mean]) and a slight increase in SPI (+12% +/- 16). The calculated Doppler US composite index was strictly related.

Conclusions: During the first weeks after OLT, a marked decrease in PBV associated with increased SPI supports suspicion of clinically relevant acute rejection.

PE-006

Rare Experience of Emergency Living Donor Liver Transplantation Due to Mush Room Poisoning Presenting with Acute Kidney Injury and Acute Liver Failure

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Aims: Liver transplantation remains the only definitive treatment for patients with acute liver failure proven to have irreversible liver injury. Rapid evaluation and consideration for liver transplantation is mandatory. Here we experienced extremely rare case, the patient with mushrooming posining undergone emergency living donor liver transplantation.

Methods: Retrospective review of medical records was performed for the patient who had suffered from a Acute liver failure and encephalopathy.

Results: A previous healthy 24-year-old man transfer to the emergency department with septic shock. He went play in a mountain stream. Initial lab findings were presented in Table 1. He was admissioned to the nephrologic part for treatment of acdisosis and oligouria and started hemodialysis When re-history taking, his family ate unknown mush room in the mountain stream. For conservative care but his mentality was change on Hospital 3rd day and didn't improved. On Hospital 7th day, He was consulted transplantation surgeon. we did emergency living donor liver transplantation on Hospital 8th day. His father donated his right liver to his son. After the transplantation, his mentality was recovered on post operative 2nd day. But immediate liver transplantation, he suffered from pneumonia-suspected invasive pulmonary infections(IPA) and use antibiotics for a long period and his liver functional recovery round 1month later. He did hemodialysis until post-operative 3month.

Conclusions: A timley diagnosis of Acute liver failure is critical and severe patients who fail to recover after treatment rapidly considerated for liver transplantation is mandatory. Clinicians should be aware of its natural history and start treatment early.

PE-007

Serum Metabolic Biomarkers of Liver Failure after Liver Resection

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Aims: Even the combination of PT and total bilirubin, known for being the most reliable predictive conventional markers shows low sensitivity. Therefore we need to find more relevant biomarkers of liver failure after liver resection focused on the liver metabolites

Methods: A total of 20 pigs were divided into 3 groups sham operation (n=6), 70% hepatectomy group (n=7), and 90% hepatectomy group (n=7). Blood sampling was performed preoperatively and at 1, 6, 14, 30, 38, and 48 hours after the operation we systematically profiled 129 primary metabolites based on gas-chromatography time-of-flight mass spectrometry.

Results: Orthogonal projection to latent structures-discriminant analysis revealed that central carbon metabolism was the most significant factor in the 90% liver-resection group in contrast to the 70% and sham groups. Subsequent binary logistic regression analysis was used to develop a predictive model for the risk of mortality following hepatectomy. The recommended variables were malic acid, methionine, tryptophan, glucose, and γ-aminobutyric acid. The AUC of the linear combination of 5 metabolites was 1.000 (95% confidence interval: 0.940–1.000, sensitivity: 100.0, specificity: 94.87).

Conclusions: Systematic prioritization based on OPLS-DA and binary logistic regression analysis proposed robust biomarker panels that can accurately predict the risk of mortality associated with hepatectomy.

PE-008

Lipidomic Signatures of Post-Hepatectomy Liver Failure Using Porcine Hepatectomy Models

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Aims: Post-hepatectomy liver failure (PHLF) is a critical, unmet need in the surgical treatment of liver diseases. A comprehensive lipidomic analysis was conducted to identify potential lipid signatures that can be used for early prediction of PHLF by examining the serum lipid profiles of pigs undergoing sham operation, 70% and 90% partial hepatectomy (PH).

Methods: Time-dependent changes in individual lipid levels were investigated using sera collected at pre-operation (PO), 14 h,

30 h, and 48 h after PH using nanoflow ultrahigh performance liquid chromatography-electrospray ionization-tandem mass spectrometry.

Results: Of the 184 quantified lipids, 9 lipids showed significant differences (> 2-fold and P<0.01) between the 70% PH and 90% PH groups at 30 h after the operation. The four phosphatidylcholine plasmalogen (PCp) (p-16:0/16:0, p-18:0/18:2, p-18:0/20:4, and p-18:0/22:6) continuously increased by several folds in the 90% PH group while these returned to PO levels after 30 h in the 70% PH group, presumably implying the failure markers. On the other hand, triacylglycerol (TG) showed an opposite trend, wherein five TGs (40:0, 42:0, 44:1, 44:2, and 48:3) in the 90% PH group showed continuous decrease while these in the 70% PH group were abruptly increased by 3~6 folds until 30 h but decreased at 48 h, implying the recovery markers.

Conclusions: Receiver operating characteristic analysis and Pearson correlation coefficients of the lipid levels in combination with total bilirubin and prothrombin time showed that the above four PCps can be utilized as potential signatures to differentiate the early stage of PHLF.

Alcoholic Liver Disease

PE-009

Serum Myostatin Levels Predicts the Risk of Hepatocellular Carcinoma in Patients with Alcoholic Cirrhosis

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Aims: Previous studies reported that serum myostatin is associated with sarcopenia. We aimed to elucidate the association between serum myostatin levels and hepatocellular carcinoma (HCC) development in patients with alcoholic liver cirrhosis (ALC).

Methods: This retrospective multi-center study assessed 201 ALC patients from 2010 to 2016 in four university-affiliated hospitals in Korea. The primary endpoint was development of HCC within 5 years. Index date was time when patients were admitted into hospitals for control of complications from liver cirrhosis. The Cox proportional hazards model analysis was used to assess the association of serum myostatin levels and HCC development in ALC patients. Area under receiver operating characteristic curve (AUROC) of serum myostatin levels for 5-year HCC development was calculated. Serum myostatin levels were measured by enzyme-linked immunosorbent assay using samples which were collected at the index date.

Results: During a median follow-up of 2.1 years, 5-year cumulative HCC incidence rates were 8.0% in total population (n=201). The median levels of serum myostatin was 3.6 ng/mL (interquartile [IQR], 2.2–6.6 ng/mL). The AUROC of serum myostatin levels for 5-year HCC development was 0.78 (95% CI, 0.70–0.82). When total patients were divided according to serum myostatin levels, there was a significant difference of HCC development within 5 years between low myostatin group and high myostatin group (HR 4.52, P=0.04). 5-year cumulative HCC incidence rates were 3% in the low myostatin group (n=100); 5-year cumulative HCC incidence rates were 12% in the high myostatin group (n=101). In Cox proportional hazards model analysis, age and serum myostatin levels were an independent risk factor for HCC development (adjusted HR [aHR] of age 1.06, P=0.004 and aHR of myostatin 1.15, P=0.02).

Conclusions: Higher serum myostatin levels were significantly associated with a higher risk of HCC development in ALC patients. Serum myostatin levels showed good predictive performance of 5-year HCC development in ALC patients. Serum myostatin levels may represent a promising predictive biomarker in ALC patients, which could identify high-risk patients who need a stringent surveillance.

Keywords: Myostatin, Cirrhosis, Hepatocellular carcinoma

PE-010

The Interval Change of Skeletal Muscle Mass and the Incidence of Hepatocellular Carcinoma in Patients with Alcoholic Liver Cirrhosis

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Aims: Sarcopenia is associated with poor prognosis in patients with liver cirrhosis. However, the effects of muscle wasting on development of hepatocellular carcinoma (HCC) is not clearly known. This study aimed to evaluate the relationship between the change of skeletal muscle mass (SMM) and incidence of HCC in patients with alcoholic liver cirrhosis.

Methods: We conducted a single center, retrospective study on 257 patients with alcoholic liver cirrhosis between 2007 and 2019. Skeletal muscle mass was measured from 3rd lumbar section of CT image at baseline and at least 1 year apart during

follow-up. The factors affecting the incidence of HCC were analyzed by cox regression analysis.

Results: HCC occurred in 50 patients during follow-up period (median 18, IQR 12-36 months). At baseline, SMM was well correlated with Child-Pugh class, MELD score, age, DM and BMI. Cox regression analysis showed that age [Hazard ratio (HR) 1.061, confidence interval (CI) 1.027~1.096, *P*<0.001), diabetes (HR 2.08, CI 1.117~3.905, *P*=0.021), Child-Pugh class (*P*=0.024), and body mass index (HR 1.085, CI 1.021~1.152, *P*=0.008) were significantly correlated with HCC incidence. But, Both SMM at baseline (HR 1.009, CI 0.997~1.022, *P*=0.122) and change of SMM during follow-up (HR 0.993, CI 0.972~1.013, *P*=0.525) were not significantly associated with incidence of HCC.

Conclusions: Old age, high BMI, advanced liver cirrhosis and diabetes were independently associated with incidence of HCC in patients with alcoholic liver cirrhosis. But, skeletal muscle mass had no significant effect on HCC development.

Keywords: Sarcopenia, Alcoholic liver cirrhosis, Hepatocellular carcinoma, Skeletal muscle mass

PE-011

Impact of PNPLA3 (rs738409-G) Polymorphism on Post-Transplant Outcomes after Liver Transplantation for Alcohol-Related Liver Disease

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Aims: We aimed to evaluate the association between PNPLA3 polymorphism and post-liver transplantation (LT) outcomes related to alcohol relapse (AR).

Methods: We retrospectively analyzed data from patients receiving LT for alcoholic liver disease (ALD) from 04/2014 to 12/2017. Liver-related clinical outcomes were assessed by the gamma-glutamyltransferase (GGT) level and alcohol-related liver failure (ARLF). Genotyping was performed using prospectively collected DNA samples in both donors and recipients.

Results: A total of 83 recipients were enrolled. Post-LT AR occurred in 31 patients (37.3%). Thirty-one patients (14 AR, 9 abstainers) showed elevated GGT levels, and 3 AR patients experienced ARLF. In the multivariate analysis, rs738409 G allele carrier and heavy drinking (HRAR score≥4) were independent risk factors for elevated GGT levels (odds ratio [OR]=8.69, *P*<0.01; OR=13.07, *P*=0.01) and ARLF (OR=4.52, *P*=0.04; OR=19.62, *P*=0.03). Among 15 heavy AR patients, being an rs738409 G allele carrier was related to GGT elevation (*P*=0.03) and ARLF (*P*=0.04), but it was not to GGT elevation in mild drinkers (n=16) or abstainers (n=52).

Conclusions: PNPLA3 polymorphism of the recipient genotype can independently affect the post-LT prognosis of LT patients for ALD, especially in heavy AR patients. Therefore, strong abstinence education is recommended in patients with this single nucleotide polymorphism.

Keywords: Alcohol-related liver disease, PNPLA3, Liver transplantation, Alcohol relapse

PE-012

Sufficient Calorie Intake Ameliorates Cognitive Impairment in Alcoholic Liver Disease

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Aims: Alcoholic liver disease (ALD) is the most common cause of chronic liver disease. And cognitive dysfunction is one of the complications and associated with calorie intake in ALD. However, relation between nutrition and cognitive function has not been fully evaluated. The aim of this study is to explore the effect of diet on cognitive function in ALD.

Methods: A total of 43 patients were enrolled and neuropsychological tests assessed according to the nutritional state (BMI<21.7 and BMI≥21.7). In animal study, mice were sub-divided into 4 groups (n=9/group; control (5% EtOH liquid diet), low fat (5% EtOH+low fat diet), high fat (5% EtOH+high fat diet), and high protein (5% EtOH+high protein diet)) for 8 weeks. For the cognitive function, we performed T-maze study weekly before and after alcohol binge.

Results: In the comparison of cognitive function (BMI<21.7 and BMI≥21.7), language score of Korea mini-mental state (7.37 ± 1.4 and 7.85 ± 0.4 *P*=0.04), rey-complex figure (72.0±25.9 and 58.4±33.6, *P*=0.05), boston naming (11.7±2.7 and 13.0±1.8, *P*=0.02), forward digit span (6.7±1 .8 and 7.5±1.6, *P*=0.04), Korean-color word stroop (24.2±26.5 and 43.6±32.4, *P*=0.006), interference score (33.9±31.9 and 52.3±33.9, *P*=0.02) showed high scores in BMI≥21.7 group. In the animal study on day 40, all groups shortened the time to find feed (low fat: *P*=0.004, high fat: *P*=0.02) compared to the control group. Interestingly, binge drinking mice reduced the time than before trained mice.

Conclusions: ALD patients with BMI<21.7 enhance their cognitive dysfunction. Although it needs more studies which correlation of calorie intake and cognitive function, this study indicates that sufficient intake of calories provides major benefits for preventing cognitive dysfunction.

Keywords: Alcoholic liver disease, Cognitive function, Calorie intake, BMI

PE-013

Rifaximin Treatment in Patients with Severe Alcoholic Hepatitis; A Multicenter, Open-Label, Pilot Randomized Controlled Trial

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Aims: The short-term mortality of severe alcoholic hepatitis (SAH) is very high, but there are no effective treatments to improve short-term mortality other than corticosteroid. This study investigated the effects of rifaximin treatment in patients with SAH.

Methods: In an open-label trial, patients with SAH (Maddrey's discriminant function≥32) were randomized to rifaximin or control group, each added to corticosteroid or pentoxifylline for 4 weeks. Randomization was stratified by SAH treatment. Liver transplantation free survival was evaluated. (NCT02485106)

Results: Total 49 patients were enrolled in this study (29 in control and 20 in rifaximin group). The mean Model for End-stage Liver Disease (MELD) score were 24.4 and 27.8 in control and rifaximin group (*P*=0.083). Rifaximin treatment was tolerable and only 1 patients stopped due to adverse event. There were no differences in 3-month and 6-month mortality between two groups (*P*=0.576 and *P*=0.239, respectively). Corticosteroid group had higher 3-month and 6-month survival than pentoxifylline group (*P*=0.03 and *P*=0.016, respectively). When stratified by SAH treatment, there were no significant 3-month and 6-month survival between control and rifaximin treatment (*P*=0.516 and *P*=0.937 in corticosteroid group and *P*=0.948 and *P*=0.620 in pentoxifylline group, respectively). Cox Proportional hazard model showed that MELD score, white blood cell count, C-reactive protein were significant factors for 6-month survival, and MELD score was only independent factor for 6-month survival (Hazard ratio 1.188, *P*=0.001).

Conclusions: In patients with SAH, adding rifaximin to corticosteroid or pentoxifylline was tolerable but had no survival benefit. MELD score was only significant factor for short-term mortality.

Keywords: Severe alcoholic hepatitis, Rifaximin, Corticosteroid, Pentoxifylline

PE-014

Recent Status of Alcohol-Related Liver Disease in Young Korean Population

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Aims: Since introduction of various antiviral agents for chronic viral hepatitis in Korea, alcohol-related liver disease (ALD) seems to increase recently. Moreover, Korea has experienced rapid societal changes in lifestyle, drinking culture, and women's human right. The aim of this study is to analyze the current epidemiologic status of ALD in young Korean adults (18 – 49 years) and provide basic data for a policy making to prevent ALD in the country.

Methods: This is a retrospective cohort study using the National Health Insurance Corporation's sample cohort 2.0. From 2006 to 2015, we investiaged patients who were hospitalized with ALD diagnosis codes (K70). Severe ALD was defined as a patient with steroids, diuretics, ascites, endoscopic variceal ligation, use of vasoconstrictor terlipressin, or lactulose during hospitalization. Annual prevalence of hospitalized patients due to ALD by age group and gender were analyzed. We also investigated health care utilization with ALD using Health Insurance Review and Assessment (HIRA) service data from 2010 to 2019.

Results: Among 665,471 paticipants (18 – 49 years) of the sample cohort, 3,805 patients (0.57%) were hospitalized with ALD. Hospitalization rate of men due to ALD was 1.72 per 100,000 person-year (PY) in 2006 and decreased steadily to 0.83 per 100,000 PY in 2015 (-48.2%). For women, hospitalization rate increased from 0.18 to 0.32 per 100,000 PV between 2006 to 2009 (+78.5%) and the rate remains stable around 0.27 per 100,000 PV between 2010 and 2015. The ratio of men to women by year has sharply decreased from 9.3 to 3.3 between 2006 and 2015. The proportion of severe ALD among hospitalized patients was about 60% and remained unchanged during 10 years and was similar between men and women. HIRA data also showed that total number of male patients (20– 49 years) with any ALD decreased 58,962 to 33,431 between 2010 to 2019 (-43.3%). However, the number of female patients was 11,356 in 2010 and decreased to 8,670 in 2019 (-23.7%).

Conclusions: ALD is clearly decreasing in young Korean population. However, the reduction is only evident in men not in women. We might see relatively more female patients with ALD than before. As like viral hepatitis, ALD in Korea seems to decrease significantly in the future.

Keywords: Alcohol-related liver disease, Current epidemiologic status of Korea, Hospitalization rate, Severe alcohol-related liver disease

PE-015

The Prognostic Impact of Acute-on-Chronic Liver Failure Grade on Short-Term Mortality in Patients with Severe Alcoholic Hepatitis

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Aims: Acute-on-chronic liver failure (ACLF) is a distinct syndrome characterized by acute deterioration of chronic liver disease, organ failure, and short-term mortality. Severe alcoholic hepatitis (SAH) is a serious complication of alcoholic liver disease and is often complicated by ACLF. This study aimed to investigate ACLF presentation and its impact on mortality in patients with SAH.

Methods: A total of 226 patients with a SAH were selected from prospective Korean ACLF data. Inclusion criteria for SAH were as follows; active alcoholism, serum total bilirubin ≥5 mg/dl, aspartate aminiotransferase >50 IU/L, aspartate aminotransferase/alanine aminotransferase ratio >1.5, PT <50%, and a Maddrey discriminant function (mDF) ≥32.

Results: Mean mDF was 66.1±34.1 and mean model for end-stage liver disease score was 26.0±6.1. Sixty-eight patients (30.1%) satisfied ACLF criteria at presentation. The 28- and 90-day mortalities were 14% and 24%, respectively. The number of patients with ACLF grade 1, 2, and 3 were 14 (6.2%), 37 (16.4%), and 17 (7.5%), respectively. The 28-day mortalities for patients with and without ACLF at baseline were 27% and 8%, respectively, *P*<0.0001. The 28-day mortalities for patients with ACLF grade 1, 2, and 3 were 15%, 20%, and 48%, respectively, *P*<0.0001.

Conclusions: ACLF was often accompanied in patients with SAH. The presence and grade of ACLF at initial presentation significantly increased short-term mortality.

Keywords: Alcoholic hepatitis, Prognosis, Acute-on-chronic liver failure

PE-016

Outcome in Patients with Severe Alcoholic Hepatitis after Model for End-Stage Liver Disease-Based Allocation System in Korea

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Aims: Model for End-Stage Liver Disease (MELD)-based allocation system has implemented in Korea since July, 2016, without mandatory abstinence period to list for liver transplantation (LT). However, impact of change in allocation policy has not been evaluated for severe alcoholic hepatitis (AH) patients

Methods: A total of 81 consecutive patients with severe AH between January 2014 and December 2018 were analyzed. Clinical course of patients between the era before and after MELD-based allocation system were assessed

Results: More patients received LT (25% to 65%) after MELD era. The increase in patients receiving deceased donor LT was dramatic (17% to 51%, *P*=0.001) than increase in patients receiving living donor LT (7% to 14%, *P*=0.30). The overall survival was better in the after MELD era (1 year survival rate: 50% vs. 80%, *P*=0.005). LT was independent factor associated with overall survival, which was significantly higher for those received LT (88% vs. 44% at 1 year, *P*<0.001). Post-LT mortality was observed in six patients with one mortality case related to recidivism. Baseline MELD and steroid response were factors associated with transplant-free survival.

Conclusions: After MELD-based allocation system, deceased donor LT was dramatically increased in patients with severe AH. LT increased overall survival of severe AH patients, but with a risk of mortality due to recidivism. As there are no mandatory abstinence period or criteria to justify use of precious liver graft from deceased donor for severe AH patient, this issue warrants urgent evaluation in Korea.

Keywords: Severe alcoholic hepatitis, Liver transplantation, Model for End-Stage Liver Disease-based allocation system

Genetic

PE-017

Molecular Genetic Predictors of the Development of Liver Pathologies in Patients with Type 2 Diabetes in the Republic of Sakha (Yakutia)

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Aims: Scientific work in Russia and abroad shows a frequent combination of type 2 diabetes and non-alcoholic fatty liver disease (NAFLD), which is characterized by the accumulation of lipids in both the hepatocytes and in the intercellular space.
Methods: The study of single nucleotide polymorphisms (SNPs) of rs58542926 gene TM6SF2 and rs738409 gene PNPLA3 was carried out in the laboratory of hereditary pathology of the Department of Molecular Genetics of the Yakutsk Scientific Center for Complex Medical Problems (NSC KMP). In total, the TM6SF2 gene sample consisted of 142 DNA samples, including 48 DNA samples of individuals with a history of chronic non-infectious liver diseases and 94 DNA samples from healthy volunteers. According to the PNPLA3 gene, 397 DNA samples were studied, including 151 DNA samples of individuals with a history of chronic non-infectious liver diseases and 246 DNA samples from healthy volunteers.
Results: A comparative analysis of the distribution of alleles of rs58542926 polymorphism of the TM6SF2 gene found that the group of patients, as well as the group of healthy ones, was characterized by a predominance of carriers of the C allele - 62% and 88%, respectively. A comparative analysis of genotypes in groups of patients and healthy revealed a predominance of individuals with the SS genotype - 82%. Moreover, the TT genotype was significantly more likely to occur in the group of people with chronic non-infectious liver diseases (31%, $P \leq 0.005$). The OR value (95% CI) for the T allele was 5.257 (2.862-9.654), for the TT homozygous genotype 10.227 (3.165-33.047).
Conclusions: When analyzing the frequency distribution of genotypes and alleles of PNPLA3 polymorphism (rs738409) among a healthy sample and a sample of patients with liver diseases, no significant differences were found. The prevalence of individuals with the G / G genotype was established both in the patient sample (60.3%) and in the control sample (59.8%). In this case, the allele, the frequency of carriage of the G allele in patients was 75.2%, in individuals in the control group – 73.0%.
Keywords: Polymorphism, PNPLA3, NAFLD, type 2 diabetes

PE-018

Clinical Virology

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Aims: The hepatitis C (HCV) virus is emerging rapidly and has been the leading cause of liver cirrhosis and hepatocellular carcinoma over the last decade. This survey is done to determine the change in prevalence of the HCV virus in past few decades, which tends to be increased greatly in a very short period of time. The HCV virus possess increased risk of window period transmission through blood transfusion. Some studies have revealed that the sero prevalence of HCV virus has been alarmingly higher in two of the three blood transfusion services. About 80% of the drug abusers are anti- HCV seropositive in Nepal. The HCV virus has a wide geographical and population specific genotype variability all over the world. This research was conducted to identify the genotype distribution of HCV virus and its association to the viral load in plasma samples. We aim to help to individualize antiviral therapy, manage economic burden and promote optimum responses in treatment of hepatitis C (HCV) virus.
Methods: This research was conducted in the Decode Genomics and Research Centre, Sinamangal, Kathmandu, Nepal. The HCV genotypes were differentiated into its seven genotypes and subtypes accordingly along with the viral load. The genotypes were identified by the comparison of amplification results obtained. The patients may have one or more genotypes. The RNA was extracted using RNA extraction with RIBO-sorb nucleic acid extraction kit variant 50. Accordingly, REVERTAL-L RT reagents kit variant 50 was used for the reverse transcription of the cDNA. The Real Time PCR was used for the amplification of the cDNA and results were analyzed by the real time thermocycler software. The viral load was calculated using Real Star® HCV RT-PCR kit 1.0.
Results: Out of the 100 patients, genotype 3a was accounted for the highest number of cases and found in 53 (53%) patients. Genotype 1a and 1b were found in 23 (23%) and 18 (18%) patients respectively. Genotype 5a was found in 3 (3%) patients. Genotype 6 was found in only 1 (1%) patient. Mixed genotype infection was found in 2 patients. Additionally, the patients with genotype 3a showed higher HCV viral load, more frequently as compared to the genotypes 1a genotypes 1a and 1b.
Conclusions: Genotype 3a was found to be predominant genotype in the context of Nepal followed by genotype 1a and 1b. Characterization of genotype helps to better treatment regimen.
Keywords: HCV (Hepatitis C virus), Viral load, RNA extraction, Genotype, PCR (Polymerase Chain Reaction)

Autoimmune Liver Disease

PE-019

The Role of Obeticholic Acid (Farnesoid X receptor agonist) on Improving Liver Biochemistry Parameters in Primary Biliary Cholangitis: A Systematic Review and Meta-Analysis

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Aims: Primary biliary cholangitis (PBC) is a chronic, progressive, autoimmune cholestatic liver disease that leading to end stage liver disease and death. Higher levels of Y-glutamiltransferase (GGT), liver enzyme and bilirubin levels correlated with disease progression and predictive value of survival outcomes. Obeticholic acid (OCA) has been reported to have great potency in activating FXR which will protect hepatocyte against bile acid toxicity. The aim of this study was to assess the effect of obeticholic acid (OCA) on liver biochemistry parameters in PBC based on randomized control trials.
Methods: Literature search was conducted using PubMed database until April 2020 to find randomized control trial (RCTs), which assessed 10 mg obeticholic acid administration on liver enzyme, Y-glutamiltransferase (GGT) and conjugated bilirubin in PBC patients. Treatment effect were considered as Mean difference and standard deviation (SD) change from the baseline. We performed data analysis using RevMan 5.3.
Results: A total of 2 trials (211 participants) were included in the meta-analysis. The result suggested that obeticholic acid has significant effect on improving ALT(-15.2U/L,95%CI:-19.58 to -10.66; *P*<0.00001), ALT(-9.12U/L,95%CI:-12.23 to -6.02; *P*<0.00001), GGT(-99.70U/L, 95%CI: -125.68 to -73.71; *P*<0.00001) and Conjungated bilirubin (-0.08U/L, 95%CI: -0.13 to –0.03; *P*<0.002).
Conclusions: Administered of 10 mg Obeticholic acid improved liver biochemistry parameters in PBC. However, further study with large-scale and better design are needed to confirm the results and eliminated the bias.
Keywords: Obeticholic Acid, Farnexoid X Receptor Agonist, Liver Biochemistry Parameter, Primary Biliary Cholangitis

PE-020

Autoimmune Hepatitis Triggered by Taking Sea Squirt

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Background: Autoimmune hepatitis is an immune disease in which the body's immune system attacks liver cells, causing inflammation in the liver. The exact cause of autoimmune hepatitis is unclear, but genetic and enviromental factors appear to triggering factors. In rarely, certain natural products can *trigger autoimmune hepatitis*. Herein report is a case of autoimmune hepatitis triggered by taking sea squirt.
Case: A 53-year-old woman was admitted because of icteric sclera and reddish urine since 1 week ago. She denied drinking, smoking. She was diagnosed with hyperlipidemia 3 years ago. She ate sea squirt to improve health for 2 weeks. On admission, BP was 120/80 mmHg, HR 80 beats/min, RR 20 breaths/min, and BT 37°C. She was diagnosed with hyperlipidemia 3 years ago. Laboratory findings revealed WBC 9,710/mm^3, Hb 13.6 g/dL, PLT 447,000/mm^3, PT 11.6 sec, PT (INR) 1.06, AST 465 IU/L, ALT 778 IU/L, total bilirubin 5.71 mg/dL, albumin 3.7 g/dL, BUN 8 mg/dL, creatinine 0.78 mg/dL, ALP 146 U/L, r-GTP 57 U/L, Viral markers (HBsAg, IgM HBV, IgM HAV, Anti HCV, HSV, EBV and CMV) were all negative. ANA was 1:40 positive. Abdominal ultrasonography showed increased periportal echos in the liver. Abdominal CT showed no defined focal mass in the abdominal solid organs. Liver biopsy revealed interface hepatitis showing lymphoplasmacytic infiltrates in the portal tracts and around periportal areas associated with lobular necroimflammatory reaction and focal intrahepatic cholestasis, suggestive of autoimmune hepatatis. Corticosteroid and azathioprine treatment was started. On 19th admission day, she was discharged with improving of her liver function. She is curruntly being treated in outpatient setting.
Conclusions: Sea squirt can induce liver damage and trigger immune reaction. The mechanism of liver injury is not clear, but it seems to be related to the trabectedin molecule in sea squirt.
Keywords: Autoimmune hepatitis, Sea squirts, Hepatotoxicity, Liver biopsy

HBV, Clinical

PE-021

Distribution of Hepatitis B Genotypes Among Hepatitis B Patients in Central Nepal

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Aims: To find the distribution of hepatitis B genotypes among hepatitis B infected patients in Central Nepal. To determine the HBeAg, HBeBa and viral load among HBsAg positive patients, to determine HBV genotypes and to correlate it with clinical problems.
Methods: This was a prospective type of study. The research was conducted in Decode Genomics and Research Center, Sinamangal, Kathmandu, Nepal. Samples were taken from HBsAg positive patients visiting DGRC within the Nepal. 106 samples was taken for this study. The basic criteria for this study were separated as Inclusion criteria and Exclusion criteria. The Inclusion criteria was only HBsAg positive cases. And, the Exclusion criteria were HIV positive cases, HBsAg negative cases and International patients. The equipment and reagents that were required in this study are listed in the ANNEX I. 3ml Blood sample had been collected on EDTA vial by following the standard procedure of blood collection. The viral DNA from blood samples had been extracted using SpinstarTM Viral Nucleic Acid Extraction kits following manufacturer protocol. The detailed protocol is included in ANNEX III. Viral load estimation on each blood samples had been done using RealStar® HBV PCR kit. Further details is included in ANNEX IV. The Hepatitis B geno-

type had been determined by PCR using type specific primers (Appendix II). And, the PCR product for the Genotyping had been analyzed in 2% Agarose gel using standard protocol.

Results: This study was conducted at Decode Genomics and Research Centre, Sinamangal, Kathmandu, Nepal. A total of 106 HBsAg positive serum samples were collected from patients visiting DGRC, in between June 2017 to November 2017, for Viral load Testing. Written consent was taken from each patient before sample collection. Out of 106 patients enrolled for this study 68 were males and 38 were females. Age of the enrolled patients was from 13 year to 78 years. Patients enrolled for the study were from different parts of Nepal visiting DGRC for treatment of active HBV infection. DNA was extracted using SpinStarTM Viral Nucleic Acid Kit 1.0. Viral load estimation were performed using RealStar® HBV PCR kit 1.0 and genotyping by the Nested PCR using type specific primers for each genotypes. Genotype D was found predominantly followed by C. The highest viral load in our study was >10 million i.e.1936410339 IU/ml which had genotype A whereas lowest viral load was 31 IU/ml had genotype C. Out of 106 patients 42 contains high viral load (>20000). Genotype C is predominant among high viral load patients followed by unknown, A and D. 30 patients contains moderate viral load (2000-20000) and low viral load was observed in 34 patients (<2000). Among moderate viral load patients genotype D was dominant followed by unknown and C while genotype D is more common among low viral load patients. Type-specific primers were used for HBV genotyping using nested PCR. Type specific primers were designed for the detection of conserved region of genotypes A, B, C, D, E and F. Out of 106 patients enrolled for the study HBV Genotypes was determined in 59 patients while genotypes were not determined in 47 patients. Among 59 patients genotype D was present in highest number (18 patients) followed by C, A, B and Genotype F was observed only in one patients. Genotype E was not found in any patients enrolled for the study. 16 patients were found to be containing recombinant Genotypes. A total of 6 types of recombinants were seen on our study. They are B/C, B/C/D, C/D, A/C, C/F and D/A. C/D (7) recombinant was predominant followed by A/C (3), B/C/D (2) and D/A (2). B/C and C/F recombinant was seen in 1 patient each.

Conclusions: Out of 106 patients enrolled for the study, HBV Genotypes was determined in 59 patients while genotypes were not determined in 47 patients. Among 59 patients genotype D was present in highest number (18 patients) followed by C, A, B and Genotype F was observed only in one patients. Genotype E was not found in any patients enrolled for the study. 16 patients were found to be containing recombinant Genotypes. A total of 6 types of recombinants were seen on our study. They are B/C, B/C/D, C/D, A/C, C/F and D/A. C/D (7) recombinant was predominant followed by A/C(3), B/C/D (2) and D/A (2). B/C and C/F recombinant was seen in 1 patient each.

Keywords: Hepatitis B Virus, Hepatitis B Genotypes, PCR,

PE-022

Validation of the Risk Prediction Scores for Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Treated with Entecavir or Tenofovir

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Aims: Several prediction scores are available for the early detection of hepatocellular carcinoma (HCC). We validated the predictive accuracy of the AASL, RESCUE-B, PAGE-B, and modified PAGE-B (mPAGE-B) scores in patients with chronic hepatitis B (CHB) treated with entecavir (ETV) or tenofovir disoproxil fumarate (TDF).

Methods: Between 2007 and 2014, 3,171 patients were recruited (1,645 with ETV and 1,517 with TDF). The predictive accuracy of each prediction score was assessed.

Results: The mean age of the study population (1,977 men and 1,194 women) was 48.8 years. Liver cirrhosis was noted in 1,040 (32.8%) patients. During follow-up (median, 58.2 months), 280 (8.8%) patients developed HCC and were significantly older; were more likely to be male; had significantly higher proportions of liver cirrhosis, hypertension, and diabetes; and had significantly higher values of the four risk scores than those who did not develop HCC (all $P<0.05$). Older age (hazard ratio [HR]=1.048), male sex (HR=2.142), liver cirrhosis (HR=3.144), and prolonged prothrombin time (HR=2.589) were independently associated with an increased risk of HCC development (all $P<0.05$), whereas a higher platelet count (HR=0.996) was independently associated with a decreased risk ($P<0.05$). The predictive accuracy of the AASL score was highest at 3 and 5 years HCC prediction (area under the curve [AUC]=0.818 and 0.816, respectively), followed by RESCUE-B, PAGE-B, and mPAGE-B scores (AUC=0.780-0.815 and 0.769-0.814, respectively).

Conclusions: Four HCC prediction scores performed acceptably in Korean patients with CHB treated with ETV or TDF. Of these, the AASL score showed the highest predictive accuracy.

Keywords: Hepatocellular carcinoma, Chronic hepatitis B, Risk prediction score, Antiviral therapy, Entecavir, Tenofovir disoproxil fumarate

PE-023

Systematic Review and Meta-Analysis of Immune Response of Increased Dose of Hepatitis B Vaccination in HIV-Infected Patients

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Aims: The prevalence of co-infection of hepatitis B virus (HBV) and human immunodeficiency virus (HIV) is high and increases risk of hepatitis B chronicity and mortality. Despite guidelines for HIV-infected patients to be immunized against HBV, the immunogenicity of the HBV vaccination in HIV-infected patients is lower than that in the HIV-seronegative population.

Methods: In this study, we performed a systematic review of the literature and meta-analysis of randomized clinical trials to investigate the response rate to an increased dose of HBV vaccination in HIV-infected patients. A fixed-effects model, with heterogeneity and sensitivity analyses, was used. We identified nine studies involving 970 HIV-positive vaccine recipients.

Results: The study results were divided into two groups, depending on the time when antibody against hepatitis surface antigen was measured. Results showed a significant increase in response rates among patients who received a double dose of the vaccine versus the standard dose in both subgroups; the pooled odds ratio (OR) was 1.76 (95% confidence interval [CI]: 1.36–2.29) and 2.28 (95% CI: 1.73–3.01) for the rate that was measured 4–6 weeks and >12 months after completion of vaccination, respectively. The total OR was 1.99 (95% CI: 1.64–2.41). No heterogeneity was found.

Conclusions: Our meta-analysis shows that a double dose of the HBV vaccine may significantly improve the immune response in HIV-infected patients. Higher immunogenicity was observed, when it was measured 4-6 weeks and >12 months after completion of the vaccination.

Keywords: HIV, HIV infections, Hepatitis B vaccines, Meta-analysis

PE-024

Tenofovir Alafenamide (TAF) vs. Tenofovir Disoproxil Fumarate (TDF) for Multiple Drug-Resistant Hepatitis B: A Randomized Controlled Trial

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Aims: To demonstrate whether tenofovir alafenamide (TAF) is efficacious in patients with hepatitis B virus (HBV) resistant to multiple drugs

Methods: This was a randomized trial to assess whether switching tenofovir disoproxil fumarate (TDF) to TAF shows non-inferior efficacy and better safety profile in patients with multidrug-resistant HBV compared to continuing TDF. Patients with HBV resistant to entecavir and/or adefovir under TDF monotherapy for at least 96 weeks were randomized 1:1 to switch to TAF or continue TDF for 48 weeks. The primary efficacy endpoint was the proportion of patients with HBV DNA <60 IU/mL in the full analysis set.

Results: Of 174 eligible patients under TDF monotherapy, 87 switched to TAF and 87 continued TDF. At baseline, 163 (93.7%) patients had HBV DNA less than 60 IU/mL (96.6% in TAF group vs. 90.8% in TDF group). At week 48, the proportion of patients with HBV DNA <60 IU/mL was 98.9% in TAF group, which was non-inferior to TDF group (97.8%; *P*=0.99). The proportion of patients with normal ALT (<=40 IU/L) at week 48 tended to be higher in TAF group compared with TDF group (92.0% vs. 79.3%; *P*=0.06). TAF group showed a significantly higher increase in bone mineral density (BMD) at spine compared with TDF group at week 48 (mean% change, +1.84% vs. 0.08%; *P*=0.01). TAF group, compared to TDF group, tended to show a larger increase in estimated glomerular filtration rate from baseline as measured by Cockcroft-Gault formula (mean % change, +8.2% vs. +4.5%; *P*=0.06).

At 48 weeks	TAF	TDF	P
HBV DNA <60 IU/mL	98.9%	97.8%	0.99
ALT, Normal (<=40 IU/L)	92.0%	79.3%	0.06
BMD at spine (g/cm^2), change from baseline	+1.84%	+0.08%	0.01
eGFR (mL/min/1.73 m^2), change from baseline	+8.2%	+4.5%	0.06

Conclusions: In CHB patients with multidrug-resistant HBV, switching TDF to TAF was as effective as TDF in virologic response with improved bone and renal safety.

Keywords: Tenofovir alafenamide, Hepatitis B virus, Multiple drug-resistance

PE-025

Twelve-Month Post-Treatment Clinical Parameters Are Superior to Pre-Treatment Parameters in Predicting Hepatocellular Carcinoma in Patients with Chronic Hepatitis B

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Aims: There are currently several prediction models for hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) receiving oral antiviral therapy. However, most models are based on pre-treatment clinical parameters. Therefore, using machine learning techniques and multicenter patient cohorts from Korea and the United States (US), the current study aimed to develop a novel and practical prediction model for HCC by using both pre- and post-treatment parameters in this population.

Methods: We included two treatment-naïve CHB cohorts who were initiated on oral antiviral therapies: the derivation cohort (n=1,480, Korea prospective SAINT cohort comprising of 9 study centers) and the validation cohort (n=426, the US retrospective Stanford Bay cohort comprising of 4 centers). Included patients were followed for 3 years or until HCC, death or loss of follow-up whichever occurred first. We employed logistic regression, decision tree, lasso regression, support vector machine, and random forest algorithms to develop the HCC prediction model and selected the most optimal method.

Results: We evaluated both pre-treatment and the 12-month clinical parameters on-treatment and found the 12-month on-treatment values to have superior HCC prediction performance. The lasso logistic regression algorithm using the presence of cirrhosis at baseline and alpha-fetoprotein and platelet at 12 months showed the best performance (AUROC=0.843 in the derivation cohort. The model performed well in the external validation cohort (AUROC=0.844) and better than other existing prediction models including the APA, PAGE-B, and GAG models (AUROC=0.769 to 0.818).

Conclusions: We provided a simple-to-use HCC prediction model based on only two readily available and objective laboratory markers (AFP and platelets) measured 12 months after antiviral initiation. The model is highly accurate with excellent validation in an external cohort from a different country (AUROC 0.844).

Keywords: Hepatocelluar carcinoma, Prediction model, Chronic Hepatitis B

PE-026

Sero-Prevalence of Viral Hepatitis B Infection in the General Population of Chitwan District, Nepal

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Aims: Hepatitis B is one of the most common viral infection worldwide. Almost one-third of the World´s population has been infected with this virus and about 350 million people live with chronic infection, sometimes causing jaundice and death of the patients. However, in developing countries like Nepal, hepatitis B infection is endemic with predominant vertical transmission leading to chronicity and death. Hence, the present study was conducted to access the prevalence of viral hepatitis B infection in the people of Chitwan district which represents almost all ethnic groups of people of Nepal.

Methods: A cross-sectional study was conducted among 283 subjects attending International Reference Laboratory (IR-Lab), Bharatpur-10, Chitwan, Nepal during the period of six months (September 2020 to February 2020). The hepatitis B surface antigen (HBsAg) was studied from the serum obtained from the participating subjects using the diagnostic HBsAg-ELISA kit. The data obtained were analyzed using the SPSS version-24.

Results: Out of 283 subjects tested for HBsAg, 74.2% (210) were male whereas 25.8% (73) were female. The subjects were from the age of 0.3 to 91 years old. The highest percentage of subjects participated in this research was 26 to 55 years old. Among 283 subjects, 2.5% (7) were diagnosed as viral hepatitis B infected patients. The prevalence of hepatitis B infection was higher (2.9%) in males than females (1.4%). The highly infected patients were the age group of 26-55 years old. The ethnic group, Gurung was found to be predominantly infected.

Conclusions: In comparison to the previous report, our finding explores that hepatitis B infection has been gradually increasing even though the literacy of the urbanized population is satisfactory than the past. It is a big challenge for the Nepalese government for viral hepatitis elimination. Implementation of newborn HBV-vaccination, as well as social awareness and health campaigns, are required.

Keywords: Viral Hepatitis B, HBsAg, Nepalese ethnicity, Prevalence

PE-027

Bone and Renal Parameters Following Switch to Tenofovir Alafenamide after 96- or 144-Weeks of Tenofovir Disoproxil Fumarate Treatment in East Asians with Chronic HBV

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Background: Tenofovir alafenamide (TAF) has shown similar efficacy to tenofovir disoproxil fumarate (TDF) with better bone and renal safety in 2 Phase 3 trials through 96 weeks. After a protocol amendment, some TDF patients received 96 weeks while others received 144 weeks of TDF treatment before rolling over to open-label (OL) TAF.

Aim: To examine whether duration of prior TDF treatment impacted changes in bone and renal parameters after 48 weeks of OL TAF treatment in the subset of East Asian (EA) patients with chronic HBV.

Methods: Among 190 EAs randomized to TDF, changes in bone mineral density (BMD) by DXA scans and renal parameters were assessed from OL baseline to Week 48 following switch to OL TAF.

Results: At Week 48, mean (SD) percent changes from OL baseline in hip-BMD were +0.92 (2.32) and +0.79 (2.47) and in spine-BMD were +1.52 (2.68) and +2.27 (3.51) for DB-TDF-144wks and DB-TDF-96wks, respectively. Similarly, median (Q1, Q3) changes from OL baseline in creatinine clearance ($eGFR_{CG}$) were +2.4

(-4.2, +10.8) and +3.0 (-3.0, +8.4) mL/min for DB-TDF-144wks and DB-TDF-96wks, respectively. Similar trends in BMD and $eGFR_{CG}$ changes were seen in non-EAs. Following switching to OL TAF, improvements in bone and renal biomarkers were also observed.

Conclusions: In EA patients who switched to TAF from TDF, improvements were seen in bone and renal parameters.

Keywords: TAF, Vemlidy, CHB, Switch

PE-028

An Exploratory, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Tenofovir with and without Ursodeoxycholic Acid in Patients with Hepatitis B Virus

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Aims: It is suggested that earlier alanine aminotransferase (ALT) normalization during antiviral treatment is associated with a lower risk of hepatic events in patients with chronic hepatitis B (CHB). This study aimed to assess the effect of ursodeoxycholic acid (UDCA) in improving liver inflammation in ALT elevated CHB patients who commence tenofovir therapy.

Methods: Eighty-nine tenofovir-naïve patients with CHB were enrolled from 6 centers. Patients were randomly assigned into 3 groups; tenofovir combined with UDCA 1000mg (n=27), UDCA 600mg (n=30), or placebo (n=32), respectively. The primary endpoint is ALT normalization rate at 4 weeks.

Results: Out of 89 patients, 10 patients dropped out, 79 patients completed 1-year follow-up. The ALT normalization rates at week 4 by central lab criteria (ALT ≤41 U/L for men, and 33 ≤U/L for women) were 24%, 13.8%, and 23.3% for UDCA 1000mg, UDCA 600 mg, and placebo groups, respectively (P>0.05). ALT normalization rates based on AASLD criteria (ALT ≤30 U/L for men, and 19 ≤U/L for women) at week 4 were not statistically different between 3 groups. ALT normalization rates by central lab criteria between 3 groups did not reach statistical significance at week 12, 24, 36 and 48. However, ALT normalization rates by AASLD criteria was higher in UDCA 1000mg group than UDCA 600mg or placebo groups at week 24, 36 and 48 (P<0.05). Improvement of liver fibrosis measured by enhanced liver fibrosis score at week 48 was not different between groups (P>0.05). Inhibitory molecules of T cell such as PD-1, CTLA-4 and FoxP3, superoxide dismutase, malondialdehyde and TNF-alpha were checked longitudinally, however, there were no significant differences among these three groups (P>0.05).

Conclusions: Combination treatment of UDCA 1000mg with tenofovir can improve ALT normalization rate at 24-48 weeks based on AASLD criteria in ALT elevated CHB patients.

Keywords: Hepatitis B, Tenofovir, Ursodeoxycholic acid

PE-029

Effects of Tenofovir vs Entecavir on Risk of Hepatocellular Carcinoma in Patients with Chronic HBV Infection : A Systematic Review and Meta-Analysis

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Aims: Tenofovir disoproxil fumarate (TDF) and entecavir are recommended as first-line treatments for chronic hepatitis B virus (HBV) infection. However, there is debate over the comparative effectiveness of these drugs in preventing hepatocellular carcinoma (HCC). We performed a systematic review and meta-analysis of the effectiveness of TDF vs entecavir in reducing the incidence of HCC among patients with chronic HBV infection.

Methods: We performed a systematic review of the MEDLINE, EMBASE, Web of Science, and Cochrane Library from 2010 through 2019 for full-text articles and conference abstracts on studies of effects of TDF vs entecavir in patients with HBV infection. Extracted data were analyzed with the random effects model. Potential sources of heterogeneity were investigated using sensitivity, meta-regression, and subgroup analyses.

Results: Our final analysis comprised 15 studies (61,787 patients; 16,101 patients given TDF and 45,686 given entecavir). TDF treatment was associated with a significantly lower risk of HCC than entecavir (hazard ratio, 0.80; 95% CI, 0.69–0.93; P=.003; I^2=13%). The lower risk of HCC in patients given TDF compared with entecavir persisted in sensitivity and subcohort analyses performed with propensity score-matched cohorts and cirrhosis subcohorts. Inclusion of patients with decompensated cirrhosis and the sample size were the factors with the largest effects on between-study heterogeneity in meta-regression analyses. There were no statistical differences in the incidence of death or transplantation (hazard ratio, 0.93; 95% CI, 0.73–1.17; P=.519; I^2=6%) between patients given TDV vs entecavir.

Conclusions: In a meta-analysis of studies of patients with chronic HBV infection, we found that TDF treatment was associated with a significantly lower (20%) risk of HCC than entecavir treatment. Randomized trials are needed to support this finding.

Keywords: Liver cancer, Therapy, Comparison, Chronic hepatitis B

PE-030

Moderate Levels of Serum HBV DNA Are Associated with the Highest Risk of Hepatocellular Carcinoma in Chronic Hepatitis B Patients

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Aims: Studies have shown a higher risk of hepatocellular carcinoma (HCC) with higher baseline serum hepatitis B virus (HBV) DNA levels in chronic hepatitis B (CHB) patients. However, the association between very high HBV DNA levels (>6 $\log_{10}$ IU/mL) and HCC risk remains unclear, especially in middle-aged and old HBeAg-positive patients.

Methods: We conducted a historical cohort study in Korea involving 6949 non-cirrhotic, treatment-naïve CHB patients with alanine aminotransferase (ALT) <2x upper limit of normal for >1 year. HBV DNA was >6 $\log_{10}$ IU/mL in 2029 (29.2%) patients. Follow-up was censored when the antiviral therapy was initiated.

Results: The mean age of the patients was 45 years. During 8.0 years of median follow-up, 363 patients (5.2%) developed HCC. By multivariable Cox regression analysis, HCC risk was highest with baseline HBV DNA levels of 6–7 $\log_{10}$ IU/mL (adjusted hazard ratio [aHR] 4.98; P<0.001), and lowest with >8 $\log_{10}$ IU/mL (aHR 0.90; P=0.71) and ≤4 $\log_{10}$ IU/mL (aHR 1.00; reference), which was independent of other predictive factors. The similar association between HBV DNA levels and HCC risk was consistently observed in all age subgroups (age <40 years, 40-49 years, and ≥50 years).

Conclusions: HCC risk was highest with medium serum HBV DNA levels of 6–7 $\log_{10}$ IU/mL in CHB patients without significant ALT elevation. Extending treatment indication to CHB patients with moderate levels of HBV DNA may be considered to further prevent HCC, regardless of ALT levels.

Keywords: Antiviral treatment, Hepatitis B virus, Hepatocellular carcinoma, Liver cancer

PE-031

The Association of Low Vitamin D Levels with Viral Response in Chronic Hepatitis B Patients

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Aims: Vitamin D is an important immunomodulator and drawing attention in chronic hepatitis B. But the relationship between Vitamin D levels and viral response of chronic hepatitis B patients is controversial. Therefore, we investigated the effects of low vitamin D on viral response of chronic hepatitis B patients.

Methods: We recruited a group of 356 CHB patients starting antiviral therapy (AVT). Vitamin D deficiency was defined as 25(OH)D3 concentration < 20 ng/mL. The rate of Hepatitis B e antigen (HBeAg) seroconversion, HBeAg loss, Hepatitis B Virus(HBV) DeoxyriboNucleic Acid(DNA) suppression (<2000 IU/mL) were compared between adequate vitamin D group and

vitamin D deficiency group by Cox proportional hazard model.
Results: HBeAg-positive patients were 173(48.6%) and 213 patients (59.8%) had vitamin D deficiency at the time of starting AVT. Vitamin D deficiency group was younger (*P*=0.001) and had higher Child-Pugh score(*P*=0.043) than adequate vitamin D group. In HBeAg-positive patients the 5-year cumulative incidence rates of HBeAg seroconversion of vitamin D deficiency group were significantly lower than that of adequate vitamin D group (*P*=0.019). And the 5-year cumulative incidence rates of HBeAg loss of vitamin D deficiency group were lower than that of adequate vitamin D group (*P*=0.079), but not significant. The 10-year cumulative incidence rate of HBeAg seroconversion (*P*=0.89) and HBeAg loss (*P*=0.2) did not reach statistical significance. In both HBeAg-positive and negative patients the 10-year cumulative incidence rates of HBV DNA suppression of vitamin D deficiency group showed lower tendency compared to that of adequate vitamin D group (*P*=0.051).
Conclusions: In conclusion, our results showed vitamin D deficiency is common among CHB patients and is associated with early viral response, although further studies are needed to clarify the underlying mechanisms.
Keywords: Vitamin D, Chronic hepatitis B, HBe Ag seroconversion, HBV DNA suppression

PE-032

Persistently Increased Risk for Hepatocellular Carcinoma Up to 12 Years after HBsAg Seroclearance in Patients with Chronic Hepatitis B

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Aims: HBsAg seroclearance is regarded as a realistic therapeutic goal in patients with chronic hepatitis B (CHB), called functional cure. However, it is unclear if hepatocellular carcinoma (HCC) risk declines over time after achieving HBsAg seroclearance in patients with CHB.
Methods: We retrospectively analyzed 1,972 patients with CHB who achieved HBsAg seroclearance at a tertiary hospital in Korea between 1997 and 2019. Incidence of HCC and risk factors for occurring HCC were evaluated and risk of HCC was stratified by PAGE-B at the time of HBsAg seroclearance.
Results: The mean patient age was 53.7 years, and 64.4% of the patients were men. Cirrhosis was present in 297 (15.1%) patients. Spontaneous HBsAg seroclearance was achieved in 1624 patients, and 348 (17.6%) was antiviral treatment induced HBsAg seroclearance. With 12,890 person-years (PYs) of observation, 49 patients developed HCC with an annual incidence of 0.38 per 100 PY (95% Confidence interval [CI]: 0.28-0.50) during a median follow-up of 5.6 years. Annual incidence of HCC appeared to be increasing over time (*P*=0.02 for trend). The annual HCC risk remained consistently above 0.2%, the threshold for HCC surveillance being cost-effective, even 12 years after HBsAg seroclearance. By multivariable analysis, male sex (adjusted hazard ratio [AHR]: 8.58), older age (1-year increase, AHR: 1.05), and low platelet count (<150,000, AHR: 4.32) were significantly predictive factors for HCC development. No patient with PAGE-B<9 (n=409, 20.7%) developed HCC during study period.

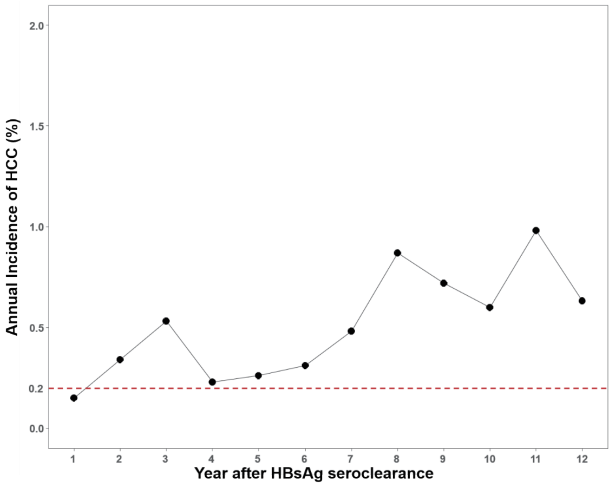

Figure. Serial changes of annual incidence of hepatocellular carcinoma after HBsAg seroclearance

Conclusions: Risk of HCC persisted and increased up to 12 years in patients with CHB after achieving HBsAg seroclearance, justifying continued HCC surveillance. However, patients with low-risk by PAGE-B at the time of HBsAg seroclearance may be safely exempted from HCC surveillance.
Keywords: HBsAg seroclearance, Hepatocellular carcinoma, Hepatitis B

PE-033

Prediction of Hepatocellular Carcinoma by On-Therapy Response of Non-Invasive Fibrosis Markers in Chronic Hepatitis B

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Aims: Antiviral therapy improves hepatic fibrosis and reduces hepatocellular carcinoma (HCC) incidence. This study aimed to evaluate whether on-therapy changes in scores for fibrosis index based on four factors and aspartate aminotransferase-to-platelet ratio index are associated with HCC development and establish an HCC risk score model incorporating non-invasive fibrosis marker (NFM) response.

Methods: This multi-center study recruited 5147 chronic hepatitis B patients (4028 for derivation cohort, 1119 for validation cohort) who were given Entecavir/Tenofovir for >12 months between 2007 and 2018. A risk prediction model for HCC was developed using predictors based on multivariable Cox models and bootstrapping was performed for validation.
Results: The 10-year cumulative HCC incidence rates were 12.6% and 13.7% in the derivation and validation cohorts, respectively. The risk of HCC significantly differed with early NFM response, with a marked reduction in HCC risk in patients achieving a significant decrease in NFM by 12 months (P<0.001). Sex, age, cirrhosis, and NFM response were independently predictive of HCC, and the FSAC model was developed based on these variables. For the 10-year prediction of HCC, FSAC showed higher c-index values than PAGE-B, CU-HCC, and REACH-B (0.84 vs. 0.76, 0.77, and 0.67, respectively; all P<0.001). The predictive performance of FSAC was corroborated in the validation cohort, with higher c-index than other models (all P<0.050).
Conclusions: On-therapy changes in NFM are an independent indicator of HCC risk. FSAC incorporating NFM response is a reliable risk score for risk estimation for HCC with better performance than other models.
Keywords: Hepatitis B virus, Fibrosis, Hepatocellular Carcinoma, Clinical Decision Rules

PE-034

Controlled Attenuation Parameter Value for the Prediction of Hepatocellular Carcinoma in Chronic Hepatitis B Patients Under Antiviral Therapy and Suppressed Viral Replication

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Aims: Controlled attenuation parameter (CAP) by transient elastography (TE) can precisely evaluate hepatic steatosis in patients with chronic hepatitis B (CHB) while the prognostic value is unclear. We aimed to determine whether CAP can predict hepatocellular carcinoma (HCC) in patients with CHB.
Methods: The performance of CAP for predicting HCC was analyzed in CHB patients who took antiviral therapy (AVT) and maintained viral suppression (HBV DNA <2000 IU/mL) between January 2012 and September 2016.
Results: Of the 935 patients, HCC occurred in 55 patients during median 6.1 years of follow-up (range: 4.1-6.5 years). In the multivariate analysis, age, bilirubin, and liver stiffness measurement (LSM) were independent predictor of HCC. However, CAP score was not an independent factor of HCC in overall patients. When stratified into two groups using known cutoff value (10 kPa) of LSM, the prognostic value of CAP was different between the two groups. In patients with low LSM (<10 kPa), hepatic steatosis (CAP ≥222 dB/m) was significantly associated with higher incidence of HCC (adjusted hazard ratio (HR) 2.67, 95% confidence interval (CI) 1.01-7.11). On the other hand, hepatic steatosis was associated with lower incidence of HCC in patients with higher LSM (≥10 kPa) (Adjusted HR 0.34, 95% CI 0.15-0.76).
Conclusions: CAP score showed different prognostic role for prediction of HCC in CHB patients according to LSM value. CAP can be a useful predictor of HCC development in CHB patients on AVT.
Keywords: Transient elastography, Controlled attenuation parameter, Chronic hepatitis B, Hepatocellular carcinoma

PE-035

Extremely Rare Risk of Hepatocellular Carcinoma after Naturally and Nucleos(t)ide Analogue Induced Hepatitis B Surface Antigen Seroclearance

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Aims: Despite a favorable clinical course, the risk of hepatocellular carcinoma (HCC) still exists in patients achieving HBsAg seroclearance. Previous study has shown that the cumulative incidence rates of HCC at 5 years after HBsAg seroclearance were 1.5%. Therefore, we investigated to the incidence of HCC after naturally and nucleos(t)ide analogue (NA) induced HBsAg seroclearance in real-life clinical practice.
Methods: A cohort study was conducted using data from Gangnam Severance Hospital. We identified all subjects with positive HBsAg between January 1, 2001 and March 21, 2018. NA use, liver biochemistries, serial HBsAg and anti-HBs results were retrieved. The primary endpoint was the incidence of HCC after naturally and NA induced HBsAg seroclearance.
Results: A total of 109 chronic hepatitis B patients with HBsAg seroclearance were included for analysis. Among them, 24 patients were excluded. HBsAg seroclearance was developed after liver transplantation in 13 patients and after the development of HCC in 11 patients. In patients with spontaneous HBsAg seroclearance (n=51), all patients had confirmed HBsAg seroclearance and there was no HBsAg seroreversion. In patients with NA-induced HBsAg seroclearance (n=34), all patients had confirmed HBsAg seroclearance and HBsAg seroreversion was observed in just one patients (male, 37years, heavy alcoholics). At a mean follow-up of 9 years, there was no incidence of HCC in patients with naturally and NA-induced HBsAg seroclearance.
Conclusions: The incidence of HCC was extremely rare after naturally and nucleos(t)ide analogue (NA) induced HBsAg sero-

clearance in real-life clinical practice. NA-induced HBsAg seroclearance is also as durable as naturally HBsAg seroclearance.
Keywords: Hepatocellular carcinoma, HBsAg seroclearance, Chronic hepatitis B

PE-036

Association between Hepatitis B Virus Appearance and Overall Survival in Hepatitis B Virus-related Hepatocellular Carcinoma in Patients with Undetectable Serum HBV DNA Levels

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Aims: At the time of hepatocellular carcinoma (HCC) diagnosis, some of hepatitis B surface antigen (HBsAg) positive HCC patients show undetectable serum hepatitis B virus (HBV) DNA levels. The evidence whether antiviral treatment (AVT) for HCC patients without active HBV replication is needed is limited.
Methods: A total of 985 HBV-related HCC patients with undetectable serum HBV DNA levels (<12 IU/mL) at the time of HCC diagnosis between 2008 and 2016 (112 AVT-naïve patients; 873 patients under AVT) were analyzed. Incidence and risk factors for HBV appearance (detection of HBV DNA in serum) during follow-up were assessed. In addition, the association between HBV appearance and overall survival was analyzed using the multivariable Cox regression model with time-dependent covariates.
Results: During a median of 33.4 months of follow-up (range: 0.2 – 124.2 months), HBV appearance was observed in 279 patients. AVT and tumor stage were independent factors associated with HBV appearance. HBV appearance rate was significantly higher for AVT-naïve patients than patients on AVT (5-year cumulative incidence rate: 65.7% vs. 31.8%, P<0.001), and for patients with advanced tumor stage than early stage (5-year cumulative incidence rate: 31.9% vs. 48.9% for mUICC stage I - II vs. III - IV P<0.001). HBV appearance was associated with a higher risk of overall mortality (adjusted hazard ratio: 5.15, 95% confidence interval: 3.60 – 7.38, adjusted for age, ALBI grade, mUICC stage, and initial treatment modality).
Conclusions: HBV appearance was associated with the increased risk of overall mortality in HBV-related HCC patients with undetectable serum HBV DNA levels at diagnosis. AVT was an independent factor for HBV appearance. These findings suggest prompt AVT should be considered for AVT-naïve, HBV-related HCC patients with undetectable serum HBV DNA levels in order to decrease HBV appearance and improve survival.
Keywords: Hepatitis B virus, Hepatocellular carcinoma, Antiviral Therapy, HBV flare

PE-037

Prevalence and Risk Factors of Cardiovascular Disease in Patients with Chronic Hepatitis B

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Aims: The association between chronic hepatitis B (CHB) and cardiovascular disease (CVD) remains uncertain. We investigated the prevalence and risk factors of CVD in patients with CHB.
Methods: Data from the Korean National Health and Nutrition Examination Surveys 2008-2011 were analyzed. The significant liver fibrosis was defined, if the highest quartile of the non-alcoholic fatty liver disease fibrosis score, the highest quintile of Forns index, or fibrosis-4 ≥2.67. The CVD risk was calculated using the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score from the 2013 ACC/AHA guideline.
Results: Among the 506 subjects with CHB, CVD history and significant liver fibrosis was identified in 25 (2.9%) and 150 (29.6%) patients, respectively. Patients with CVD history were significantly older and showed a significantly higher prevalence of hypertension, metabolic syndrome, and significant liver fibrosis, and had a significantly higher platelet count, lower aspartate and alanine aminotransferase level, higher triglyceride level, lower high-density lipoprotein level, and higher ASCVD risk than those without (all P<0.05). In multivariate analysis, higher ASCVD risk (OR [odds ratio] =1.090) and significant liver fibrosis (OR=4.341) independently predicted the risk of CVD history (P<0.05). The prevalence of CVD risk (6.7% vs. 1.4%; OR=5.014) and high ASCVD risk (>15%) (34.0% vs. 7.3%; OR=6.538) was significantly higher in patients with significant liver fibrosis than those without (all P<0.05).
Conclusions: Significant liver fibrosis was independently associated with the risk of CVD history in patients with CHB. Prospective studies should validate the longitudinal association between fibrotic burden and CVD development in patients with CHB.
Keywords: Chronic hepatitis B, Cardiovascular disease, Liver fibrosis, Risk factor

PE-038

Revised Antiviral Therapy Guideline Reduced the Risk of Hepatitis B-related Hepatocellular Carcinoma in Korean Cirrhotic Patients

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Aims: On September 2015, the Korean Association for the Study of Liver (KASL) guideline on initiating antiviral therapy (AVT) for patients with chronic hepatitis B (CHB)-related cirrhosis changed from HBV DNA level ≥2,000 IU/L and aminotransferase (AST) or alanine aminotransferase (ALT) levels over the upper normal limit to HBV DNA level ≥2,000 IU/L, regardless of AST or ALT levels. This study investigated whether the KASL guideline change reduced the risk of CHB-related hepatocellular carcinoma (HCC) in patients with cirrhosis in South Korea.
Methods: A total of 429 patients with CHB-related cirrhosis who initiated AVT between 2014 and 2016 were recruited. The risk of HCC development was compared between patients who initiated AVT before and after September 2015 (previous [n=196, 45.7%] vs. current guideline [n=233, 54.3%]).
Results: Univariate analysis showed that AVT initiation according to previous guideline, older age, and male gender significantly predicted increased risk of HCC development (all P<0.05). Subsequent multivariate analysis showed that AVT initiation according to previous guideline (HR=1.833), older age (HR=1.041), and male gender (HR=2.719) independently predicted increased risk of HCC development (all P<0.05). Additionally, multivariate analysis showed that AVT initiation according to previous guideline (HR=2.400) and male gender (HR=3.058) independently predicted mortality (P<0.05). The cumulative incidences of HCC and mortality were significantly higher in patients who initiated AVT before guideline change than in those who initiated AVT after guideline change (all P<0.05, log-rank test).
Conclusions: The prognosis of patients with CHB-related cirrhosis who initiated AVT improved after KASL guideline modifications.
Keywords: Hepatitis B, Antiviral therapy, Hepatocellular carcinoma, Korean Association for the Study of Liver

PE-039

Changes of HBsAg Quantity and its Relation with HBeAg Seroconversion Following 48 Weeks Pegylated-interferon-alpha Treatment in Patients with HBeAg Positive Chronic Hepatitis B after Long Term Nucleos(t)ide Analogue Maintenance Therapy; Roll Over Trial

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Aims: Durable post-treatment response is uncommon in patients with chronic hepatitis B (CHB) on nucleos(t)ide analogue (NA) therapy. The aim of this study is to investigate pegylated interferon (PegIFN) after long term NA therapy might enhance the antiviral efficacy leading to HBeAg seroconversion and eventually HBsAg loss and/or seroconversion.
Methods: The patient with HBeAg-positive CHB who had been treated with any NA except telbivudine at least 72 weeks, who have an undetectable HBV DNA (<400 copies/mL) at least 48 weeks, were randomised 1:1 to receive PegIFN alfa-2a 180 ug/week or previous NA for 48 weeks. The primary endpoint was change in $\log_{10}$ HBsAg titer during antiviral therapy (ClinicalTrials.gov: NCT01769833). Post treatment HBsAg titer analysis was performed at every 12 weeks until 96 weeks after end of 48 weeks of PegIFN alfa-2a or NA therapy.
Results: Total 150 patients were randomized; 75 received PegIFN alfa-2a. On treatment HBsAg decline from 24 to 48 weeks and was significantly higher in patients who switched to PegIFN alfa-2a than those who continued NA and maximal difference of HBsAg titer was shown at 36 weeks (mean±SD, 0.378±0.572 vs. 0.013±0.241; P<0.001). However, during follow-up period, this difference in HBsAg titer was disappeared and HBsAg titer became similar between two groups (HBsAg titer at 144 weeks: mean±SD, 0.221±0.526 vs. 0.196±0.163; P=0.243). HBeAg seroconversion was significantly higher in patients receiving PegIFN alfa-2a during [21.2% (14/66) vs 9.7% (5/69) at 48 weeks; P=0.026] and after treatment [28.4% (19/67) vs 8.5% (5/59) at 144 weeks; P=0.006]. HBsAg loss was observed in one patient receiving PegIFN alfa-2a during follow-up period. On-treatment HBV DNA elevation rate (> 2000 IU/mL) was significantly higher in patients who switched to PegIFN alfa-2a than those who continued NA and its difference was maximal at 48 weeks [35.8% (24/67) vs. 0% (0/65); P<0.001)]. Antiviral treatment was restarted for patients with PegIFN alfa-2a when HBV DNA was elevated with or without ALT flare [92.3% (60/65) at 72 weeks and 95.4% (62/65) at 96 weeks]. Only treatment with PegIFN alfa-2a was significantly associated with HBeAg seroconversion at 48 weeks (P=0.026). PegIFN alfa-2a was well-tolerated.
Conclusions: This final analysis showed that, for patients who achieve virological suppression with oral NA, switching to a 48 weeks PegIFN alfa-2a treatment significantly decrease HBsAg titer and increases rates of HBeAg seroconversion. However, HBV DNA elevation was developed frequently during treatment and decrease in HBsAg titer was not maintained during post-treatment follow-up.
Keywords: Chronic hepatitis B, Pegylated interferon, Nucleos(t)ide analogue, Hepatitis B surface antigen

PE-040

Increased Risk for Developing Atrial Fibrillation or Flutter in Hepatitis B Carriers: A Population-based Follow-Up Study

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Aims: Recent studies have revealed significant associations between atrial fibrillation (Afib) or flutter (AF) and hepatic disorders such as non-alcoholic fatty liver disease and chronic hepatitis C. In this study, we hypothesized that chronic hepatitis B virus (HBV) infection would increase the risk of Afib/AF.

Methods: To test this hypothesis, we used data from 43,255 adults (>19 years) who had periodic preventive medical checkups from 2005 to 2009 at the Health Screening and Promotion Center at Asan Medical Center and were followed up longer than one year. All subjects received a comprehensive health assessment, and their results were obtained through the institution's Information Technology of Service Management system. Information on past medical history, smoking and alcohol consumption, and current drug history were extracted from standardized questionnaire responses. Electrocardiograms, based on which the diagnosis of irregular heartbeats was made, were available for all patients at baseline and at every checkup during follow-up (median: 4 tests/person).

Results: In the baseline examination, 1,995 subjects were chronically infected with HBV, and 41,260 did not have hepatitis B or C. After 1:4 propensity score matching, 1,995 HBV carriers and 7,975 controls without any viral hepatitis were finally constructed. Over a mean follow-up time of 6.5±3.5 years, Afib/AF was observed in 18 HBV carriers (0.9%) and 38 controls (0.48%) (P<0.05). Multivariate Cox analysis also showed that patients with hepatitis B had a significantly higher incidence of Afib/AF [adjusted hazard ratio (HR), 1.679], as did men (2.692), the elderly (1.080), obese individuals (1.966), and heavy drinkers (1.866) (Ps<0.05). For HBV carriers, heavy alcohol consumption (≥4 times/week) was the only factor independently correlated with the development of Afib/AF (adjusted HR, 4.997; P<0.05).

Conclusions: We found that chronic HBV infection carried increased risk of Afib/AF. The best way to prevent atrial arrhythmia in HBV carriers could be to quit drinking.

Keywords: Atrial fibrillation, Hepatitis B carriers

PE-041

Addition of Liver Stiffness Enhances the Predictive Accuracy of the PAGE-B Model for Hepatitis B-Related Hepatocellular Carcinoma

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Aims: The modified PAGE-B (mPAGE-B) and PAGE-B models reliably predict the risk of developing chronic hepatitis B (CHB)-related hepatocellular carcinoma (HCC). We investigated whether the addition of liver stiffness (LS) value assessed using transient elastography enhanced the predictive accuracies of these models.

Methods: Patients with CHB who started to receive antiviral therapy (AVT) between 2007 and 2017 were enrolled. The training (Yonsei University Hospital) and validation (7 Korean referral institutes) cohorts contained 1,211 and 973 patients, respectively.

Results: Based on multivariate analysis, older age (hazard ratio [HR]=1.051, 95% confidence interval [CI]=1.031-1.071), male sex (HR=2.265, 95% CI=1.463-3.506), lower platelet count (HR=0.993, 95% CI=0.989-0.997), and greater LS values (HR=1.015, 95% CI=1.002-1.028) were independently associated with an increased risk of HCC development (all P<0.05). Thus, we developed an mPAGE^{LS}-B model (maximum score 34) that included age, male sex, platelet count, and LS value. The integrated area under the curve (iAUC) of the mPAGE^{LS} model was greater than those of the PAGE-B and mPAGE-B models (0.760 vs. 0.714 and 0.716, respectively) in the derivation dataset. The cumulative HCC incidence was significantly higher in the high-risk (mPAGE-B^{LS} score ≥ 24) group than in the intermediate-risk (mPAGE^{LS}-B score 12-24) or low-risk (mPAGE^{LS}-B score < 12) group (all P<0.001). Similar results were observed in the validation cohort.

Conclusions: The predictive accuracies of the PAGE-B and mPAGE-B models were validated in Korean patients with CHB receiving AVT. However, the mPAGE^{LS}-B model featuring the addition of LS value showed higher predictability than the

PAGE-B and mPAGE-B models.

Keywords: Liver stiffness, PAGE-B model, Hepatocellular carcinoma, Chronic hepatitis B

PE-042

Predictive Performance of CAGE-B and SAGE-B Models in Asian Treatment Naive Patients who Started Entecavir for Chronic Heaptitis B

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Aims: Recently, CAGE-B and SAGE-B models were used to assess the risk of developing hepatocellular carcinoma (HCC) in Caucasian patients with chronic hepatitis B (CHB) under sustained antiviral therapy (AVT). We checked the predictive performance of these models in Asian patients with CHB.

Methods: We reviewed 737 treatment-naïve patients with CHB who started entecavir between 2006 and 2011, and who were followed up for more than 5 years without HCC development within 5 years of AVT. The predictive performance of CAGE-B and SAGE-B scores were calculated using area under the receiver operating curves (AUROCs).

Results: A total of 338 (45.9%) patients had liver cirrhosis at the start of AVT. And liver stiffness value at 5 years of AVT was 8.8 kPa. CAGE-B and SAGE-B scores at 5 years of AVT were 7.5 and 6.5, respectively. After 5 years of AVT, 66 (9.0%) patients developed HCC. The AUROC of CAGE-B and SAGE-B scores were 0.775 and 0.770 at 7 years and 0.805 and 0.793 at 10 years of AVT, respectively. The cumulative incidence rate of HCC was significantly higher in the high-risk group according to CAGE-B and SAGE-B-based risk stratification than in those of medium and low-risk groups (all P<0.05). The SAGE-B score showed a higher likelihood ratio (χ 2) (55.2 vs. 52.0) and linear trend (χ 2) (53.3 vs. 47.5) than the CAGE-B score, whereas the SAGE-B score showed lower akaike information criteria (50.4 vs. 63.7) than the CAGE-B score.

Conclusions: Both SAGE-B and CAGE-B showed acceptable predictive performance in predicting HCC after 5 years of AVT in Asian patients with CHB.

Keywords: Risk prediction, Chronic hepatitis B, Liver stiffness

PE-043

Comparison of the Occurrence of Hepatocellular Carcinoma in Patients of Chronic Hepatitis B Treated with Entecavir and Tenofovir

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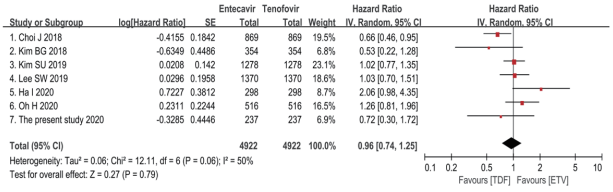
Aims: In chronic hepatitis B (CHB), nucleos(t)ide analogues (NAs) cannot exterminate the virus, and only suppress its proliferation. Thus, even though NAs improve the liver function, the risk of hepatocellular carcinoma (HCC) persists over time. Since a large cohort study which suggested the superiority of tenofovir over entecavir in reducing HCC risk, there is a great deal of controversy in choosing NAs. In this study, we aimed to meta-analyze the published data from Korea to date together with the unpublished data of our institution to derive the robust conclusion.

Methods: We searched on-line database and derived 6 publications from Korea. In addition, we investigated 535 treatment-naïve patients with CHB who were first treated with entecavir (n=298) and tenofovir (n=237) between 2008 and 2016 at Korea University Medical Center (Ansan and Guro Hospitals). We used Kaplan-Meier method, Cox regression model, propensity score matching and meta-analysis.

Results: From the 6 publications, 9,844 patients were included, 556 developed HCC. From our institutions, HCC was developed in 59 patients during a median follow-up of 21.6 months. After 1:1 propensity score matching, the kind of antiviral agent did not affect the development of HCC (HR, 0.72; 95% CI 0.31-1.71; P=0.46). Combined with the results of six domestic studies, the tenofovir group did not show significant suppression of HCC development compared to the entecavir group (HR, 0.96; 95% CI 0.74-1.25).



Conclusions: In a meta-analysis of seven studies of HBV-endemic area including our own institutional data, HCC occurrence was not significantly different between patients with treated with entecavir or tenofovir.

Keywords: Chronic Hepatitis B, Tenofovir, Entecavir, Hepatocellular carcinoma

PE-044

Risk and Risk Score Performance for Hepatocellular Carcinoma Development in Patients with HBsAg Seroclearance

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Aims: Hepatocellular carcinoma (HCC) can develop after hepatitis B surface antigen (HBsAg) seroclearance. However, whether HCC risk differs between antiviral therapy (AVT)-induced or spontaneous seroclearance cases, and ways to identify at-risk populations remain unclear. We compared the HCC risk between AVT-induced and spontaneous cases and tested whether several HCC risk prediction models could be applied to HBsAg seroclearance patients.

Methods: A retrospective cohort of 1,200 patients (median age: 56 years; 824 males; 165 with cirrhosis; 216 AVT-induced cases) who achieved HBsAg seroclearance were analyzed for the development of HCC after HBsAg seroclearance. The performance of five HCC prediction models, CU-HCC, GAG-HCC, REACH-B, PAGE-B, and modified PAGE-B, was assessed.

Results: During a median of 4.8 years of follow-up (range: 0.5 – 17.8 years), HCC developed in 23 patients (1.9%). The HCC incidence rate was higher in the AVT-induced cases than in the spontaneous cases (3.9% vs. 0.9% at five years). AVT and cirrhosis were independent factors associated with HCC, with HCC incidence rates of 0.5%, 1.2%, 4.0%, and 10.5% at five years for spontaneous/no-cirrhosis, AVT-induced/no-cirrhosis, spontaneous/cirrhosis, and AVT-induced/cirrhosis patients, respectively. The area under the receiver operating curve (AUROC) for HCC development at five years was highest for CU-HCC scores (0.82). The HCC incidence was high for high CU-HCC scores (14.3% at five years) and high GAG-HCC scores (7.9% at five years), and was very low for low PAGE-B scores (0% at five years) or low modified PAGE-B scores (0% at five years).

Conclusions: AVT-induced HBsAg seroclearance was associated with higher HCC risk, especially for patients with cirrhosis, indicating that they need careful monitoring for HCC risk. The HCC risk models were able to stratify the HCC risk in patients with HBsAg seroclearance.

Keywords: HBsAg seroclearance, Hepatocellular carcinoma, Antiviral therapy

PE-045

Hepatic Decompensation in Cirrhotic Patients Receiving Antiviral Therapy for Chronic Hepatitis B

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Aims: It is unclear if anti-hepatitis B virus (HBV) treatment can eliminate incident hepatic decompensation. Here we report the incidence and predictors of hepatic decompensation among cirrhotic patients receiving antiviral therapy for chronic hepatitis B.

Methods: This is a post hoc analysis of two prospective HBV cohorts from Hong Kong and South Korea. Patients with liver stiffness measurement (LSM) ≥10 kPa and compensated liver disease at baseline were included. The primary endpoint was incident hepatic decompensation (jaundice or cirrhotic complications) with competing risk analysis.

Results: 818 patients (mean age, 54.9 years; 519 male [63.4%]) were included in the final analysis. During a mean follow-up of 58.1 months, 32 (3.9%) patients developed hepatic decompensation, among whom 34% were secondary to HCC. Three (0.4%) patients experienced variceal bleeding alone, 27 (3.3%) had non-bleeding decompensation and 13 (1.6%) had more than 2 decompensating events. On multivariable analysis, baseline LSM (adjusted hazard ratio [aHR] 1.03), diabetes (aHR 3.27), platelet (aHR 0.99), and international normalized ratio (aHR 7.99) were independent predictors of hepatic decompensation. 30/506 (5.9%) patients fulfilling the Baveno VI criteria (LSM ≥20 kPa and/or platelet count $<150 \times 10^9$/L) and 2/312 (0.6%) patients not fulfilling the criteria developed hepatic decompensation ($P<0.001$).

Conclusions: Hepatic decompensation is uncommon but not eliminated in patients receiving antiviral therapy for HBV-related cirrhosis, and only a third of decompensating events are secondary to HCC. The Baveno VI criteria, which was originally designed to detect varices needing treatment, can be effectively applied in this population to identify patients at risk of decompensation.

Keywords: Cirrhosis, Decompensation, Competing risk, Antiviral therapy

PE-046

Safety and Efficacy with Entecavir and Two Types of Tenofovir Prodrug for Chronic Hepatitis B Infection

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Aims: Chronic hepatitis B (CHB) is a major cause of cirrhosis and hepatocellular carcinoma (HCC), and the use of antiviral agents that suppress the viral replication is the most effective way to control it. As a treatment for chronic hepatitis B, tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and entecavir (ETV) are recommended as primary treatment. This study aimed to evaluate the efficacy and safety of ETV, TDF and TAF in real world clinical data.

Methods: We reviewed the data retrospectively from electronic medical record at the Kyung Hee University Hospital at Gangdong. 363 CHB patients who were treated with ETV (n=163), TDF (n=154) or TAF (n=46) from July 2007 to September 2019

were enrolled. To evaluate the efficacy and safely of the three groups after treatment of each regimen, HBeAg seroconversion, the changes in HBV DNA levels, presence of liver cirrhosis (LC), liver function tests and creatinine were checked. We also evaluated cumulative incidence rate of complete virological response (CVR), LC-related complications and HCC during the treatment period.

Results: The mean age of patients was 51 years and male patients were 66.4%. The mean duration of treated with ETV, TDF and TAF was 49.0 months (interquartile range, 27.0~74.0). The proportion of NA naive patients was 93.3%, 73.4%, and 78.2% in ETV, TDF, and TAF groups (P<0.001). In terms of safety, cholesterol was mildly increased in ETV and TAF groups and statistically decreased in TDF group. (P<0.001) ALP and eGFR change was not significantly different in the three groups at 48 weeks. (P=0.826, 0.048, respectively). There was no significant difference in LC related complications after 48 weeks in each group (P=0.235). In terms of efficacy, HBeAg seroconversion, CVR and ALT normalization at 48 weeks were evaluated, but these were not statistically different among the three groups (P=0.142, 0.538, 0.520, respectively). Cumulative incidence rate of LC-related complications requiring hospitalization were not statistically difference between ETV and TDF group. (P=0.959) Also there was no significant difference in cumulative incidence rate of HCC between ETV and TDF group. (P=0.894)

Conclusions: ETV, TDF and TAF are similarly safe and effective antiviral agents for CHB at 48weeks. CVR, cirrhosis related complications, HCC incidence rates, creatinine clearance are not statistically different in the three groups during the follow up period

Keywords: Entecavir; tenofovir, Tenofovir disoproxil fumaratet, Tenofovir alafenamide, Safety, Efficacy

PE-047

Incidence and Risk Factors for Hepatocellular Carcinoma in Young Age in Patients with Chronic Hepatitis B Viral Infection

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Aims: Some young adults with chronic hepatitis B virus (HBV) infection might be at high risk for hepatocellular carcinoma (HCC), enough to justify regular HCC surveillance despite the young age of the patients. However, ways to identify at-risk individuals who may benefit from HCC surveillance need further evaluations.

Methods: A hospital-based retrospective cohort of 2,612 chronic HBV mono-infected young adults (median age: 36 years, males 46%) were analyzed. The primary outcome was the development of HCC at a young age. Young-onset HCC was defined in males aged < 40 and females aged < 50 years. We calculated the HCC incidence/1000 person-years in the overall cohort and pre-defined subgroups of patients, assessed the independent risk factors, and tested criteria that can be used to identify surveillance targets.

Results: The HCC incidence was low (2.89/1000 person-years) in the overall cohort. However, the HCC incidence varied widely according to baseline characteristics: lowest among young adults with FIB-4 ≤ 0.70 (0.22/1000 person-years), and highest in young adults with radiological cirrhosis (22.5/1000 person-years). The sensitivity of radiologic cirrhosis was sub-optimal (73.5%) for identifying young adults who may develop young-onset HCC. When the FIB-4 index was added, the sensitivity increased (91.2%) with an acceptable tradeoff in specificity (89.5% to 85.9%).

Conclusions: Among young Asian adults with chronic HBV infections, some subgroups were at high risk of developing young-onset HCC that justify HCC surveillance, and could be identified by using FIB-4 index, along with radiologic cirrhosis.

Keywords: Hepatocellular carcinoma, Surveillance, Chronic hepatitis B, FIB-4

PE-048

Tenofovir Alafenamide for Chronic Hepatitis B Patients with Advanced Fibrosis and Partial Virologic Responses to Oral Nucleos(T)Ide Analogues– Interim Report

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Aims: Insufficient data regarding the treatment strategy for partial response to nucleot(s)ide analogue (NUC) raised the aim of investigating tenofovir alafenamide (TAF) switching for chronic

hepatitis B (CHB) patients with advanced fibrosis and partial response to other NUCs.

Methods: CHB patients with advanced fibrosis (stage 3 or 4) and under NUC (except TAF) therapy with detectable hepatitis B virus (HBV) DNA for >52 weeks are enrolled to TAF 25 mg/day for 96 weeks. The objectives are viral suppression, alanine aminotransferase (ALT) normalization and safety.

Results: From Feb. 2019, 34 patients, including 21 (61.8%) with entecavir, 10 (29.4%) TDF and 3 (8.8%) lamivudine or adefovir, were enrolled (15 [44.1%] male, median 53 years). The fibroscan demonstrated a mean of 10.5 kPa (7 [20.6%] cirrhotic). Sixteen (47.1%) patients were HBV e antigen positive, seven (20.6%) had YMDD mutation. The median HBV DNA level declined from 68.5 IU/mL at enrollment to 27.0 IU/mL at 4th week, and undetectable at 12th, 24th, 36th week, respectively, after TAF switching, with undetectable HBV DNA in 14/34 (41.2%), 17/33 (51.5%), 15/25 (60.0%), and 9/15 (60.0%) patients and rate of ALT normalization (≤40 U/L) of 85.3%, 85.3%, 84.8%, 92.0%, and 80.0%, respectively, after TAF switching. (figure 1) Two patients experienced transient virological breakthrough and another one developed at the final time follow up. Serum creatinine and eGFR levels were stable after TAF switching (figure 1). Two patients early terminated including one at 12th week due to personal reason, and another one accidently died at 20th week due to acute heart attack. Others suffered only mild degrees of adverse events which were considered unrelated to treatment.

Conclusions: The preliminary results demonstrated the TAF switching is effective and safe in viral suppression for CHB patients with advanced fibrosis and partial virologic responses to other NUCs.

Keywords: HBV, TAF, Advanced Fibrosis

PE-049

Red Cell Distribution Width, a Useful Non-invasive test of Liver Fibrosis in Chronic Hepatitis Patients

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Aims: In recent years, lot of non-invasive tests have been examined for estimating the severity of liver fibrosis in patients with chronic viral hepatitis. Red cell distribution width (RDW) have been studied in a variety of etiological diseases. Emerging evidence suggests that RDW is a novel potential marker of inflammatory responses. We aimed to investigate the clinical relevance of elevated RDW in the patients with chronic liver disease.

Methods: We enrolled in this retrospective study 130 patients with chronic hepatitis B (CHB), chronic hepatitis C (CHC), HBV related liver cirrhosis (LC) and HCV related LC in Chingeltei District Health Unit between January 2019 and December 2019. Complete blood count, liver function tests and imaging studies were performed for all subjects. Comparisons were made between the tested indexes of the various groups using Stata 15 software.

Results: Of the 130 patients, 104 (80%) were men and 26 (20%) were women. The mean age of the patients was 52.1 years. RDW was significantly higher in HBV related LC (19.3%) than CHB (10.7%) patients, CHC (10.4%) or HCV related LC (11.9%). RDW was slightly higher in CHB patients than CHC (P<0.001). RDW was positively correlated with Child-Turcotte-Pugh score (r = 0.317; P<0.001) and AST to Platelet Ratio Index (APRI) (r = 0.229; P<0.001).

Conclusions: RDW may be a useful diagnostic tool for assessing the hepatic fibrosis and cirrhosis in CHB patients.

Keywords: Chronic hepatitis, Liver cirrhosis, Red cell distribution width, Non-invasive test

PE-050

Risk Assessment of Hepatocellular Carcinoma Using Fibrosis-4 Score between Chronic Hepatitis B Patients with Immune Tolerant Phase and Those with Undergoing Antiviral Therapy

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Aims: Chronic hepatitis B (CHB) patients with immune tolerant (IT)-phase is not generally indicative of antiviral therapy (AVT). We assessed the risk of hepatocellular carcinoma (HCC) during untreated IT-phase stringently defined by lower FIB-4 index, compared to those undergoing AVT.

Methods: Among initially screened 125 untreated patients with hepatitis B e antigen positive, HBV-DNA>20,000 IU/ml, and normal alanine aminotransferase from 2012 to 2018, those with FIB-4 index<1.45 were defined as IT-group (n=91). The cumulative probability of HCC was estimated using Kaplan-Meier analysis. Those with history of HCC or cirrhosis were excluded at baseline. Enrolled patients were followed up till HCC development (intention-to-treat [ITT] analysis), whereas those whose follow-up for HCC development was censored at the time when experiencing phase switch (per-protocol [PP] analysis).

Results: Cumulative probabilities of HCC at 1-, 3-, and 5-years among IT-group were all 0.0% in (n=91), compared to AVT-treated patients with FIB-4 index<1.45 during the same period (n=928); 0.2%, 0.6%, and 1.4%, respectively (P=0.264 for ITT analysis and P=0.533 for PP analysis). Among initially screened 125 untreated patients, those with FIB-4 index≥1.45 (n=26) had the higher risk of HCC compared to IT-group (n=91) (P=0.005). Furthermore, among AVT-treated patients, those with FIB-4 index≥1.45 (n=1,052) had the higher risk of HCC

compared to their counterpart (n=928) (*P*<0.001).

Conclusions: The risk of HCC is almost negligible among IT-group stringently defined through lower FIB-4 index. However, given that the still higher HCC risk among untreated patients with higher FIB-4, appropriate criteria for AVT should be established.

Keywords: Immune-tolerance, Hepatitis B, Antiviral therapy, Hepatocellular carcinoma

PE-051

Two Years Data of Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate for the Treatment of Patients with Chronic Hepatitis B

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Aims: In 96-week results from double-blind, randomized phase III trials, Tenofovir Alafenamide (TAF) continues to be as effective as Tenofovir Disoproxil Fumarate (TDF) with continued improved renal and bone safety. We compared the efficacy and safety of the two drugs in patients with chronic hepatitis B (CHB) for 2 years.

Methods: A total of 890 patients with CHB treated with tenofovir alafenamide (TAF, n=77) or tenofovir disoproxil fumarate (TDF, n=813) in two tertiary referral centers between November 1, 2017, and December 31, 2017, were analyzed. Eligible patients were aged at least 18 years with chronic HBV infection (with serum HBV DNA concentrations of >2, 000 IU/mL), serum alanine aminotransferase concentrations of greater than 40 U/L and at no more than twenty times the upper limit of normal, and estimated glomerular filtrate rate (eGFR) of at least 50 mL/min (by the Chronic kidney disease epidemiology collaboration). To reduce selection bias and the effect of potential confounders, propensity scores were calculated by logistic regression based on age, gender, diabetes, compensated cirrhosis, and hepatitis B e antigen (HBeAg) status, initial ALT, initial HBV DNA, total bilirubin, albumin, and platelet counts. Differences between the two groups were balanced by a 1:1 PS-matched analysis (TAF, n=77 vs. TDF, n=77). The primary efficacy endpoint was the proportion of patients who had HBV DNA less than 20 IU/mL at week 96; Serum phosphorus, eGFR, and lipid profile were assessed to evaluate the safety.

Results: Baseline characteristics were not different between the two groups. Biochemical response (ALT<40 IU/L) rate in TAF and TDF group was 77.9% (60/77) vs 79.2% (61/77) at 1 year, 92.2% (71/77) vs. 89.6% (69/77) at 2 years. Virological response rates (HBV DNA <20IU/mL) was 62.3% (48/77) vs. 66.2% (51/77) at 1 year, 85.7% (66/77) vs. 84.4% (65/77) at 2 years. There were no statistical differences in biochemical and virological response rates. The mean reduction in serum HBV DNA from baseline to 1 and 2 years were similar in TAF and TDF group (-4.7 vs -5.1 and -5.2 vs -5.2 $\log_{10}$IU/mL, *P*=0.995). HBeAg seroconversion was 21.6% (8/37) vs 8.6% (3/35) at 2 years (*P*=0.191). A virological breakthrough was not seen in both groups. At year 2, mean change in eGFR was similar in both groups (TAF +4.7 mL/min vs TDF -1.4 mL/min; *P*=0·121), mean change in phosphorus was also similar in both group (TAF -0.05 mg/dL vs TDF -0.01 mg/dL; *P*=0·611).

Conclusions: In patients with HBeAg positive and negative CHB, the efficacy and safety of TAF were similar to those of TDF at 2 years.

Keywords: Chronic hepatitis B, Tenofovir Alafenamide, Tenofovir Disoproxil Fumarate, Efficacy

PE-052

Alcohol Intake and Mortality in Patients with Chronic Viral Hepatitis: A Nationwide Cohort Study

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Aims: We evaluated the association between alcohol intake and all-cause and cause-specific mortality in subjects with chronic viral hepatitis, using nationwide population-based cohort study.

Methods: A total of 364,361 men and women 40–84 years of age who underwent health screening exam between January 2002 and December 2013 that included assessment of frequency and amount of alcohol consumption were assessed for all-cause and cause-specific mortality.

Results: In participants without chronic viral hepatitis, the fully-adjusted hazard ratios (HR) for all-cause mortality comparing light, moderate, and heavy drinkers to non-drinkers were 0.90 (95% CI 0.85–0.96), 1.06 (95% CI 0.99–1.13), and 1.48 (95% CI 1.30–1.68), respectively. In participants with chronic viral hepatitis, the corresponding HRs were 1.15 (95% CI 1.01–1.30), 1.18 (95% CI 1.01–1.37), and 1.66 (95% CI 1.26–2.20), respectively (P-value for alcohol intake by chronic viral hepatitis interaction <0.001). Compared to participants without chronic

viral hepatitis, those with chronic viral hepatitis had substantially elevated liver cancer or liver disease (HR 11.76, 95% CI 10.58–13.07) and extrahepatic cancer mortality (HR 1.41, 95% CI 1.30–1.54). In patients with chronic viral hepatitis, the high mortality due to liver cancer or liver disease and the positive association of alcohol intake with liver cancer or liver disease mortality explained the positive association of alcohol intake with all-cause mortality.

Conclusions: Even light to moderate alcohol intake was associated with increased all-cause mortality in individuals with chronic viral hepatitis. Clinicians and public health campaigns should advise against any amount of alcohol intake in individuals with chronic viral hepatitis.

Keywords: Alcohol intake, Chronic viral hepatitis, Mortality

PE-053

Risk Factors of Hepatitis B Virus Infection in Mongolia

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Aims: To study risk factors of HBV transmission.

Background: Mongolia introduced HBV vaccination into routine immunization schedules for newborns and children under1 year of age in 1991, which substantially decreased the incidence of HBV infection.

Methods: The study was conducted 200 patients with acute HBV infection, treated in Mongolia from 2015-2017.

Results: The mean age of the patients were 26±6.4, of those 57.5% were males and 42.5% were females and 41% were married. 17(8.5%) were vaccinated, 116 were unvaccinated and 67(33.5%) they don't know whether they were vaccinated or not. 99(49.5%) survey participants were born before 1991, 87(43.5%) were bornbetween 1992-1997 and 14(7%) were born since 1997. A specially developed questionnaire was used to determine the risk factors for HBV infection (last six months):

Risk factors	n	%
Multiple sexual partners	105	52.5%
History of dental surgery	32	16%
Tattoo	22	11%
History of hospitalization	81	40.5%
Surgical procedures	26	13%
Acupuncture	22	11%
Piercing	14	7%
Shares toothbrush with others	18	9%
Family member with HBV infection	39	19.5%
Shares razor with others	28	14%
Shares nailclipper with others	170	85%

In the serology test, 178(89%) were HBsAg and anti-HBcIgM-both positive and 22(11%) were HBsAg positive and anti-HBcIgM negative.

Conclusions: HBV vaccination is effective method for preventing HBV infection. Most common risk factors of HBV infection are household and sexual contacts of people with HBV and having multiple sexual partners.

Keywords: HBV, Risk factor, Tattoo, Mongolia

PE-054

Comparative Study of Persistent Immunity to HBV after Vaccination and Naturally Acquired Immunity Post HBV Infection in Mongolia

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Aims: To determine the generation of persistent immunity from HBV vaccination or after HBV infection. HBV and HCV are high prevalent in Mongolia, around one fourth Mongolian has HCV or HBV. According to the study, 39.4% of people who had HBV infection got HBV vaccination which leads to viral problem in Mongolian health care system. Since 1991 all newborns have been vaccinated with HBV vaccine. And people who born before that year did not take the HBV vaccination.

Methods: 492 patients have enrolled who were investigated with quantitative HBsAb using Sysmex HISCL-800 at Happy Veritas Clinic and Diagnostic Center and MNUMS. The vaccination scheme consists of three doses. Vaccination is successful if the antibody titer is higher than 10 mlU/L. Also we have conducted questionnaires about HBV vaccination and risk factor for taking hepatitis infections from patients.

Results: In this study 492 patients have participated 313(63%) female and 179 (37%) male, out of which 471(96%) people born before 1991 and remaining 21(4%), people born after 1991. 12 people (57%) who born after 1991 or vaccinated within 24 hours after birth were quantification HBsAb low titer (<10mlU/L), remaining (43%) were qHBsAb titer (>10mlU/L), while 297 people (64%) who born before 1991 were qHBsAb titer (<10mlU/L),and remaining 36% of patients had persistent HBV vaccine. The 99 people who born before 1991 have enrolled in HBV vaccination voluntarily while 372 people did not take HBV vaccine at all.

Conclusions: Persistent immunity against HBV is generated not only in person who have taken HBV vaccination but also in person who have had slight HBV infection. It was considered that people aged between 50 and 60 years could not get persistent immunity against HBV. We assumed that persistent immunity against HBV depends on age, not other factor and sex.

Keywords: HBV, Vaccination, Center, Factor

PE-055

The Immunogenicity of Healthcare Workers of Hepatitis B Vaccination in Mongolia

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Aims: To define immunogenicity of Hepatitis B vaccination among health workers in Mongolia.

Introduction: A safe working environment for healthcare workers should include the offer of HBV immunization not only for their protection, but also to prevent transmission from HCWs to patients. The immunogenicity of a two-dose HBV vaccine course would be estimated to provide more than 75% sero-protection.

Methods: This is a cross-sectional hospital based survey which will be conducted among healthcare workers to evaluate HBV vaccination coverage and KAP towards to the HBV infection and vaccination. Statistical analysis was done by using an SPSS-21 and conducted relevant statistical tests. In total, 1200 health workers were responded to this survey. 3 main laboratory serological tests was performed among survey participants HBsAg, Anti-HBc total, and Anti-HBs.

Results: The protection level of the subjects was 57.6% >100 mIU/ ml, 24.8%, 11-100 mIU/ mL and 17.6%, 0-10 mIU/ mL. The mean of Immune due to natural infection level was 459.71±392.95 mIU/ml and immune due to HBV vaccination level was 516.20±412.68 mIU/ml. In relatively, high percentage of health workers who are working less than 5 years were had immune due to vaccination. Whereas, 62.7% of health workers who had immune due to natural infection were working in health facility more than 6 years.

Conclusions: On hepatitis B vaccination efficacy done in Mongolia, of the vaccinated HCWs, 57.6% >100 mIU/ ml, 24.8%, 11-100 mIU/ mL and 17.6%, 0-10 mIU/mL.

Keywords: HBV vaccination, Healthcare workers, HBV, Mongolia

PE-056

Study on HBV Vaccination Coverage among Healthcare Workers in Mongolia

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Aims: To define HBV vaccination coverage among Mongolian healthcare workers.

Introduction: Mongolia has a large burden of viral hepatitis, especially chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, which are associated with cancer and cirrhosis. The occupational risk for transmission of HBV, HCV and HIV among healthcare workers (HCWs) is well recognized.

Methods: This is a cross-sectional hospital based survey which will be conducted among healthcare workers to evaluate HBV vaccination coverage and KAP towards to the HBV infection and vaccination. In total, 1200 health care workers were attended to the survey.

Results: More than half of survey respondents were had full 3 doses of HBV vaccination. About 4.5% of them had infected with HBV. About 64.0% of them were health workers who are currently working at risk position and most of them had contact with blood, blood products and other body fluids, as well as the risk of needle-stick injuries. 40.0% of respondents who had full doses of HBV vaccination and 56.9% of them had immune due to natural infection. Whereas, 16.7% of respondents who did not received full doses of HBV vaccination were had immune due to natural infection. In general, 1 of 2 respondents had immune due to natural infection.

Conclusions: The HBV vaccination coverage among health workers are relatively sufficient. However, already infected percentages of among health workers are high in Mongolia.

Keywords: HBV vaccination, Vaccination coverage HCW, Mongolia

PE-057

Study on Fibrosis Change with Transient Elastography in Chronic Hepatitis B Virus Treatment with Tenofovir

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Background: Tenofovir disoproxil fumarate (TDF) is one of the first optimal choices to be used in the treatment of chronic hepatitis B. FibroScan is non-invasive methods to assess liver fibrosis.

Aims: To evaluate the therapeutic effect of TDF on fibrosis via FibroScan after treatment.

Methods: This study was conducted in 63 chronic hepatitis B patients who had the indication of antiviral therapy at 103 Cam Khe Clinic from March 2019 to March 2020. All patients with chronic hepatitis B treated with TDF during 6 months. Liver fibrosis stages was appreciated using transient hepatic elastography by Fibroscan before and after 6 months treatment.

Results: The average age of patients was 46 years, with men accounted for 69% of the total. After treatment, normalization of ALT 71.26%, viral response of 90.23%, HBV DNA below the detection level was 66.3%. Liver fibrosis evaluated by FibroScan before and after 6 months treatment were 7.15 ± 1.56 kPa, and 3.58 ± 1.19 kPa eveluated by FibroScan.

Conclusions: TDF was effective for patients after treatment on

liver fibrosis assessed by FibroScan in chronic hepatitis B patients.

Keywords : FibroScan, Chronic hepatitis B, Tenofovir disoproxil fumarate (TDF), Liver fibrosis

PE-058

Management of Choledochal Cyst: An Institutional Review from a Tertiary Referral Center in Nepal

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Aims: Choledochal cysts (CC) are a rare congenital cystic dilation of the biliary tract.

Methods: This is a retrospective study of 32 consecutive patients of CC who underwent multidisciplinary management in last 2 and half years at a tertiary referral center from Nepal.

Results: A total of 32 patients, 9 males and 23 females were operated. The average age at diagnosis was 25 years (range from 2 to 56 years). The most common presenting symptoms were pain 31(96.88%), jaundice 10(31.25%) and mass 5 (15.63%). Triad of pain, jaundice and mass was present in 4 (12.5%). Transabdominal Ultrasonography (100%) was the initial diagnostic modality of choice followed by MRCP (68.75%), and CECT (31.25%). ERCP was done for stent placement in 3 (9.38%) patients with severe cholangitis. Type IVA (37.5%) was the most common type of CC followed by type IC (31.23%), type IB (15.65%), type IA (12.5%) and type IVB (3.12%). Abnormal pancreaticobiliary duct junction was observed in 3 (9.38%) patients. All patients underwent open cyst excision with Roux-en-Y hepaticojejunostomy (HJ). There were 2 patients who underwent relaparotomy for efferent loop obstruction and Peterson hernia. None of our patient had cholangiocarcinoma on pathological examination.

Conclusions: Choledochal cyst is rare cystic dilatation of biliary tract. Surgery (Cyst excision with Roux-en-Y hepaticojejunostomy) is treatment of choice. Although the incidence of cholangiocarcinoma is less, long-term surveillance is essential.

HBV, Basic

PE-059

Knowledge of Hepatitis B Virus Infection among Health Science Students of Pokhara Univ., Gandaki Province, Nepal

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Aims: Hepatitis B virus infection (HBV) is public health problem in Nepal. The prevalence of HBV was found to be below 1% (0.9%), however some subgroup of population showed high prevalence by various studies. The study aimed to determine the knowledge of Hepatitis B virus infection among health science students of Pokhara University, Nepal.

Methods: A cross-sectional survey was done among 200 students of health and allied science of Pokhara University using a structured self-administered questionnaire method. The questionnaire was prepared based on the previous studies. Students from public health, laboratory science, pharmacy and nursing disciplines were enrolled in the study. The information was collected from January to February, 2020. Mean knowledge score of HBV was measured based on 28 related questions as it was done in previous study, in which each correct answer was coded 1 and incorrect answer as 0, resulting the maximum score of 28 for all right answers. Descriptive statistics, and chi-square test, independent sample t test and one –way ANOVA test were applied.

Results: Of the total, 74.5% of the respondents were females; and mean age of the respondents was 20.6 (SD ±1.48) years. Mean knowledge score of HBV was 19.48 (SD±2.72) out of 28. The mean knowledge score was 19.90 (SD± 2.67) among females and 18.33 (SD±2.53) among males; there was significant difference in the mean knowledge score between males and females (p value <0.05). Similarly, there was also significant difference in the mean knowledge score among the students of different disciplines of health science (p value <0.05); the highest mean was observed among nursing students which was 21.22 (SD+2.64). Regarding the individual questions, 98% respondents agreed that hepatitis B infection is caused by a virus. Among all, 16.5% respondents agreed that hepatitis B infection can be spread by mosquitoes; the statement was significantly different by sex (P<0.05). Of the total, 41.9% agreed that hepatitis B can be spread through close personal contact such as kissing or talking, 29.5% agreed that sharing dishes with HBV positive patients can cause the spread of virus; 97% reported that hepatitis B is spread through blood-to-blood contact; and 86.5% respondents mentioned that sexual transmission is a common way hepatitis B is spread. Of total, 91% students agreed that there is a vaccine for HBV. Among all, 84% students agreed that HBV is associated with an increased risk of liver cancer and 87.5% mentioned that HBV can lead to liver cirrhosis. Of the total, 58.5% agreed that having a medical and/or dental procedure increases a person's chances of contracting HBV; 69.5% students believed that symptoms appear soon after the entrance of HBV into the body; 55.8% agreed that symptoms always appear after the entrance of HBV to the body; 38.5% students agreed that people with HBV should be restricted from working in the food industry; and 64.5% students reported that there is a pharmaceutical treatment available for hepatitis B; and the agreement with all the above

statements had statistically significant association with sex (p value <0.05).

Conclusions: The mean knowledge score of HBV infection was found satisfactory among health science students of Pokhara University, Gandaki province, Nepal. Significant differences were observed in the mean knowledge score of HBV by sex and different disciplines of health science. The curriculum of all health science disciplines should be comprehensive to cover all aspect of HBV infection

Keywords: HBV, Knowledge, Health science students, Gender

PE-060

An Alternatively Spliced Sirtuin 2 Isoform 5 Inhibits Hepatitis B Virus Replication from cccDNA by Repressing Epigenetic Modifications Made by Histone Lysine Methyltransferases

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Aims: Sirtuin 2 (Sirt2), an NAD^+-dependent protein deacetylase, deacetylates tubulin, AKT, and other proteins. Previously, we showed that Sirt2 isoform 1 (Sirt2.1) increased replication of hepatitis B virus (HBV).

Methods: Here, we show that HBV replication upregulates expression of Sirt2 primary and alternatively spliced transcripts, and their respective isoforms 1, 2, and 5. Since Sirt2 isoform 5 (Sirt2.5) is a catalytically inactive nuclear protein with a spliced-out nuclear export signal (NES), we speculated that its different localization may affect its activity.

Results: Overexpression of Sirt2.5 reduced expression of HBV mRNAs, replicative intermediate DNAs, and covalently closed circular DNA (cccDNA), an activity opposite to that of Sirt2.1 and Sirt2.2. Unlike the Sirt2.1–AKT interaction, the Sirt2.5–AKT interaction was weakened by HBV replication. Unlike Sirt2.1, Sirt2.5 activated the AKT/GSK-3ß/ß-catenin signaling pathway very weakly and independently of HBV replication. When the NES and an N-terminal truncated catalytic domain were added to the Sirt2.5 construct, it localized in the cytoplasm and increased HBV replication (like Sirt2.1 and Sirt2.2). Chromatin immunoprecipitation assays revealed that more Sirt2.5 was recruited to cccDNA than Sirt2.1. Also, recruitment of histone lysine methyltransferases (HKMTs) such as SETDB1 and SUV39H1, EZH2, and PR-Set7, and their respective transcriptional repressive markers H3K9me3, H3K27me3, and H4K20me1, to cccDNA increased in Sirt2.5-overexpressing cells. Among these, the Sirt2.5–PR-Set7 and –SETDB1 interactions increased upon HBV replication.

Conclusions: These results demonstrate that Sirt2.5 reduces cccDNA levels and viral transcription through epigenetic modification of cccDNA via direct and/or indirect association with HKMTs, thereby exhibiting anti-HBV activity.

Keywords: Hepatitis B virus, Sirtuin2, Transcription, CccDNA

HCV,Clinical

PE-061

Long-Term Outcomes of Children with Hepatitis C Virus Infection after Kidney Transplantation in Kazakhstan

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Introduction: Hepatitis C virus (HCV) infection is an important co-morbidity in patients after kidney transplantation (KT) affecting patient and graft survival. In the era of Direct Acting Antiviral (DAA) drugs the current standards of management strongly suggest to treat HCV positive patient with end-stage renal disease (ESRD) before KT. However, in the conditions where this treatment is not available, KT remains the only life-saving option for children with ESRD who is not able to sustain on dialysis any longer.

Aim: Currently, there is limited data available about outcomes of pediatric patients with HCV after kidney transplantation. We studied the prevalence, clinical profile and outcome of HCV infection in KT pediatric recipients (KTPR) in Kazakhstan for the first time after the launching the National Pediatric KT Program in 2012.

Methods: We studied pediatric patients who underwent KT from January 2012 to December 2018 at the Department of Nephrology, Dialysis and Transplantation, National Research Center of Mother and Child Health, University Medical Center, Nur-Sultan. HCV infection was defined as a positive anti-HCV antibody and/or HCV RNA PCR positivity. Control group included KTPRs with no evidence of HCV or hepatitis B virus (HBV) infection.

Results: A total of 73 KTPRs were included. The mean age was 10.6 ± 4.5 years, male:female ratio was 1:1 and mean duration of post-transplant follow-up was 32 months. 9 patients (12%) had evidence of HCV infection. All HCV-positive patients underwent KT before DAAs were available in the country. Among them 4 patients were treated with interferon before KT, 4 patients had HCV infection by the time of KT and 1 patient developed de-novo HCV infection after KT. Although there was no statistical significant difference in patient survival (log-

rank *P*=0.82) and graft survival (log-rank *P*=0.416) between HCV-positive group and controls, the only death in HCV group was registered in the patient who had de-novo HCV infection after KT. 2 patients who were treated from HCV infection before KT lost their kidney grafts and returned on dialysis. Among 4 patients with persistent HCV infection by the time of KT, 2 were successfully treated with DAAs 5 years after KT without any side effects or worsening of graft function. 2 KTPRs still have chronic HCV infection Stage 0 – 1 with low viral load, normal liver function tests and normal kidney graft function over the 6 years after KT.

Conclusions: In our cohort HCV-positive KTPRs did not have any difference in patient and graft survival comparing to KTPRs without HCV infection. The worst outcome had patient with de-novo developed HCV infection after KT. HCV treatment with DAA after KT was successful without deterioration of kidney graft function. Limitation: low number of HCV-positive KTPRs.

Keywords: HCV, Kidney transplantation, Children

PE-062

Long-Term Course of Cirrhosis Regression: Lessons from Patients with HCV Cirrhosis Following Successful Sofosbuvir-Based Treatment

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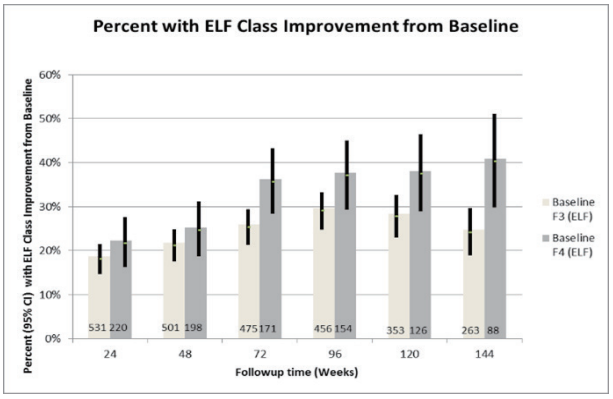
Aims: In patients with HCV cirrhosis, a sustained virologic response (SVR) is associated with improved clinical outcomes; however, the temporal course of changes in fibrosis is poorly understood. Our aim was to evaluate changes in noninvasive tests of fibrosis (NITs) in this setting to gain insights into the natural history of cirrhosis regression following removal of the causative exposure.

Methods: We studied patients with HCV cirrhosis who achieved SVR with sofosbuvir (SOF)-based regimens (in a trial or clinical practice) in an ongoing, prospective cirrhosis registry (NCT02292706). Patients underwent routine clinical and laboratory assessments, including semi-annual Child-Pugh-Turcotte (CPT) scoring and measurement of the Enhanced Liver Fibrosis (ELF) test, as well as annual liver stiffness measurement by transient elastography (LS by TE). Changes in fibrosis were estimated based on ELF response (defined as ≥0.5 unit reduction), and shifts in estimated fibrosis categories based on ELF (F3, ELF 9.8-11.3; F4, ELF >11.3) and LS by TE (F3, 9.6-12.5 kPa; F4, >12.5 kPa). Logistic regression was used to identify predictors of fibrosis improvement as defined by NITs.

Results: 1,574 subjects with HCV cirrhosis (32% female, 39% BMI ≥30 kg/m^2, 7% CPT class B/C) were included in this study; median interval between SVR and registry enrollment was 38 weeks (IQR 27-60). At enrollment, median (IQR) ELF was 14.3 (9.5, 22.1); 586 (37%) and 247 (16%) patients had ELF scores consistent with F3 and F4 fibrosis, respectively. Median LS by TE was 9.9 kPa (9.2, 10.8); 761 (57%) and 227 (17%) patients had LS consistent with F3 and F4 fibrosis, respectively. As of May 2019, median duration of follow-up after registry enrollment was 123 weeks (IQR 96, 168). At week 144, 49% of those with baseline CPT class B/C had improved CPT class, while 98% of those with baseline CPT class A remained in CPT class A. During follow-up, changes in ELF and LS by TE suggested fibrosis improvement in an increasing proportion of patients with both F3 and F4 fibrosis at enrollment (Figure 1). ELF score improved by ≥0.5 units at week 144 in 27% and 47% of patients with baseline F3 and F4 fibrosis, respectively. Predictors of ELF improvement included higher ELF (*P*<0.001) and AST (*P*=0.049), and lower platelets (*P*=0.02) and BMI (*P*=0.10) at registry baseline.



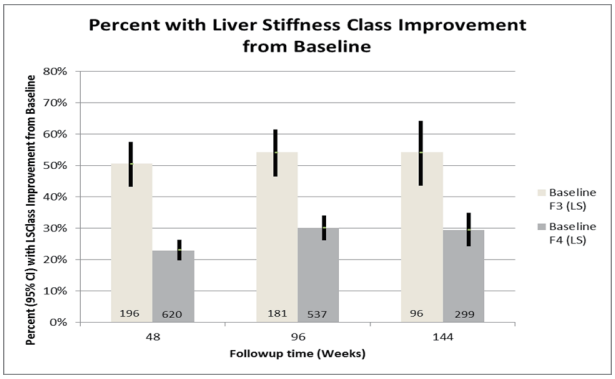


Figure 1.

Conclusions: In patients with cirrhosis in whom HCV has been eradicated by SOF-based therapy, NITs suggest significant fibrosis improvement in 25-50% of patients within 3 years. Associations between reductions in these NITs and improvements in clinical outcomes require evaluation during longer-term follow-up.

Keywords: HCV, SOF-based regimen, Cirrhosis regression

PE-063

C-Reactive Protein (CRP) as an Inflammatory Marker: A Case Control Study on HCV Infected HIV and Non-Infected Healthy Individuals

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Aims: HIV is the chronic viral infection documented worldwide and HCV infection in HIV is a major infection. C-reactive protein is one of the acute-phase protein used as biomarker of inflammation. CRP is hepatic in origin which increases their concentrations during certain inflammatory disorders. CRP levels in human serum are normally quite low (around 1µl/mL), but it increases several hundred folds during the acute-phase inflammation.

Methods: A Case control study was carried out in 244 participants including 122 HCV infected HIV and 122 non-infected (healthy) individuals for the comparison of CRP concentration using Nephelometry method by MISPA i2. The blood samples for case were taken from ART center of Western regional hospital and for control samples were taken from Pokhara valley through counseling and Questionnaires and ethical permission was obtained from IRC.

Results: Among the 122 HCV infected participants 16(13.11%) individuals had CRP concentration >6mg/L and healthy 122 participants only 2(1.63%) participants had CRP concentration >6mg/L bearing of positive prevalence rate. This showed the significance level of *P*=0.001 and OR=9.057 with nine fold higher prevalence in the case and control. Male participant were found to have higher level of CRP (>6mg/L) in case, among 16 CRP positive, 9(7.4%) were male and 7(5.7%) were female. In control equal prevalence of positive CRP concentration (>6mg/L) was sheen between male and female 1(.8%). The sex wise distribution showed no significance with the CRP level. The mean CRP concentration in HIV infected participants was 2.07mg/L and in non-infected (healthy) participants was 1.40mg/L.

Conclusions: Highest prevalence of the positive CRP concentration was among the case in our study which might be due to the defect in immune system of HCV-HIV infected individuals than of healthy individuals.

Keywords: CRP, HCV, HIV, Inflammation

PE-064

Study on Correlation between Serum Ferritin Levels and Liver Stiffness Assessed by Fibroscan in Patients with Chronic Hepatitis C

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Aims: Chronic hepatitis C is a major infectious disease which is mainly cause of morbidity worldwide in patients with liver disease, and liver transplantation. Raised ferritin levels play an important role of intervening the process which is associated with hepatic injury. Screening with non-invasive strategies can detect the disease at early stage and intervention could be initiated. To determine correlation between serum ferritin levels and liver stiffness values in patients of chronic hepatitis C.

Methods: A cross-sectional study was conducted at 103 Cam Khe Clinic from May 2019 to April 2020. 93 patients with chronic hepatitis C fulfilling inclusion criteria were included in this study. Liver fibrosis stages was appreciated using transient hepatic elastography by Fibroscan, the activities of serum liver function biomarker enzymes and serum ferritin levels were determined by automated analyser.

Results: The average age of patients was 48 years, with men accounted for 78% of the total. The mean serum ferritin value was 148.19 ng/ml, liver stiffness measurements range from 12.5 to 75.5 kPa, with a median value of 17.39 ± 15.98 kPa. Significantly elevated levels of serum ferritin ($P<0.001$), were detected in patients with severe fibrosis compared to mild fibrosis. Concentration of serum ferritin was increased with the evolution of fibrosis in all stages from F0 to F4 and this increase was significant ($P<0.01$) in cirrhotic patients (F4). There was a positive correlation between serum level of ferritin and progression of fibrosis (0.979391) ($r = 0.976$).

Conclusions: There is significant correlation between serum ferritin and liver stiffness. Serum ferritin concentration may be used as liver fibrosis biomarkers.

Keywords: Chronic hepatitis C, Ferritin, Fibroscan, Liver stiffness

PE-065

Prevalence of Hepatitis C Virus Infection among Nepalese Traumatic Patients

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Aims: Hepatitis C virus (HCV) infection is a major public health problem in the world affecting millions of people worldwide. HCV is prominently associated with significant morbidity and mortality in developing and developed countries due to its serious liver complication. The prevalence of HCV infection is almost 170 million persons globally and 0.1%- 1.7% in Nepal. To eradicate the spreading of HCV, the Nepalese government has been running lots of campaigns since last many years. The main aim of this study was to investigate the prevalence of HCV infection among the traumatic patients which would uncover the current status for the effectiveness of Nepalese health policy.

Methods: A cross-sectional study was carried out among 265 traumatic patients attending Alive Hospital, Chitwan, Nepal during the period of 1 year (January 2019 to February 2020). The antibody produced against the hepatitis C virus was detected from the serum obtained from the patients using the HCV-ELISA kit. The data analysis was done using SPSS.

Results: Among 265 patients tested for HCV, 74.0% (196) were male and 26.0% (69) were female. The patients were from the age of 0.6 to 84 years old. The patients with the age of 15-30 years were higher (37.4%) than another age group. 1.1% (3) out of 265 were positive for HCV infection. 98.9% (262) patients were negative for the HCV antibody. The prevalence of HCV was higher (0.754%) in males than females (0.284%) (P-value <0.05). The highly infected patients were the age group of 31-55 years old. Additionally, the Buddhist community was predominantly infected.

Conclusions: We conclude that HCV infection in the central region of Nepal is decreasing as compared to the previous reports and is relatively lower than in another developmental region of Nepal. It might be a possibility that increased mortality due to liver-related causes and an aging population may have contributed to a reduction in infection.

Keywords: HCV, Hepatitis C virus infection, Prevalence, Nepalese ethnicity

PE-066

Safety and Effectiveness of HARVONI® (Ledipasvir/Sofosbuvir, LDV/SOF) from the 4th Year Post-Marketing Surveillance (PMS) Data in Korea

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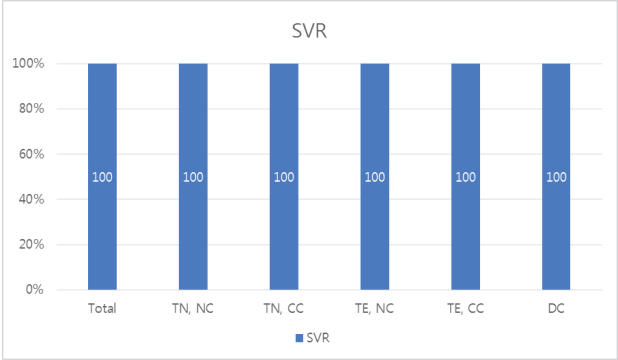
Aims: The 4th PMS data of LDV/SOF was analyzed. We identified the incidence proportion of adverse event (AE), adverse drug reaction (ADR), serious adverse event (SAE) within post-treatment week 12, and sustained virologic response(SVR) rate at post-treatment week 12.

Methods: In this open-label, non-interventional study, case report forms of 112 patients were collected from 20 institutions in Korea from October 13th, 2018 to October 12th, 2019. 93 patients were included in the safety analysis set and 64 patients were included in the effective analysis set.

Results: Of the 93 patients included in the safety analysis, all were infected with HCV genotype 1. 47% (44/93) were male patients and 43% (40/93) of patients were above age 65. 13% (12/93) of patients had previous HCV treatment experience. 69% (64/93) of patients were treated with LDV/SOF only and 31% (29/93) of patients were treated with LDV/SOF+RBV. When compared to LDV/SOF group, LDV/SOF+RBV group had higher percentages of compensated cirrhotic patients (38% vs 31%) and decompensated cirrhotic patients (45% vs 0%). The incidence proportion of AE from start date to 12 weeks after administration completion or discontinuation was 43% (40/93, 78 events). The AE incidence proportion was higher in LDV/SOF+RBV group (19/29, 66%) compared to LDV/SOF only group (21/64, 33%). 3 patients discontinued treatment due to adverse events but all of the adverse events had unlikely causal relationship with LDV/SOF. The incidence proportion of ADR was 13% (12/93, 19 events), SAEs was 7.53% (7/93, 10 events). The SVR12 of total patients included in the effective analysis set was 100%



Among 90 patients with complete baseline data, 41% (37/90) of patients fulfilled 8 weeks of LDV/SOF treatment indications. .

Conclusions: In conclusion, the 4th PMS on Harvoni® has proven

its safety and efficacy in Korean patients.
Keywords: LDV/SOF, PMS, Safety, Efficacy

PE-067

Low Incidence of Hepatocellular Carcinoma after Antiviral Therapy in Patients with Chronic Hepatitis C and Hemophilia

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Aims: Chronic hepatitis C (CHC) is a major comorbidity in patients with hemophilia. the management of hepatitic C virus (HCV) infection and control of various complications are emerging as important factors to increase the long term prognosis of hemophilia patients. Therefore, we assessed the long term outcome of peginterferon plus rivavirin (PEG) and direct acting antivirals (DAA) in HCV patients with hemophilia.
Methods: Patients (n=205) were enrolled between March 2007 and July 2019. 141 patients were treated with PEG (genotype 1, n=98; genotype 2, n=42; genotype 3a, n=1). 64 patients were treated with DAA (genotype 1, n=44; genotype 2, n=19; genotype 4, n=1). We evaluated sustained virological response (SVR), incidence of hepatocellular carcinoma (HCC).
Results: Mean follow-up periods were 9.9 and 3.4 years in PEG and DAA, respectively. In genotype 1, SVR was 66.3% (65/98) and 90.9% (40/44) in PEG and DAA groups, respectively. In genotype 2, the SVR was 73.8% (31/42) and 89.4% (17/19) in PEG and DAA groups, respectively. HCC developed in 3.5% (5/141) patients treated with PEG. Among them, the mean age was 77 (range 66-83) and 4 patients were genotype 1(genotype 1a : 1, genotype 1b : 3). 3 patients had liver cirrhosis and 2 out of 3 patients (Genotype 1a : 1, genotype 2 : 1) had SVR with PEG. 1 patient who had liver cirrhosis was treated with DAA after 4 years and achieved SVR. However, HCC occurred 2 years later. 3 patients died of brain hemorrhage, pneumonia and leukemia.

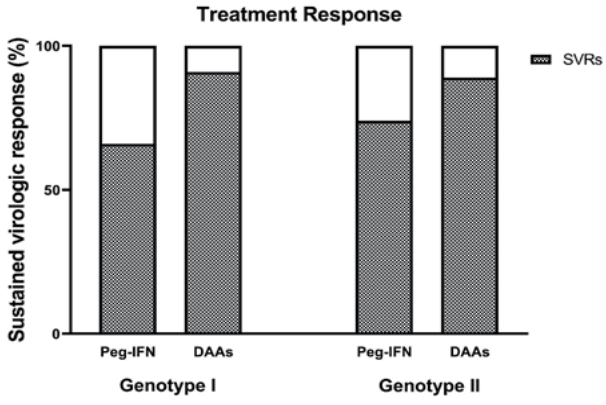

Figure 1. Treatment response

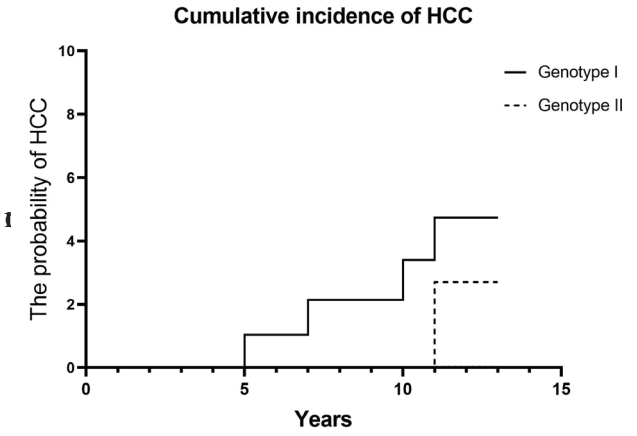

Figure 2. Cumulative incidence of Hepatocellular

Conclusions: PEG showed stable SVR and low incidence of HCC after SVR. Although the follow-up period is short, oral DAA treatment showed more stable SVR than PEG and no development of HCC after SVR in CHC patients with hemophilia.
Keywords: Hepatitis c, Hemophilia, Hepatocellular carcinoma

PE-068

Decreased of Alpha-Fetoprotein Level Among Patients with Liver Cirrhosis that Related to HCV Treated with Combination Therapy with Ledipasvir and Sofosbuvir

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Aims: Hepatocellular carcinoma (HCC) is considered one of the most lethal cancers, with most of cases diagnosed at advanced stage. The prevalence of HCC is high in Mongolia with men 116.6 cases and women 74.8 cases per 100,000 person-years. The hepatitis C virus (HCV) infection is one of the major causes of chronic hepatitis and hepatocellular carcinoma (HCC) in Mongolia. Viral infection with HCV can cause fluctuations in AFP that makes it difficult to differentiate between underlying liver disease and the development of HCC. The lack of specificity has limited the role of serum alpha-fetoprotein (AFP) for hepatocellular carcinoma (HCC) screening among patients with cirrhosis related to hepatitis C virus (HCV) infection.
Methods: Here we report 25 cases decreased of AFP level in patients with cirrhosis treated 24 weeks combination therapy with ledipasvir and sofosbuvir between 2017 to 2020 were referred to the Liver Unit, Dornod Medical center Mongolia. All patients had been tested for blood chemistries, liver function markers, such as alanine aminotransferase (ALT), total bilirubin, prothrombin, international normalized ratio (INR), creatinine, AFP and HCV-RNA.
Results: Of all patients, fifteen were man and ten were woman.

The average age of the testimonies was 53 (between 40 and 67 years). All patients had HCV genotype 1b and had HCV-RNA positive. The combination of the therapy with ledipasvir and sofosbuvir had significantly decreased level of HCV-RNA from 2172560 to not detected (P<0.05), ALT from 119.4 to 28.4 (P<0.05), AFP from 42.8 to 12.2 (P<0.05).

Conclusions: In conclusion, the combination of the therapy with ledipasvir and sofosbuvir is decreased AFP level and improved liver function tests in HCV related liver Cirrhosis of those patients.

Keywords: Alpha-fetoprotein, Hepatocellular carcinoma

PE-069

Public Health

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Aims: Hepatitis C virus (HCV) infection is a public health problem in Nepal. The objective of the study was to assess the knowledge of hepatitis C virus infection among health science students of Pokhara University, Pokhara, Nepal.

Methods: A cross-sectional study was conducted among health science students of Pokhara University in Pokhara, Nepal. A self-administered structured questionnaire was prepared and administered among students to collect information on socio-demographic and HCV infection. Two hundred students from Laboratory science, Pharmacy, Public health and Nursing disciplines were enrolled in the study. The data was collected from January to February, 2020. Mean knowledge score of HCV was measured from 29 questions related to it, in which each correct answer was coded 1 and incorrect answer as 0, resulting the maximum of 29, as it was measured in previous studies. Frequency, mean, chi-square test, and independent sample t test, one- way ANOVA were computed. Level of significance was set at 5%.

Results: Of the total 200 students, 25.5% respondents were males; and median age of the participants was 21 years ranging from 17 to 26 years; 95% respondents were unmarried. Of them, 12.5% had ever made tattoo piercing and 25.5% had ever donated blood in their lives. Mean knowledge score of HCV was 19.28 (SD±3.00) out of 29 maximum, as measured from 29 questions. The mean knowledge score of HCV was 19.34 (SD ± 2.95) among females and 19.10 (SD ±3.18) among males; there was no significant difference in the mean knowledge score between males and females (p value >0.05). In addition, there was no significant difference in the mean knowledge score among the students of different programs of health science (p value >0.05). Regarding the individual questions, 93.5% respondents reported that hepatitis C is caused by a virus. Among all, 16.0% respondents agreed that HCV can be spread by mosquitoes; 37.5% believed that it can be spread through close personal contact such as kissing or talking; 89% respondents agreed that hepatitis C can be spread through sharing injecting equipment, such as needles and operation tools; and 74% respondents mentioned that sexual transmission is a common way of HCV transmission. Of the total, 53.5% agreed that having a medical and/or dental procedure increases a person's chances of contracting hepatitis C; 41.7% students believed that symptoms appear soon after the entrance of HCV into the body; 55.5% agreed that symptoms always appear after the entrance of HCV to the body. Of total, 82% agreed that hepatitis C virus is associated with an increased risk of liver cancer; 83% mentioned hepatitis C can lead to liver cirrhosis; and 62.5% agreed that HCV is a mutant virus. Among total, 35.5% agreed that people with HCV infection should be restricted from working in the food industry; 65.5% agreed that special diet is recommended for patients with HCV; and 63% respondents mentioned that there is a vaccine for the prevention of HCV infection.

Conclusions: The overall mean knowledge score of HCV infection was found satisfactory; however knowledge on some specific items/questions, especially on prevention and treatment related questions seemed impaired. Comprehensive information about all aspects of HCV infection should be provided to all students of health science.

Keywords: HCV, Knowledge, Health science students, Nepal

PE-070

The Effectiveness and Safety in Genotype 1b HCV Infected Treatment Naïve Patients Who Are Treated by Ledipasvir/sofosbuvir

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Aims: Combination of ledipasvir (LDV)/sofosbuvir (SOF) has been approved in Mongolia for the treatment of genotype 1b hepatitis C virus (HCV) infected patients.

Methods: This retrospective study analyzed 928 patients with HCV infection who were treated with LDV/SOF from February 2016 to January 2019, were retrospectively enrolled from Dornod Medical center. Virologic response was measured at 4 weeks (rapid virologic response, RVR), at 12 weeks (end of treatment response, ETR), and at 12 weeks after the end of treatment (sustained virologic response, SVR12). Safety was assessed by review of adverse events, physical examinations, and laboratory findings.

Results: Of the 928 patients (male, n=436 [47%] female n=491 [53%] ; mean age, 49.7 years; liver cirrhosis 269 [29%]), 659 patients (71.0%) were chronic hepatitis, mean AST (84.3 IU/L), mean ALT (63.8 IU/L), and mean HCV RNA level (3,578,290 IU/mL). In all patient, SVR12 was achieved in 920 (99.2%).

5 patients early stopped the treatment because of headache problem, 3 patient were over 70 year old, stopped the medication due to gastrointestinal troubles. During or after DAA treatment, hepatocellular carcinoma developed in 1 patients whose age was over 67 years.

Conclusions: LDV/SOF treatment for HCV GT1b infected Mongolian subjects achieved very high SVR rates. However, in some older patients, HCC can develop during or after DAAs treatment.

Keywords: Hepatitis C virus, Direct-aciting antivirals, Sustained virologic response

PE-071

Real-Life Effectiveness and Safety of Glecaprevir/Pibrentasvir for Korean Patients with Chronic Hepatitis C at Single Institution

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Aims: Glecaprevir/pibrentasvir (G/P) is a pangenotypic direct-acting combination of antiviral agents used to treat chronic hepatitis C virus (HCV) infections. There are limited real-life data on G/P for Korean patients. We evaluated the real-life effectiveness and safety of G/P at single institution in Korea.

Methods: This was a retrospective, observational, cohort study. The primary effectiveness endpoint was sustained virologic response at 12 weeks after treatment completion (SVR12). Safety and tolerability were also assessed.

Results: Of 267 patients with chronic HCV infections who received G/P, females were 148 (55.4%) and the median age was 63.0 years (range: 25–87 years). Eighty-three (31.1%) had HCV genotype-1 and 182 (68.2%) had HCV-2. A total of 212 (79.4%) were HCV treatment-naive, 200 (74.9%) received the 8-week treatment, 13 (4.9%) received prior treatment for hepatocellular carcinoma, 37 (13.7%) had chronic kidney disease stage 3 or more, and 10 (3.7%) were receiving dialysis. Intention-to-treat (ITT) analysis indicated that 256 (95.9%) achieved SVR12. A modified ITT analysis indicated the SVR12 was 97.7% (256/262). Six patients failed therapy because of post-treatment relapse. The SVR12 was significantly lower in those who received prior sofosbuvir treatment (P=0.002) and those with detectable HCV RNA at week 4 (P=0.027). Seventy (26.2%) patients experienced at least one adverse event, most of which were mild.

Conclusions: These real-life data indicated that G/P treatment of patients with HCV infections had high effectiveness and was well-tolerated, regardless of viral genotype and the presence of comorbidities.

Keywords: Hepatitis C virus, Glecaprevir, Pibrentasivir, Sustained virologic response

PE-072

Lipid Profile Investigation of Anti-HCV Positive Newly Diagnosed Diabetics in Eastern Mongolia

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Aims: Dyslipidemia prevalence is reported significantly higher in HCV patients, particularly among that viral RNA positive. In addition, chronic HCV infection is a known risk factor for developing diabetes in adults. Diabetes mellitus is a complex metabolic disorder that is profoundly associated with dyslipidemia and therefore could possibly share common pathophysiology through inflammation in the liver towards altering lipid metabolism.

Mongolia has one of the highest HCV prevalence rates in the world, and at least 10% of the general population is expected to have HCV infection. With the rising impact of NCDs rate including obesity, we, therefore, aimed to examine the clinical relevance of dyslipidemia among diabetics and the role of HCV infection.

Methods: We conducted a case-series analysis of newly diagnosed diabetic patients in the eastern-most province of Dornod, Mongolia. Participants were recruited from a cohort of 2019, were impaired fasting glucose initial diagnosis was made by primary healthcare centers. A total of 44 patients was included in the analysis for anthropometry, abdominal ultrasound, HBV and HCV serology, complete blood cell analysis, clinical chemistry including liver function tests, and viral load analysis. Consent forms were provided prior to investigation and statistical analysis was performed on GraphPad Prism 8.0 software. Continues variable were presented in Mean±SEM and the statistical significance level was set at P<0.05.

Results: Participants average age was 50.14±1.46 and male (56.8%) to female (43.2%) ratio was 1.32:1. Fasting glucose level, c peptide, insulin, and HBA1C did not differ between Anti-HCV positive and negative newly diagnosed diabetics (P>0.05). Among clinical lipid profiles, triglyceride levels were higher in the Anti-HCV positive population (P<0.05). HDL level was significantly lower in the Anti-HCV positive participants (P<0.05). Meanwhile there was no difference in cholesterol and LDL levels (P>0.05).

Conclusions: Triglyceride and HDL levels were significantly altered in HCV positive than Anti-HCV negative participants in this newly diagnosed diabetics cohort.

Keywords: Dyslipidemia, Anti-HCV

PE-073

The Improvement or Regression of Fibrosis after Treatment with Sofosbuvir Plus Ribavirin for HCV Genotype 2 Infection

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Aims: Sofosbuvir (SOF) and ribavirin (RBV) for 12 or 16 weeks is recommended for treatment of patients with HCV genotype (GT) 2 infected patients in KASL guideline based on clinical trials. Whether sustained virological response of HCV infection has any beneficial effect on improvement of liver fibrosis associated with chronic HCV infection remains unclear. We investigated to assess the effects on liver fibrosis of at least 2 years through follow-up liver biopsy and fibroelastography after treatment with sofosbuvir plus ribavirin for HCV G2 infection.

Methods: Three tertiary center, prospective observational cohort study evaluates clinical practice data (Korea university Anam, Guro, and Ansan) between January 2015 and December 2019. Clinical data were centrally collected from medical records. The efficacy outcome was sustained virological response 12 weeks after therapy (SVR12). The degree of liver fibrosis was evaluated by APRI score, FIB-4, fibroelestography and paired liver tissue biopsy.

Results: 146 patients were visited and 131 patients were treated SOF plus RBV during 12 weeks (n=122) or 16 weeks (n=9). Overall, EVR, ETR, and SVR12 by ITT analysis were 90.0%, 96.2% and 87%. In addition, EVR, ETR, and SVR12 by PP analysis 97.5%, 99.2% and 96.3%, respectively. In subgroup analysis, SVR12 in patients with treatment-naïve and treatment-experience were 97.2% or 94.7%, respectively. SVR12 in patients with and without cirrhosis were 94.4% and 97.4%, respectively. Finally 106 patients showed sutained virological response and follow up 2 year after treatment. The mean APRI score was 0.57 before treatment, but improved to 0.27 at 2 year after treatment (P=0.004). The mean FIB-4 score was 2.15 before treatment, but improved to 1.53 at 2 year after treatment (P=0.004). The mean fibroelastography value was 10.81 kPa before treatment, but improved to 4.75 kPa at 2 year after treatment (P=0.008). Follow-up liver tissue biopsies were done in 8 patients and fibrosis was evaluated by Metavir score (F0-4). Almost all patient except one showed improvement of cirrhosis (≥1 unit decrease in Metavir score, P=0.031).

Conclusions: SOF and RBV was safe and effective for treatment of patients with HCV GT2 infection. In patients with sustained virological response 2 year after SOF and RBV, the improvement or regression of liver fibrosis could be observed in biochemical and histological aspect.

Keywords: Hepatitis C virus, Regression, Fibrosis, Sofosbuvir, Ribavirin, Fiborosis

PE-074

HCV Management in Mongolia

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Aims: To determine situation and implementation of HCV policy management

Introduction: Mongolia has a large burden of viral hepatitis, especially chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, which are associated with cancer and cirrhosis.Therefore, there is need of to assess policy implementation, milestones of diagnostic and treatment development of HCV in our country.

Methods: Descriptive study, analyzed policy and strategic documents and statistics issued by government organizations, reviewed treatment result published studies.

Results: Since 2014, 19 policy documents were approved and updated national viral hepatitis guideline three times. In 2017 Mongolia established The Whole Liver Program (HPCE)2017-2020. It aims to eliminate HCV in Mongolia by 2020 and to significantly reduce viral hepatitisinduced liver cirrhosis and HCC related mortalities.Within the framework of the program, free general population hepatitis screening,two free-ofcharge HCV viral load testing and no-out-of-pocket-cost HCV treatment campaigns have been initiated nationwide. 959,320 people were screened viral hepatitis, 94,280 people were tested viral load, 19,896 people were treated.

Conclusions: The HPCE Program in Mongolia is serving as a model for other countries in their fight against viral hepatitis.

Keywords: HCV Management, HCV, Elimination program, Mongolia

PE-075

Current Status New Direct Acting Anti-Viral Treatment of Hepatitis C in Mongolia

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Aims: During last several years, internationally available diagnostics, treatments and medicines of HCV have changed dramatically. Interferon-based therapy for HCV has comparatively low

result of treatment effect, more side effects, long treatment duration, high cost of single dose and limited option of treatment. Since introduction of direct antiviral agents including in 2011 Boceprevir, Telaprevir, in 2013 Simeprevir, Sofosbuvir, in 2014 Harvoni (ledipasvir/sofosbuvir), Daklinza (daclatasvir), Vikera Pack (ombitasvir/paritaprevir/dasabuvir), the new era HCV treatment came up. Thanks to those new drugs HCV infection became one of the curable diseases, and entire world is targeting free from HCV /WHO/. Therefore, there is need of to access milestones of diagnostic and treatment development of HCV in our country. Our study aims to determine implementation of global trend for HCV diagnostic and treatment in Mongolia.

Methods: This study is qualitative one and we analyzed policy and strategic documents and statistics issued by Mongolian Government, Ministry of Health, National Center for Communicable Disease, Mongolian National University of Medical Sciences and other organizations.

Results: Ministry of Health played very large role in introduction of new management of HCV into the country. It provided all the legal ground and support to service providers at all levels of care. New guideline was approved which includes all new schemes of the treatment, diagnostic methods, new drugs were registered, specialist doctors were trained and access of the new drug were widened thanks to joining the Access program from Gilead Sciences. It can be said that the tentative result of DAA treatment is successful, compare few years ago interferon treatment effect was fewer than 20 percent to the 99 percent effective of current new treatment.

Conclusions: All those achievements show that Mongolia has been able to introduce a comprehensive and efficient short-term treatment for HCV and free the population of that disease which may increase the mortality level due to liver cancer.

Keywords: Anti-viral treatment, Ledipasvir, Sofosbuvir, HCV

PE-076

Safety of Sofosbuvir-Based Regimens for the Treatment of Chronic HCV Infection in Patients with Mild or Moderate Renal Impairment

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Aims: The major metabolite of sofosbuvir (SOF), GS-331007, is cleared renally and tends to accumulate in patients with chronic kidney disease (CKD). However, there are a substantial amount of data showing that this accumulation is not clinically significant, even in patients with end stage renal disease.

Methods: This retrospective analysis of 37 Phase 2 and 38 Phase 3 studies presents the safety profile of SOF-based therapies (LDV/SOF, SOF/VEL and SOF/VEL/VOX) in patients with mild to moderate CKD as well as in patients with normal renal function.

Results: 8,181 patients were included in this analysis. Mean baseline eGFR was 118.2, 69.3, and 43.6 mL/min/1.73m^2 for patients with normal renal function (n=6575), mild (n=1499), or moderate (n=107) renal impairment, respectively. The mean eGFR at post-treatment follow-up week 4 was 114.4, 69.9, and 46.3 mL/min/1.73m^2 for patients with normal renal function (n=5519), mild (n=1285), or moderate (n=90) renal impairment, respectively. When comparing baseline levels with those of post-treatment follow-up week 4, there was no clinical difference observed. Baseline characteristics were generally similar across groups, except patients with impaired renal function were older. Table 1 provides a summary of adverse events (AEs). Rates of Grade 3-4 AEs and discontinuations due to AEs were similar across groups. Patients with moderate renal impairment had higher rates of SAEs but most were not treatment-related.

Conclusions: Sofosbuvir-based regimens were safe and well-tolerated in patients with mild or moderate renal impairment. Renal function remained stable throughout treatment, and similar rates of AEs were observed across all treatment groups.

Keywords: HCV, Sofosbuvir, CKD, Renal safety

HCV, Basic

PE-077

RAS and Ledipasvir/Sofosbuvir Therapy with Patients CHC in Mongolia

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Aims: To investigate the effectiveness of LDV/SOF and the impact of RAS on the treatment outcome in Mongolian CHC patients.

Introduction: Mongolia has the highest prevalence of hepatitis C virus (HCV) infection worldwide. Ledipasvir/sofosbuvir (LDV/SOF) was introduced to Mongolia since 2016 for HCV eradication.It has been reported that HCV resistance-associated substitutions (RASs) would affect theeffectiveness of LDV/SOF in western chronic hepatitis C (CHC) patients.

Methods: Patients with genotype (GT) 1b HCV infection were prospectively enrolled inMongolia and treated with LDV/SOF

for 12 weeks. The proportion of pre-treatment NS5AY93H RAS in viral quasispecies was measured with next-generation sequencing. The endpointof LDV/SOF effectiveness was sustained virological response at post-treatment week 12(SVR12).

Results: A total of 94 CHC patients were evaluated. The baseline Y93H proportion was <1% in74 patients, 1e15% in 7, 15e50% in 2, and 50% in 11. All patients completed 12-week LDV/SOFtreatment and the SVR rate was 90.4%. The rate of failure to achieve SVR12 for patients withY93H < 1%, 1e15%, and _15% were 0%, 14.3%, and 61.5%, respectively (p for trend Z0.001). Inunivariable analysis, older age, baseline alanine transaminase level <40 U/mL, and a higherproportion of Y93H were associated with treatment failure. In multivariable analysis, only a higher proportion of Y93H was associated with treatment failure (p Z 0.022).

Conclusions: LDV/SOF therapy achieves a high SVR rate in Mongolian CHC GT1b patients withoutbaseline Y93H RAS. A higher proportion of Y93H may severely undermine the effectiveness ofLDV/SOF.

Keywords: Chronic hepatitis C, Resistance-associated substitution, Sofosbuvir, Mongolia

Liver Cancer, Clinical

PE-078

Familial Hepatocellular Carcinoma

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Aims: Familial hepatocellular carcinoma: "A model for studying preventive and therapeutic measures, Hepatocellular cancer (HCC) is the fifth most common cancer worldwide with more than 80% of case found in endemic areas of hepatitis B such as Africa or East Asia. A family history of liver cancer increases HCC risk, independently of hepatitis. Only limited attention has been given to the role of primary genetic and epigenetic factors in HCC.The aim of the study was to identify case studies on familial HCC, the primary genetic and epigenetic factors, and the clues it renders to prevention and therapy.

Methods: Electronic searches of the Medline (PubMed) database was performed to identify original published case studies on familial HCC.

Results: Fifteen cases of familial HCC were reported between 1965- 2016. Familial clusters of HBV/C serum markers was associated with an over 70-fold elevated HCC risk, poor prognosis and an earlier age of onset. A multifactorial inheritance including novel DICER 1 germline mutation and altered liver zonation contributed to the risk. Global gene expression profiling revealed a small set of genes, SPINK 1, a secretory trypsin inhibitor as a potential HCC marker. An over expression of the apolipoprotein family and serum amyloid A were reported. Epigenetic variation studies on monozygotic twins with familial HCC identified the susceptibility loci sensitive to modification by the environment.

Conclusions: The hepatitis B virus is directly oncogenic, and by incorporating into host genetic material can cause HCC in the absence of cirrhosis. The highest risk of HCC may occur in families in which a hereditary component is acting in concert with hepatitis B virus. The understanding of the disturbances of the hepatic epigenome may render the clues to the pathogenesis and management of hepatocellular carcinoma. Hepatitis vaccination should be given the highest priority, and screening of first degree relatives to detect early, asymptomatic disease is mandatory.

Keywords: Familial, Hepatocellular, Hepatic epigenome, Carcinoma

PE-079

Prognostic Value of Alpha-Fetoprotein in Patients Who Achieved Complete Response to Transarterial Chemoembolization for Hepatocellular Carcinoma

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Aims: Alpha-fetoprotein (AFP) is a prognostic marker for hepatocellular carcinoma (HCC). We investigated the prognostic value of AFP level at complete response (CR) after transarterial chemoembolization (TACE) in patients with HCC.

Methods: Between 2005 and 2018, 890 patients with HCC who achieved CR after TACE were recruited. An AFP responder was defined, when a patient showed an elevated AFP level (>10 ng/mL) at TACE, but showed normalization or >50% reduction at

CR.

Results: Of total, 569 (63.9%) patients with naïve HCC and 321 (36.1%) with recurrent HCC after complete resection were treated. At TACE, 305 (34.3%) patients had multiple tumors, 219 (24.6%) had a maximal tumor size >3 cm, and 22 (2.5%) had portal vein tumor thrombosis. At CR, the median AFP level was 6.36 ng/mL. After CR, 473 (53.1%) patients experienced recur and 417 (46.9%) died (the median progression-free survival [PFS] and overall survival [OS] were 16.3 and 62.8 months, respectively). The high AFP level at CR (>20 ng/mL) was independently associated with a shorter PFS (hazard ratio [HR]=1.403) and OS (HR=1.284), together with tumor multiplicity at TACE (HR=1.518 and 1.666, respectively). The AFP non-responders at CR (76.2%, n=359 of 471) showed a shorter PFS (median 10.5 vs. 15.5 months, HR=1.375) and OS (median 41.4 vs. 61.8 months, HR=1.424) compared to responders (all *P*=0.001).

Conclusions: High AFP and AFP non-responder were independently associated with poor outcome at CR after TACE. The AFP has a clinical implication for detailed risk stratification even at CR after TACE.

Keywords: Hepatocellular carcinoma, Tumor marker, Alpha-fetoprotein, Transarterial chemoembolization

PE-080

A Comparison of Factors Associated with the Temporal Improvement in the Overall Survival of BCLC stage 0 Hepatocellular Carcinoma Patients

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Aims: We compared the clinical outcome of Barcelona Clinical Liver Cancer (BCLC) stage 0 hepatocellular carcinoma (HCC) patients in a different time period, to see whether the outcomes of BCLC stage 0 patients has improved, and if so, what are the reasons behind the noted improved outcome.

Methods: A total of 591 patients with BCLC stage 0 HCC diagnosed and managed at Samsung Medical Center, Seoul, Korea between year 2007-2009 and year 2013-2015 were analyzed in this study. The patients were grouped into two group based on year of diagnosis (earlier cohort; 2007-2009 and later cohort; 2013-2015).

Results: The overall survival was improved for BCLC stage 0 patients at later cohort (5-year survival rate: 82.1% vs. 92.0% for earlier cohort and later cohort, *P*=0.015). However, in reviewing a fully-adjusted model, the treatment period was not an independent factor for overall survival (HR 0.66, 95% CI 0.39-1.13), especially when the albumin-bilirubin grade was adjusted. In this case, the age, albumin-bilirubin grade, and initial treatment modality were considered to be an independent factor which was associated with the patient's overall survival. When cause-specific mortality was assessed, the incidence of liver cirrhosis-related death was increased from 10.4% to 33.3%, while the incidence of HCC-related death decreased from 57.5% to 28.6% in the latter cohort. The initial treatment modality and treatment period were a risk factor for HCC-related death; whereby older age and ALBI grade 2 were risk factor for liver cirrhosis-related death, respectively. As noted, the temporal improvement in overall survival was most noticeable for those treated with ablation, and patients showed a similar overall survival to patients treated with resection (96.0% vs. 93.9% at 5-years, *P*=0.40).

Conclusions: The survival improvement of BCLC stage 0 patients was largely explained by better liver function at diagnosis. Mortality from liver cirrhosis-related death was increasing, which calls for careful attention for finding strategies for preserving the liver function for BCLC stage 0 patients.

Keywords: Hepatocellular Carcinoma, Albumin-bilirubin grade, Prognosis

PE-081

Salvage Living Donor Liver Transplantation for Hepatocellular Carcinoma Recurrence after Hepatectomy: Quantitative Prognostic Prediction using ADV Score

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Aims: Salvage liver transplantation is a treatment for recurrent hepatocellular carcinoma (HCC) after hepatectomy. ADV score is calculated by multiplying a-fetoprotein and des-γ-carboxyprothrombin concentrations and tumor volume. Prognostic accuracy of ADV score was assessed in patients undergoing salvage living donor liver transplantation (LDLT) and their outcomes were compared with patients undergoing primary LDLT.

Methods: This was a retrospective observational study. Outcomes were compared in 125 patients undergoing salvage LDLT from 2007 to 2018 and in 500 propensity score-matched patients undergoing primary LDLT.

Results: In patients undergoing salvage LDLT, the median intervals between hepatectomy and tumor recurrence, between first HCC diagnosis and salvage LDLT, and between hepatectomy and salvage LDLT were 12.0, 37.2, and 29.3 months, respectively. Disease-free survival (DFS, *P*=0.98) and overall survival (OS, *P*=0.44) rates did not differ significantly in patients undergoing salvage and primary LDLT. ADV score was significantly predictive of DFS and OS in patients undergoing salvage and primary LDLT (*P*<0.001). DFS after hepatectomy (*P*=0.52) and interval between hepatectomy and LDLT (*P*=0.82) did not affect DFS after salvage LDLT. Milan criteria and ADV score were in-

dependently prognostic of DFS and OS following salvage LDLT, and the prognosis of patients within and beyond Milan criteria was further stratified by ADV score.

Conclusions: Risk factors and post-transplant outcomes were similar in patients undergoing salvage and primary LDLT. ADV score is a surrogate biomarker for post-transplant prognosis in salvage and primary LDLT recipients. A prognostic model incorporating ADV scores can help determine whether to perform salvage LDLT.

Keywords: Hepatectomy, Tumor marker, Neoadjuvant therapy, Tumor biology

PE-082

Features of Extrahepatic Metastasis after Radiofrequency Ablation for Hepatocellular Carcinoma

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Aims: To elucidate the characteristics and risk factors of EHM after RFA for HCC.

Methods: From January 2008 to December 2017, we retrospectively enrolled 661 patients who underwent RFA as first-line treatment for HCC at 2 tertiary hospitals. The inclusion criteria were age ≥18 years, a diagnosis of HCC, and treatment-naivety. Abdominal computed tomography (CT) or magnetic resonance imaging (MRI) and alpha-fetoprotein measurements were routinely performed at 1 month after RFA and followed-up at intervals of 3–6 months. Univariate analyses were performed using the chi-squared test or Student's t-test, and univariate and multivariate analyses were performed via logistic regression, as appropriate.

Results: EHM was diagnosed in 44 patients (6.7%) during a median follow-up period of 1,204 days. The 10-year cumulative rate of HCC recurrence and EHM was 92.7% and 33.7%, respectively. Initial recurrence was most often intrahepatic, and the rate of extrahepatic recurrence at initial recurrence was only 1.2%. The median time to the diagnosis of EHM was 2.68 years, and 68.2% of patients developed EHM within 2 years of the first recurrence, regardless of recurrence-free survival and 75.0% of patients developed EHM within 5 years after first recurrence. EHM was mostly diagnosed via abdominal CT/MRI in 33 (75.0%) and 38 of 44 patients (86.4%) with EHM had either positive abdominal CT scan results or serum AFP level elevation. In multivariate analysis, recurrence-free survival <2 years, ablation zone/tumor size <2, and alpha-fetoprotein level >400 IU/mL were associated with a high EHM risk.

Conclusions: EHM occurs following multiple intrahepatic recurrences after RFA and combined contrast-enhanced abdominal CT and serum AFP were useful for surveillance. Patients especially with high-risk factors require close follow-up for EHM.

Keywords: Hepatocellular carcinoma, Metastasis, Radiofrequency ablation, Risk factor

PE-083

Resection or Ablation versus Transarterial Therapy for Child-Pugh a Patients with Single Small (≤3 cm) Hepatocellular Carcinoma

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Aims: We retrospectively compared therapeutic outcomes between surgical resection (SR) or radiofrequency ablation (RFA) versus transarterial therapy for Child-Pugh A patients with a single small hepatocellular carcinoma (HCC).

Methods: Using a nationwide Korean registry, we identified 2,314 Child-Pugh A patients with SR (n=722), RFA (n=731), or transarterial therapy (n=861) for a single (≤3 cm) T1/T2 stage HCC from 2008 through 2014. We compared the post-treatment overall survivals (OSs) of transarterial therapy with either SR or RFA after Inverse Probability of treatment Weighting (IPW). Median follow-up period was 50 months (range 1-107 months).

Results: After IPW, cumulative OS rates after SR or RFA were significantly higher than those after transarterial therapy in all subjects (all p-values<0.05). OS rates after SR or RFA were better than those after transarterial therapy in patients with hepatitis B- or C virus (HBV or HCV) (all p-values<0.05), and in patients aged <65 years (all p-values<0.05). Cumulative OSs between RFA and transarterial therapy were statistically comparable in patients with HCC of 2-3cm and aged ≥65 years, respectively. For all subjects, the weighted Cox proportional hazards model using IPW provided adjusted hazard ratios (95% confidence interval) for OSs after SR versus transarterial therapy and after RFA versus transarterial therapy of 0.42 (0.30-0.60) (*P*<0.001) and 0.78 (0.61-0.99) (*P*=0.044), respectively.

Conclusions: In Child-Pugh A patients with a single (=3cm) T1/T2 HCC, SR or RFA provides better OSs than transarterial therapy, regardless of HCC etiology (HBV or HCV), especially in patients with HCC of <2cm and aged <65 years.

Keywords: Hepatocellular carcinoma, Single (≤3 cm), Overall

survival, Transarterial therapy, Surgical resection, Radiofrequency ablation

PE-084

Clinical Status of Radiotherapy for Hepatobiliary Cancer in Korea between 1999 and 2017

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Aims: Radiotherapy (RT) is one of treatment modalities for hepatobiliary cancer. To analyze the actual utilization for hepatobiliary cancer of RT in Korea, the current study was performed.

Methods: The incidence of hepatobiliary cancer was analyzed using annual reports from the Korea Central Cancer Registry. The status of radiotherapy between 1999 and 2017 was analyzed using data obtained from the Korean Society for Radiation Oncology and the Health Insurance Review and Assessment Service.

Results: In 1999, total 16,255 hepatobiliary cancer patients were developed, of which 729 (4.5%) have been treated with radiotherapy. In 2017, 22,251 hepatobiliary cancer patients were developed, of which 5,811 (26.1%) have been treated with radiotherapy. According to analyses of specific treatment modalities, the number of patients treated with intensity-modulated radiotherapy (IMRT), stereotactic body radiation therapy (SBRT), and proton therapy increased from 150 (2.6%), 539 (14.6%), and 0 (0.0%) in 2012 to 2,035 (35.0%), 1,186 (20.4%), and 231 (4.0%) in 2017, respectively.

Conclusions: The number of patients who underwent RT in Korea has increased steadily from 1999 to 2017. The IMRT utilization rate remarkably increased in the past 5 years, and the number of patients treated with advanced treatment modalities such as IMRT, SBRT, and proton therapy is expected to increase.

Keywords: Liver neoplasm, Radiotherapy, Hepatobiliary cancer

PE-085

Pre-Treatment Liver Stiffness Assessed by MR Elastography Is a Potential Biomarker for Sorafenib-Treated Patients with Advanced Hepatocellular Carcinoma

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Aims: Liver stiffness (LS) is an emerging imaging-based prognostic biomarker for patients with chronic liver disease. We investigated whether LS quantified using magnetic resonance elastography (MRE) could predict the prognosis of advanced hepatocellular carcinoma (HCC) patients treated with sorafenib.

Methods: We selected 50 sorafenib-treated advanced HCC patients who underwent MRE within 3 months before drug administration from a prospectively maintained cohort of chronic liver disease patients, according to the inclusion and exclusion criteria. Univariate and multivariate analyses were performed to evaluate the prognostic role of laboratory data, tumor characteristics, and MRE-assessed LS for overall survival (OS), progression-free survival (PFS), and significant liver injury (≥grade 3) after sorafenib administration.

Results: High MRE-assessed LS was significantly associated with poor OS (kPa; hazard ratio [HR], 1.54; 95% confidence interval [CI], 1.23–1.92; P<0.001) as well as higher serum alpha-fetoprotein (AFP, ≥400 ng/mL) and advanced tumor stage (modified Union for International Cancer Control [mUICC] IVb). Higher MRE-assessed LS was also significantly associated with the development of significant liver injury after sorafenib administration (kPa; HR, 1.62; 95% CI, 1.21–2.17; P=0.001). PFS analysis identified higher serum AFP (≥400 ng/mL) and advanced tumor stage (modified UICC IVb) as significant risk factors for early disease progression, whereas LS was not associated with PFS.

Conclusions: Higher MRE-assessed LS is a potential biomarker for predicting poor OS and significant liver injury in advanced HCC patients treated with sorafenib.

Keywords: Hepatocellular carcinoma, Magnetic resonance elastography, Liver stiffness, Liver injury, Sorafenib, Prognosis

PE-086

Efficacy and Safety of Nivolumab after Failure of Sorafenib for Advanced Hepatocellular Carcinoma (HCC): A Prospective Cohort Study

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Aims: Nivolumab showed promising anti-tumor efficacy in advanced HCC in prior phase I/II CheckMate-040 trial. We analyzed clinical outcomes of HCC patients enrolled in our biomarker prospective cohort and treated with nivolumab after failure of sorafenib.

Methods: Single-center, prospective cohort study. 46 patients with unresectable or metastatic HCC who received nivolumab after failure of sorafenib in Asan Medical Center, Seoul, Korea, between May 2018 and March 2020, were included. Nivolumab was given at 3mg/kg intravenously, every 2 weeks.

Results: Median age was 59 years and 82.6% (n=38) were male. 76.1% (n=35) had HBV infection and 67.4% (n=31) were Child-Pugh A. All patients were BCLC stage C, and extrahepatic metastasis and major vascular invasion were de-

tected in 44 (95.7%) and 23 (50.0%), respectively. Median time-to-progression (TTP) on prior sorafenib was 2.6 months (95% CI, 1.4-3.8). Nivolumab was administered as 2nd-, 3rd- and 4th-line treatment in 28 (60.9%), 14 (30.4%) and 4 (8.7%), respectively. The number of treatment cycle was median 4 (range, 1-35). Objective response rate (ORR) was 15.2% (1 CR, 6 PR) and median time-to-response (TTR) was 1.7 months (range, 1.3-4.0). Median duration of response (DOR) was 6.0 months (range, 3.6-15.6) and 2 patients are ongoing (10.18+ to 18.92+ months) at data cut-off. Median progression-free survival (PFS) was 1.7 months (95% CI, 1.6-1.8) and overall survival (OS) was 5.4 months (95% CI, 2.8-7.9). 6-month PFS and OS rates were 26.8% and 49.2%, respectively. AEs were anorexia (13.0%), fatigue (6.5%), diarrhea (4.3%), and thyroid dysfunction (2.2%).

Conclusions: Nivolumab showed modest efficacy in this study. In patients who achieved objective response (15.2%), median DOR was promising as 6 months. Although CheckMate-459, a randomized phase 3 study evaluating nivolumab vs sorafenib as 1st-line treatment, failed to meet the primary endpoint, our findings indicate that nivolumab may have therapeutic implications in sorafenib-progressed HCC patients.

Keywords: HCC, Nivolumab, Immunotherapy

PE-087

Effects and Safety of Nivolumab in Child-Pugh B Patients with Hepatocellular Carcinoma: A Retrospective Cohort Study

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Aims: Nivolumab showed durable response and safety in patients with hepatocellular carcinoma (HCC) in the previous trials. However, real-world data of nivolumab in HCC patients, especially those with Child-Pugh class B, is lacking. We aimed to investigate the efficacy and safety of nivolumab in a real-world cohort of patients with advanced HCC.

Methods: This study retrospectively evaluated 203 patients with HCC who were treated with nivolumab between July 2017 to February 2019. Radiologic evaluation was based on mRECIST. Survival outcomes were estimated by Kaplan-Meier method and Cox proportional hazard model. Logistic regression model was used to identify the predictive factors of treatment response.

Results: Of 203 patients, 132 patients were within Child-Pugh class A and 71 patients were within Child-Pugh class B. Objective response rate was lower in patients with Child-Pugh class B than A (2.8% vs. 15.9%; *P*=0.010 by unweighted analysis and *P*=0.034 by weighted analysis) and Child-Pugh class was an independent predictor for objective response (Odds ratio, 0.21; 95% confidence interval; 0.05–0.93; *P*=0.040). Median overall survival was shorter in Child-Pugh B patients (11.3 vs. 42.9 weeks; *P*<0.001 by both unweighted and weighted analyses). However, other efficacy outcomes including disease control rate, time to progression, and progression-free survival were comparable between Child-Pugh A and B patients by unadjusted, adjusted, matched, and weighted analyses. There was no significant difference in terms of safety between Child-Pugh A and B patients.

Conclusions: Given the limited treatment options for advanced HCC in Child-Pugh B patients, nivolumab may be a viable option despite lower response in these patients. Further studies are needed in this patient population.

Keywords: Liver cancer, Immune checkpoint inhibitor, Effectiveness, Safety

PE-088

Comparison of Two Transarterial Chemoembolization Strategies for Hepatocellular Carcinoma

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Aims: This retrospective study aimed to compare the efficacy of and tolerance to two center-related conventional transarterial chemoembolization (TACE) strategies in the management of unresectable hepatocellular carcinoma (HCC).

Methods: All HCC patients in whom TACE was initiated in the two centers from July 2008 to June 2016 were included. The TACE strategy performed in center 1 was "on demand" with selective injections of idarubicin, whereas the TACE strategy in center 2 was based "on scheduled" non-selective injections of epirubicin. Toxicity was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events.

Results: One hundred and fifty HCC patients were included. Median time to treatment failure was significantly higher in center 1, 13.1 months vs. 7.9 months in center 2 (hazard ratio, 2.32; *P*<10-3 in multivariate analysis). Median overall survival was 21.1 months in center 1 vs. 18.4 months in center 2 (*P*=NS). The proportion of grade ≥ 3 adverse events and mean hospitalisation duration for the overall TACE treatment were significantly greater in center 2 than in center 1: 56% vs. 32% (*P*<0.01) and 14.2 ± 7.2 days vs. 10.3 ± 7.0 days (*P*<0.01), respectively.

Conclusions: Our results failed to show any significant survival differences between two center-related TACE strategies but showed a significantly smaller proportion of grade ≥ 3 adverse events and shorter hospitalisation for the overall treatment when the "on-demand" strategy was used.

Keywords: Transarterial chemoembolization, Hepatocellular carcinoma, National Cancer Institute Common Terminology Criteria for Adverse Events, Injections of idarubicin

PE-089

Role Functioning Is Associated with Survival in Patients with Hepatocellular Carcinoma

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Aims: Our study's aim was to evaluate the association of quality of life (QOL) with survival among a cohort of cirrhotic patients with HCC that was diverse with respect to liver function and tumor stage.

Methods: We conducted a prospective cohort study among cirrhotic patients with HCC from a large urban safety-net hospital between September 2010 and April 2017. Patients completed two self-administered surveys, the EORTC QLQ-C30 and QLQ-HCC18, prior to the treatment. We used generalized linear models to identify correlates of QOL. Survival curves were generated using Kaplan-Meier analysis and compared using log rank test to determine whether QOL is associated with survival.

Results: A total of 130 treatment-naïve patients completed both surveys. Patients reported high cognitive and social function (median scores 67) but poor global QOL (median score 50) and poor role function (median score 50). QOL was associated with cirrhosis-related (*P*=0.02) and tumor-related (*P*=0.02) components of Barcelona Clinic Liver Cancer (BCLC) tumor stage. QOL was associated with survival on univariate analysis (HR 0.37, 95% CI 0.16-0.85) but became nonsignificant (HR 0.82, 95% CI 0.37-1.80) after adjusting for BCLC stage and treatment. Role functioning was significantly associated with survival (HR 0.40, 95% CI 0.20-0.81), after adjusting for Caucasian race (HR 0.31, 95% CI 0.16-0.59), BCLC stage (HR 1.51, 95% CI 0.21-1.89), and treatment (HR 0.57, 95% CI 0.33-0.97).

Conclusions: Role function has prognostic significance and is important to assess in patients with HCC.

Keywords: Hepatocellular carcinoma, Cirrhotic patients, Cohort study, Kaplan-Meier analysis

PE-090

Clinical Implication of the Body Composition in Old Adults Patients with Hepatocellular Carcinoma Treated with Trans-Arterial Chemoembolization

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Aims: As aging is worldwide phenomenon, the elderly patients with hepatocellular carcinoma (HCC) have been increased. However, little is known about the prognosis of trans-arterial chemoembolization (TACE) in elderly HCC patients. As the body composition reflects frailty and geriatric conditions in older adults, its clinical significance has been emphasized. So, we investigated the prognostic factors of elderly HCC patients treated with TACE including body composition and clarify its clinical significance.

Methods: A total of 237 patients with HCC, aged 65 or older, who received TACE as initial treatment were included [age (years, mean ± SD: 70.0 ± 4.5); sex (M/F: 168/69); etiology (HBV/HCV/NBNC: 139/51/47); Barcelona Clinic Liver Cancer (BCLC) stage (A/B: 136/101)]. They were followed up regularly for a median of 44 months (range, 22.6 – 69.2). When diagnosed with HCC, we analyzed skeletal muscle index (SMI), calculated as the total abdominal muscle area divided by height squared in meters, and visceral to subcutaneous fat ratio (VSR) around third lumbar vertebra using CT scan. We defined muscle depletion with visceral adiposity (MDVA) as SMI less than 50 percentile and VSR more than 50 percentile, sex specifically. We analyzed the survival rates in relation to the presence of MDVA and other clinical factors.

Results: The medians of SMI were 49.5 cm^2/m^2 (range 45.3 – 54.9) and 43.6 cm^2/m^2 (range 38.4 – 48.1) and those of VSR were 1.0 (range 0.7 – 1.4) and 0.5 (range 0.4 - 0.7) for men and women, respectively. About 60.8% patients had multiple HCCs, and average size of maximal diameter of tumor was 3.9 ± 2.9 cm. The Model for end stage liver disease (MELD) score was 8.4 ± 2.3. During the follow-up periods, 170 patients (71.7%) died and overall cumulative survival rates were 88.9% at 1 year and 59.8% at 3 years after TACE. The mortality was not quite different from BCLC stage (the survival rate of BCLC A vs. B; 89.5% vs. 88.1% at 1 year; 61.1% vs. 58.1% at 3 years, *P*=0.653). The MDVA group showed significantly lower survival rates compared with those without MDVA. (85.1% vs. 90.4% at 1 year and 47.8% vs. 64.7% at 3 years, *P*=0.016). Also, multivariate analysis revealed that in addition to older age (HR 1.077, *P*<0.001), presence of ascites (HR 2.364, *P*=0.009), and higher MELD score(HR 1.104, *P*<0.001), the presence of MDVA (HR 1.448, *P*=0.026) was an important prognostic factor to predict mortality after TACE in elderly patients with HCC.

Conclusions: Our data indicate that body composition, especially MDVA, might be a crucial factor for clinical outcome in aged 65 years or more HCC patients treated with TACE along with age, presence of ascites, and liver function.

Keywords: Hepatocellular carcinoma, Trans-arterial chemoembolization, Body composition, Elderly

PE-091

Long-Term Outcomes of Liver-Directed Concurrent Chemoradiotherapy for Hepatocellular Carcinoma with Major Portal Vein Invasion

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Aims: We aimed to assess therapeutic efficacy of liver-directed concurrent chemoradiotherapy (LD-CCRT) in HCC patients with major portal vein (PV) invasion

Methods: HCC patients with PV invasion (main trunk or the 1st order branch) between 2008 and 2016 were enrolled. During a 5-week radiotherapy course, concurrent hepatic arterial infusion with 5-fluorouracil (5FU) and leucovorin were administered through an implanted port on the first and last 5 days. Four weeks after LD-CCRT, hepatic arterial infusion chemotherapy (HAIC) using 5FU and cisplatin were administered for maintenance. The endpoints were overall survival (OS), progression-free survival (PFS), and response rates.

Results: 152 patients were enrolled, and objective response rate was 48.0% at 4 weeks after LD-CCRT which has increased up to 55.3% during HAIC maintenance. After LD-CCRT, biological responses in alpha-fetoprotein (AFP) and protein induced by the absence of vitamin K or antagonist-II levels (PIVKA-II) were achieved in 46.2% and 52.6% of patients, respectively. Sixteen patients (10.5%) underwent curative resection or liver transplantation after down-staging. Median OS and PFS were 14.0 and 7.0 months, respectively.

Conclusions: LD-CCRT followed by maintenance HAIC yielded favorable OS and PFS in advanced HCC patients with major PV invasion. Tumor reduction by initial LD-CCRT enabled down-staging, subsequent curative treatment, and long-term survival in 10.5% of patients. Further prospective trials are required to confirm these results.

Keywords: Hepatocellular carcinoma, Portal vein invasion, Concurrent chemoradiotherapy, Prognosis

PE-92

Efficacy and Safety of Regorafenib for Advanced Hepatocellular Carcinoma after Progression on Sorafenib: A Retrospective Analysis of Real World Data

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Aims: Regorafenib is an oral multikinase inhibitor indicated as second-line therapy for patients with advanced hepatocellular carcinoma (HCC) who have progressed after sorafenib. This study aimed to assess the clinical efficacy and safety of regorafenib in real life.

Methods: Consecutive patients between August 2017 and December 2019 with advanced HCC receiving regorafenib were retrospectively included from seven University hospitals in Korea. Radiological responses and adverse events were evaluated using the modified Response Evaluation Criteria in Solid Tumors and the Common Terminology Criteria for Adverse Events version 4.0, respectively.

Results: A total of 96 patients were administered regorafenib as second-line therapy after progression on sorafenib. Eighty-eight (91.7%) and 82 (85.4%) patients were classified as BCLC stage C and Child-pugh A. The median follow up was 6.2 months (range 0.5–23.6) after initiation of regorafenib commencement. The median progression-free survival was 4.2 months (95% CI, 2.8–5.6months), and the median overall survival (OS) was 14.0 months (95% CI, 9.0–19.0 months). The most common grade 3-4 toxicities were hand-foot skin reaction (n=9, 9.4%) and increased aspartate aminotransferase (n=4, 4.2%). Twenty seven out of 83 patients who had discontinued regorafenib received sequential systemic therapy after regorafenib.

Conclusions: Our real life data demonstrate that regorafenib is a well-tolerated and effective treatment option for patients with advanced HCC who have progressed after sorafenib.

Keywords: Hepatocellular carcinoma, Regorafenib, Second line therapy, Sorafenib

PE-93

Metformin Use Increases Tumor Response Rate of Transcatheter Arterial Chemoembolization in Hepatocellular Carcinoma

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Aims: Metformin has received attention in cancer prevention strategy because of its potential for biological specificity. Retrospective studies and meta-analyses have reported that metformin reduced the risk of developing hepatocellular carcinoma (HCC) in cirrhotic patients with diabetes. Moreover, *in vitro* data suggested that metformin may enhance anticancer effect of cytotoxic drugs and radiotherapy in hepatoma cells. Therefore, this study aimed to assess whether metformin enhances therapeutic efficacy of transcatheter arterial chemoembolization (TACE) in HCC.

Methods: This retrospective analysis included all consecutive HCC patients who underwent TACE in our institute between

April 2003 and February 2020. Study population was limited to treatment-naïve patients who had single nodular HCC without vascular or ductal or extrahepatic invasion. Treatment response was assessed according the modified Response Evaluation Criteria in Solid Tumors criteria. Logistic regression analysis was used to determine predictors of tumor response by TACE.

Results: Among the 709 patients with single nodular HCC who received TACE, 105 were diabetics on metformin, 74 diabetics without metformin and 530 were control without diabetes. The overall response rate was 61.5% for complete response and 72.5% for objective response rate (ORR; complete response + partial response). In univariate analysis, metformin use increased ORR compared to diabetics without metformin (odds ratio [OR] = 2.3, 95% confidence interval [CI] = 1.34 - 4.1, *P*<0.001), along with small tumor size (< 3 cm) (OR = 2.47, 95% CI = 1.76 - 3.46, *P*<0.001). Multivariate analysis confirmed the independent associations between metformin use and ORR (OR = 4.1, CI = 2.0 - 8.4, *P*<0.001), along with tumor size < 3cm (OR = 2.6, CI=1.8 - 3.7, *P*<0.001) and absence of diabetes (OR = 1.8, CI = 1.1 - 3.0, *P*=0.029).

Conclusions: Metformin use enhances tumor response of TACE for single nodular HCC.

Keywords: Hepatocellular carcinoma, Transcatheter arterial chemoembolization, Metformin

PE-94

A Prognostic Prediction Model of Transarterial Radioembolization in Hepatocellular Carcinoma: SNAP-HCC

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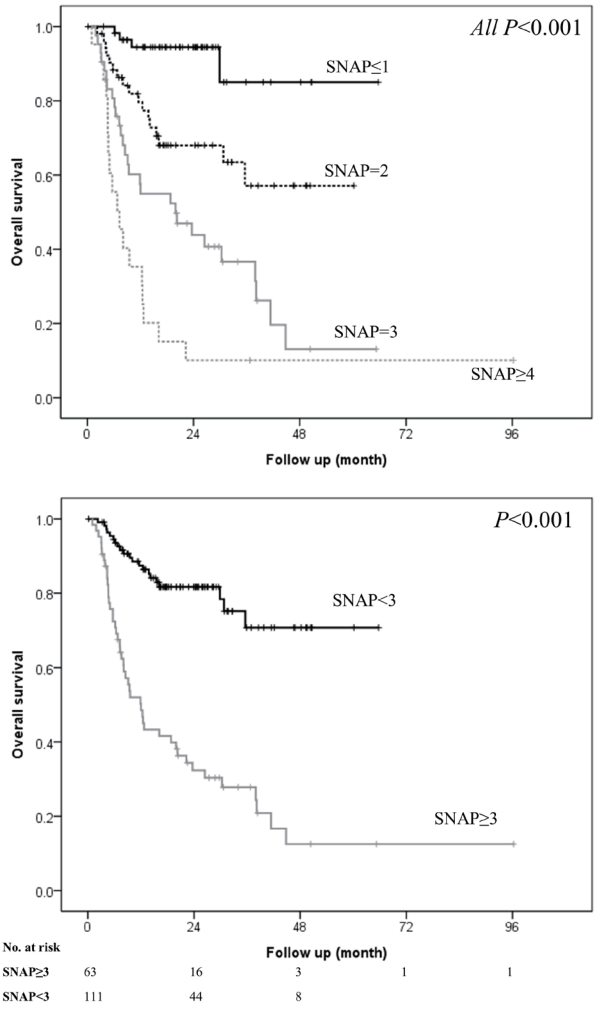
Aims: Transarterial radioembolization (TARE) has been one of the treatment options for hepatocellular carcinoma (HCC). However, the indication of TARE was not well-established and prognosis after TARE still remains difficult to predict among individual patients. The aim of this study was to develop a prognostic scoring model to guide TARE initiation.

Methods: A total of 174 consecutive patients who underwent TARE for HCC as an initial treatment in Korea were included. The primary outcome was overall survival (OS) from the date which TARE was performed. We developed a prediction model using independent risk factors for OS and conducted a validation with bootstrap.

Results: Median maximal tumors size was 8.15 cm (interquartile range (IQR), 5.8–12.0) and median tumor number was 2 (IQR, 1–3). Median albumin level was 4.0 g/dl (IQR, 3.6–4.2). Portal vein invasion was found in 80 patients [46%, Vp1–3 (39.7%) and Vp4 (6.3%)]. Using four independent risk factors associated with OS (maximal tumor Size, tumor Number, serum Albumin, and Portal vein invasion), a scoring system (SNAP-HCC) was developed. Harrell C-index values for OS were 0.756 (95% confidence interval: 0.729–0.783) in validation using bootstrap. The patient group according to SNAP-HCC score (0–5) were well-discriminated and showed significantly different OS among each group (all *P*<0.001). Patients with SNAP-HCC<3 showed significantly longer OS than patients with SNAP-HCC≥3 (*P*<0.001) (Figure). The expected survival probabilities at years 1, and 3 were 0.81 and 0.73 in the low-risk group (SNA*P*<3); and 0.32 and 0.14 in the high-risk group (SNA*P*≥3), respectively.



Conclusions: SNAP-HCC score system could predict a prognosis of HCC patients who underwent TARE as an initial treatment. This model could be helpful for making a decision for selecting HCC treatment.

Keywords: Hepatocellular carcinoma, Transarterial radioembolization, Prediction model, Yttrium-90

PE-95

Clinical Characteristics and Risk Factors of Extrahepatic Metastasis after Curative Hepatectomy

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Aims: The aim of this study was to investigate the clinical features and risk factors of EHM after curative hepatectomy for HCC.

Methods: From January of 2004 to December of 2013, 402 treatment-naïve patients who underwent curative hepatectomy for hepatocellular carcinoma was enrolled from two tertiary hospitals. Univariate analyses were performed using the chi-squared test or Student's t-test, and univariate and multivariate analyses regarding EHM occurrence were performed via Cox-proportianal hazards regression.

Results: EHM was diagnosed in 41 patients (10.2%) during a median follow-up period of 5.91 years. The 10-year cumulative rate of HCC recurrence and EHM was 75.9% and 15.0%, respectively. Pulmonary metastasis was the most common site of EHM (48.8%) followed by lymph nodes (19.5%), bone (14.6%), peritoneum (9.8%) and adrenal glands (9.8%). The median duration to 1st recurrence and EHM was 1.21 years and 1.81 years, respectively. In 39.0% of patients, intrahepatic HCC recurrence was not noted at diagnosis of EHM. The most of patients was diagnosed with abdomen enhanced CT (73.2%) followed by chest enhanced CT (12.2%). The risk factors associated with EHM was 1st recurrence free survival less than 9 months and mUICC T stage (III, IV) at 1st recurrence. (HR 3.480, and 6.872 and p-value 0.008, and <0.001, respectively).

Conclusions: EHM after curative hepatectomy develops significantly without intrahepatic recurrence. Regular surveillance for EHM especially in patients with high mUICC T stage at recurrence and short recurrence free survival less than 9 months are required.

Keywords: Hepatocellular carcinoma, Extra-hepatic metastasis, Hepatectomy, Surgery risk factor, Surveillance

PE-96

Fatal Renal Subcapsular Hematoma after Transcatheter Arterial Chemoembolization in Patients with Hepatocellular Carcinoma

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Aims: Renal subcapsular hematoma has been reported in patients undergoing urological intervention or in patients with renal malignancy. Renal subcapsular hematoma after abdominal angiography has been rarely reported. We report two patients with hepatocellular carcinoma (HCC) who experienced fatal renal subcapsular hematoma after transcatheter arterial chemoembolization (TACE).

Methods: Case 1: A 77-year-old female was admitted to treat HCC for the 6th TACE. The patient had hypertension, diabetes, liver cirrhosis associated with HBV. After the TACE, decrease in awareness occurred. Vital signs were unstable with blood pressure 57/35 mmHg and pulse rate 118 times/minute. Portable abdominal sonography showed right renal subcapsular hematoma. Contrast media leakage was observed at the branch of the upper polar division of renal artery on the angiography.

Case 2: An 84-year-old female was admitted to treat HCC with the first TACE. The patient had hypertension, diabetes, liver cirrhosis associated with HBV. Decrease in consciousness occurred immediately after TACE and vital signs were unstable with blood pressure 80/40 mmHg, pulse rate 79 times/minute. Hematoma around the right kidney was detected in the non-contrast abdominal CT scan (Figure 1).

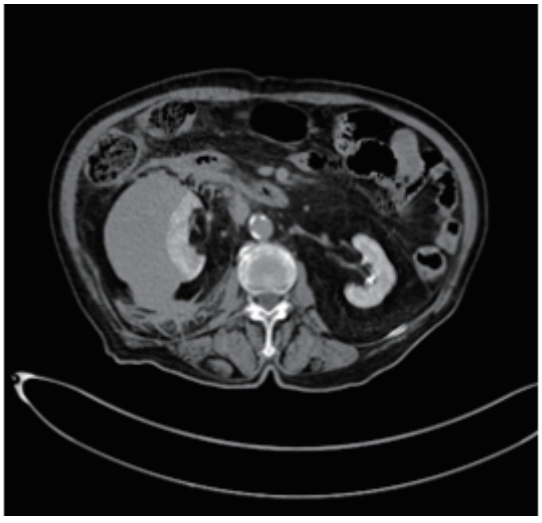

Figure 1.

Results: Case 1: Embolization was performed for bleeding control. Even though successful embolization and aggressive supportive care with transfusion, she died due to hypovolemic shock and multi-organ failure.

Case 2: Embolization was performed on the bleeding lesion identified by angiography. Afterwards, the patient continued to show lowered blood pressure and decreased consciousness in spite of aggressive transfusion and resuscitation. She died due to metabolic acidosis, hypovolemic shock, and multi-organ

failure.

Conclusions: Thrombocytopenia and hypertension are known as risk factors for hematoma formation, and vascular intervention may require careful manipulation in patients with HCC who have cirrhosis and hypertension. We report these cases to keep in mind the occurrence of renal subcapsular hematoma, a rare but serious complication of vascular intervention for treatment of HCC.

Keywords: Renal Subcapsular Hematoma, Patients with Hepatocellular Carcinoma, liver cirrhosis, Transcatheter Arterial Chemoembolization

PE-97

The Efficacy and Safety of Concurrent Chemoradiotherapy in Patients with Unresectable Hepatocellular Carcinoma

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Aims: Treatment responses of unresectable hepatocellular carcinoma (HCC) remain unacceptably low and treatment modalities are limited. We compared the efficacy and safety of concurrent chemoradiotherapy (CCRT).

Methods: In retrospective cohort study, data on 74 patients with unresectable HCC, with Child-Turcotte-Pugh (CTP) scores of 5-8, were collected from a university hospital between January 2009 and October 2018. All patients were treated with CCRT (5-fluorouracil 500mg/m^2 via intraarterial chemoport at Day 1 to 5 and Day 20 to 25, plus radiotherapy 6,250 cGy/25 times at Day 1 to 25).

Results: From 74 patients with unresectable HCC, 71.6% were classified as Child-Pugh (CP)-A, 86.4% as Barcelona Clinic Liver Cancer (BCLC)-C. The median overall survival (OS) and time to progression (TTP) were 13 months, and 8 months in the CCRT group. In univariate analysis, operation, ECOG, Child-Pugh score, diffuse type, main portal vein invasion, bile duct invasion, albumin, PT, HBV DNA were significant prognostic factors of OS (*P*=0.014, 0.005, 0.024, 0.029, 0.012, 0.008, 0.017, 0.000, 0.023), whereas operation, antiviral agent, ECOG, Child-Pugh score, age, creatinine, albumin, HBV DNA, PIVKA-II were significant prognostic factors of TTP (*P*=0.000, 0.008, 0.012, 0.031, 0.023, 0.023, 0.024, 0.024, 0.006). In multivariate analysis, operation, diffuse type, ECOG were significant prognostic factors of OS (*P*=0.028, 0.037, 0.043), whereas operation, antiviral agent, Child-Pugh score were significant prognostic factors of TTP (*P*=0.008, 0.044, 0.037). Major complications included hyperbilirubinemia (44.8%), ALT elevation (34.5%), ascites (13.8%), gastric ulcer (14.5%), catheter-related complications (3.4%) and radiation pneumonitis (2.3%).

Conclusions: For managing unresectable HCC, CCRT may be a valuable and safe treatment modality.

Keywords: Concurrent chemoradiotherapy, CCRT, Unresectable hepatocellular carcinoma

PE-98

Sorafenib for 9,923 Patients with Hepatocellular Carcinoma: An Analysis from National Health Insurance Claim Data in South Korea

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Aims: The purpose of this study was to investigate the characteristics, treatment patterns including subsequent treatment and outcomes of sorafenib of whole HCC patients in South Korea.

Methods: This is a retrospective, single-arm, and observational study. Data sources came from the national health insurance data. Included patients were those who had been diagnosed as HCC and received sorafenib between 1 July 2008 and 31 December 2014. A total of 9,923 patients were recruited in this study.

Results: The mean age of 9,923 patients were 59 years with male predominance (84.6%). The mean HCC-prevalent duration was 663 days (22.1 months). The most common etiology of HCC was hepatitis B (66%). Before sorafenib treatment, 6,669 (67.2%) patients received other kinds of therapies for HCC including transarterial chemoembolization (TACE), resection and radiation therapy. During sorafenib therapy, 1,565 (15.8%) received combined treatment with other modalities. After sorafenib therapy, 2,591 (26.1%) patients received rescue therapies, of which TACE was the most common modality applied in 1,498 (15.1%) patients. The mean duration of sorafenib administration in all the patients was 105.7 days. In 7,159 (72.2%) patients, the initial and mean sorafenib dose were the same. There were 7,023 (70.8%) patients whose initial sorafenib dose was 600-800mg. The survival was longest in patients with recommended starting dose of 800mg, followed by dose reduction to 400mg (15.0 months). The second longest survival was demonstrated in patients with starting dose of 800mg, followed by dose reduction to 400-600mg (9.6 months). A total of 3,591 patients underwent rescue therapy after sorafenib, and the median OS was 14.5 months which

were longer than 4.6 months in 7,332 patients who received supportive care after sorafenib. The most commonly applied treatment after sorafenib was TACE (30.8%).

Conclusions: Real-life data show that the efficacy of sorafenib seems to be similar with that in clinical trials. Appropriate subsequent therapy after sorafenib might prolong the patient survival.

Keywords: Hepatocellular carcinoma, Sorafenib, Outcome

PE-99

Impact of Ratio of the Ablation Zone-Tumor Area in Recurrence of Hepatocellular Carcinoma After Radiofrequency Ablation

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Aims: Recurrence of hepatocellular carcinoma (HCC) after curative treatment is known as a dismal prognostic factor. Although risk factors for recurrence after radiofrequency ablation (RFA) for HCC have been reported, the ratio of the ablation-tumor area in recurrence of HCC after RFA is not well known. Therefore, we aimed to investigate the ratio of the ablation zone-tumor area in recurrence of HCC after RFA.

Methods: We retrospectively reviewed data from treatment naïve HCC patients and enrolled patients who underwent RFA for the treatment of HCC from 2008 to 2017 at three tertiary hospitals. We evaluated the characteristics of tumor recurrence after RFA and analyzed the predictors associated with tumor recurrence in patients with HCC after RFA.

Results: A total of 778 HCC patients treated with RFA was enrolled for the study. The mean age was 66.2 ± 10.4 years and 74.6% of patients were male. Most patients (96.9%) had underlying liver cirrhosis and the most common etiology of chronic liver disease was chronic hepatitis B (59.4%). The mean tumor size was 2.4 ± 1.1 cm and 83.2% of the tumor lesion was single. The mean area of the tumor was 4.5 ± 3.8 cm^2 and that of ablation zone was 14.8 ± 8.4 cm^2. There were 393 recurred patients during the follow-up period. Intrahepatic recurrence occurred in 97.6%. Of note, the recurrence from the RFA site accounted for one-fifth (19.2%) among the recurred patients. We further analyzed the factors related to the recurrence after RFA in patients with HCC. In multivariate analysis, the number of tumors, Child class B, and the ratio of the ablation zone and tumor area < 2 were predictors associated with tumor recurrence in HCC patients after RFA.

Conclusions: The number of tumors, Child class B, and the relative ratio of the ablation-to-tumor area < 2 are independently associated with tumor recurrence in patients with HCC after RFA. Therefore, we suggest close surveillance for HCC recurrence after RFA, especially in these high-risk patients.

Keywords: Carcinoma, Hepatocellular, Radiofrequency Ablation, Recurrence, Treatment outcome

PE-100

Hepatocellular Carcinoma in Korea between 2012 and 2014: An Analysis of Korean Nationwide Cancer Registry

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Aims: Considering the high prevalence and the mortality of hepatocellular carcinoma (HCC) in Korea, accurate statistics for HCC is important. We evaluated the characteristics of newly diagnosed Korean HCC patients between 2012 and 2014.

Methods: Data from The Korean Primary Liver Cancer Registry (KPLCR) which consists of approximately 15% random sample of entire HCC patients in the Korean Central Cancer Registry were utilized. Baseline characteristics, treatment modalities, and overall survival (OS) of 4,572 patients with HCC registered in the KPLCR between 2012 and 2014 have been investigated.

Results: At the time of HCC diagnosis, mean age was 60.0±10.8 years, with male predominance (79.6%). Hepatitis B virus was the predominant etiology (59.1%). The Barcelona Clinic Liver Cancer (BCLC) stages at diagnosis were 3.9%, 36.9%, 12.5%, 39.4% and 7.3% for BCLC stage 0, A, B, C, and D, respectively. The proportion of HCC diagnosed at BCLC stage 0 or A between 2012 and 2014 were significantly lower compared to that between 2008 and 2011 (40.8% vs. 48.3%, P<0.001). Transarterial therapy (37.5%) was the most commonly performed initial treatment, followed by surgical resection (19.8%), best supportive care (19.1%), and local ablation therapies (10.6%). The median survival was 2.9 years, and the

1-, 3-, and 5-year OS rates were 67.7%, 49.3% and 41.9%, respectively. The OS of HCC patients between 2012 and 2014 was significantly longer than that of patients between 2008 and 2011 (log-rank test, *P*<0.001).

Conclusions: About half of the patients (46.7%) were diagnosed at advanced HCC (BCLC stage C or D). Although large proportion of HCC patients between 2012 and 2014 were diagnosed at advanced stages, the OS has been improved which warrants further analysis.

Keywords: Epidemiology, Hepatocellular carcinoma, Hepatitis B, Korea

PE-101

The Overall Survival of Hepatocellular Carcinoma after Resection According to the Cause of Liver Disease

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Aims: Some studies have shown a poor prognosis for hepatocellular carcinoma (HCC) patients whose etiology is viral. This study is to evaluate the outcomes of the patients diagnosed to resectable HCC, according to the etiology of the disease due to the differences in prognosis between viral and non-alcoholic fatty liver disease (NAFLD).

Methods: A total of 264 patients who received hepatectomy for the treatment of HCC between 2005 and 2019 were performed a review of medical records. They were divided into groups according to the cause of liver disease, followed by overall and disease-free survival analysis for comparison.

Results: The cause of HCC consisted of 222 hepatitis B virus (HBV) (69.4%), 14 hepatitis C virus (HCV) (4.4%), and 28 non-alcoholic steatohepatitis (NASH) (7.9%). There was no statistically significant difference in the sex, tumor stage (BCLC and AJCC 7th) of the groups of patients divided according to the etiology of HCC. However, the mean age was higher in NAFLD (NAFLD 72 years, vs. HBV 62 years, HCV 68 years, *P*<0.001). The presence of liver cirrhosis was lower in NAFLD (NAFLD 14.3%, vs. HBV 51.8%, HCV 50%, *P*=0.001). Overall survival (OS) at five years of the patients with HBV, HCV and NAFLD were 88.2%, 74.1%, and 74.6%, respectively (*P*=0.031). Disease-free survival at five years of patients with HBV, HCV and NAFLD were 72.5%, 69.3%, and 77.9%, respectively (*P*=0.370). In multivariate analysis, age and baseline AFP were the significant prognostic factors of OS (hazard ratio [HR] for age; 0.938, confidential interval; 0.886-0.994, *P*=0.03, HR for AFP; 1.000; 1.000-1.000, *P*=0.001).

Conclusions: Baseline age and AFP levels showed significant prognostic differences among the groups of HCC patients of the various etiologies. NAFLD induced HCC had shown slightly lower OS at five years than viral induced HCC.

Keywords: Hepatocellular carcinoma, Resection, Overall survival, Etiology, Non-alcoholic fatty liver disease

PE-102

Lifestyle Risk Factors and Comorbidities Contribute to the Overall Survival in Patients with Hepatocellular Carcinoma

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Aims: We aimed to investigate potential impact of comorbidity- and lifestyle-related risk factors on the overall survival (OS) of HCC patients.

Methods: Between Aug. 2010 and Jan. 2020, 459 patients were screened for eligibility in a prospective cohort. After excluding patients without baseline or survival data (n=12) or insufficient data on lifestyle risk factors and comorbidities (n=34), 413 were included in the analysis.

Results: Allowing multiple etiologies, underlying liver diseases were alcohol-related liver disease (173, 41.6%), nonalcoholic steatohepatitis (NASH; 121, 29.3%), hepatitis C (126, 30.5%) or B (93, 22.5%). Diabetes was present in 133 patients (32.2%). Patients with significant alcohol consumption were 215 (52.1%) and those with current or past smoking were 183 (44.3%), respectively. Adjusted hazard ratios (aHRs) for lifestyle risk factors and comorbidities were 1.442 (95% CI, 1.044–1.990; *P*=0.026) for diabetes, and 1.772 (95% CI, 1.250–2.373; *P*<0.001) for smoking, respectively. A predictive model for OS was derived based on the risk factors including alcohol intake, smoking, presence of NASH or diabetes. Higher lifestyle-comorbidity score (L-C score) showed significantly poorer OS (0–4 vs. 5–7; aHR=2.106; 95% CI, 1.460–3.036; *P*<0.001). Interaction between each treatment modality and L-C score was not significant (all *P*>0.05), and prognostic prediction with L-C score was consistent with correction of lead time bias and propensity score analysis.

Conclusions: The combined risk score of lifestyle and comorbidities was an independent predictor for OS in this cohort. Patients at risk of HCC need to pay attention to modifiable lifestyle risk factors and comorbidities.

Keywords: hepatocellular carcinoma, Lifestyle, Comorbidity, Survival

PE-103

Long-Term Outcomes for Patients with Hepatocellular Carcinoma Treated Transarterial Radioembolization : Multi-Center Study

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Aims: Transarterial radioembolization (TARE) has become widely utilized in treating hepatocellular carcinoma (HCC), which is one of most common cause of cancer mortality worldwide. We investigated long-term clinical outcomes for patients with HCC treated TARE in multi-medical center in Korea.

Methods: A total of 149 patients who treated TARE between 2008 and 2014 in multi-medical center were recruited. HCC stage prior to treatment was classified according to Barcelona clinic liver cancer (BCLC) stage, BCLC C and D stage were defined as an advanced stage. The baseline liver function was calculated by Child-Pugh score. The tumor response rates were measured according to modified response evaluation criteria. Overall survival (OS) and progression free survival (PFS) were estimated by the Kaplan-Meier method.

Results: Advanced HCC stage and Child-Pugh score A was identified in 62 (41.6%) and 133 (89.3%) patients, respectively. Portal vein thrombosis was identified in 43 (28.9%) patients. The median OS and PFS was 16.5 months and 6.1 months, respectively. The complete or partial response, stable disease, and progressive disease rate after 3 months was 36.0%, 43.4%, and 20.6%, respectively. The OS and PFS were significantly different among groups stratified by Child-Pugh score and presence of portal vein thrombosis (all P<0.05 by log-rank test). Also, OS and PFS were significantly lower in advanced HCC stage compared to no advanced HCC stage (all P<0.05 by log-rank test). In multivariate analysis, advanced HCC stage (OS, HR [hazard ratio] =1.630; PFS, HR=1.993) and previous history of HCC therapy (OS, HR=2.344; PFS, HR=2.099) independently contributed to the OS and PFS (P<0.05).

Conclusions: Radioembolization for patients with early and advanced HCC is a safe and effective treatment which can be utilized even in patients with compromised liver function. Further comparative studies with other treatment methods are needed for each stage of HCC.

Keywords: Trasnarterial radioembolization, Hepatocellular carcinoma, Survival, Risk factors

PE-104

Development of Hand Foot Skin Reaction Is Associated with Good Prognosis for HCC Patients Treated with Sorafenib: A Prospective Cohort Study

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Aims: Sorafenib is a standard first-line systemic therapy of advanced hepatocellular carcinoma (HCC). However there are few studies that have examined prognostic factors of sorafenib therapy in prospective cohort. We analyze prognostic factors of HCC patients who were treated with sorafenib.

Methods: Between May 2016 and May 2018, 288 advanced HCC patients treated with sorafenib were prospectively enrolled at 13 hospitals. Originally, this study has been performed to investigated the efficacy of Urea cream. We analyzed various prognostic factors of sorafenib for overall survival (OS) and progression free survival (PFS) by Univariate and Multivariate analyses using Cox proportional hazards regression model.

Results: We included 288 patients in the present analysis. The median age was 61 years. Among the 288 patients, 241 (83.7%) were male. Chronic hepatitis B (68.4%) was main etiologic factor in development of HCC. Most of the patients (85.4%) were in the advanced Barcelona Clinic Liver Cancer Stage. Hand-foot skin reactions (HFSR) were observed in 142 patients (49.2%). The univariate analysis identified presence of HFSR, serum albumin level as potential prognostic factor for PFS. In multivariate analysis for PFS, presence of HFSR (HR 0.212; 95% CI: 0.091-0.495, P<0.001) and serum albumin level (HR 0.30, 95% CI: 0.158-0.568, P<0.001) were significant factors of PFS. Prognostic factors for OS were analyzed in the same method. In univariate analysis, presence of ascites, serum albumin level and creatinine level, presence of HFSR were potential prognostic factors for OS. In multivariate analysis for OS,

presence of HFSR (HR 0.144; 95% CI: 0.063-0.330, p 0.002), albumin level (HR ratio 0.283; 95% CI: 0.148-0.544, *P*<0.001), creatinine level (HR 1.395; 95% CI 1.133-1.717, p 0.002) were significant factors of OS. BCLC stage, presence of portal vein invasion, presence of distant metastasis were not statistically significant in the present analysis.

Conclusions: Developing HFSR from sorafenib therapy and high serum albumin level were independently associated with good OS and PFS. Developing HFSR have been suggested as valuable indicator of good sorafenib prognosis.

Keywords: HCC, Sorafenib, HFSR

PE-105

Prognostic Role of CA 19-9 in Patients with Hepatocellular Carcinoma

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Aims: Serum carbohydrate antigen 19-9 (CA 19-9) is a commonly used tumor marker for pancreatic and biliary cancer. However, it was recently suggested that CA 19-9 level could be elevated in hepatocellular carcinoma (HCC) patients with aggressive phenotype or stemness features. This study aimed to evaluate the significance and prognostic role of serum CA 19-9 in patients diagnosed with HCC.

Methods: This study enrolled 534 consecutive patients newly diagnosed with HCC and with serum CA 19-9 values at baseline between 2008 and 2017. Patients with combined hepatocellular-cholangiocarcinoma and other malignancies at baseline were excluded.

Results: During a median follow-up of 27.5 months (range 0.1-141.1), 178 patients (33.6%) survived and 180 (34.0%) expired. Baseline CA 19-9 level was within normal range in 410 patients (77.5%) and elevated (CA 19-9 > 37 U/mL) in 119 (22.5%). Patients with elevated CA 19-9 had a larger tumor size, a higher proportion of multiple tumors and portal vein tumor thrombosis than patients with normal CA 19-9 (all P values were < 0.05), and therefore presented with more advanced tumor characteristics. The cumulative overall survival (OS) in patients with elevated CA 19-9 was significantly lower than that in patients with normal CA 19-9 (*P*<0.001). In the multivariate analysis, elevated CA 19-9 was an independent prognostic factor for OS (HR, 1.52; 95% CI, 1.06–2.16; *P*=0.021). Subgroup analysis revealed that elevated CA 19-9 was associated with poor prognosis across all BCLC stages. The validity of CA 19-9 increased particularly in patients with CTP class A or AFP > 100 ng/ml.

Conclusions: Elevated CA 19-9 level is significantly associated with poor prognosis and advanced tumor characteristics in HCC patients. The CA 19-9 test is a simple adjuvant method that can be performed to predict the prognosis of HCC patients.

Keywords: Hepatocellular carcinoma, CA 19-9

PE-106

Lymphocyte to Monocyte Ratio Based Nomogram for Predicting Outcomes of Hepatocellular Carcinoma Treated with Sorafenib

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Aims: The ability of the pretreatment lymphocyte to monocyte ratio (LMR) to predict outcomes of patients with hepatocellular carcinoma (HCC) receiving sorafenib is not conclusively determined.

Methods: We retrospectively studied patients treated with sorafenib for HCC in two tertiary referral centres in Asia and North America. Primary endpoints were overall survival (OS) and progression-free survival (PFS). Predictive factors for the outcomes were determined by Cox proportional hazards models. A risk-assessment tool was developed.

Results: Compared to the North America cohort, the Asia cohort was more heavily pretreated (72.1% vs. 35.2%; *P*<0.001), had higher hepatitis B virus infection (87.6% vs. 5.6%; *P*<0.001), and more distant metastases (83.2% vs. 25.4%; *P*<0.001). Lower monocyte count in the Asia cohort (median, 462.7 vs. 600.0/μL; *P*=0.023) resulted in a higher LMR (median, 2.6 vs. 1.8; *P*<0.001). High LMR was associated with a significantly higher OS (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.81–0.97; *P*=0.007). This was confirmed in a sensitivity analysis including patients treated in Asia only (HR, 0.89; 95% CI, 0.81–0.97; *P*=0.010). An OS nomogram was constructed with following variables selected in the multivariate Cox model: LMR, treatment location, previous treatment, performance status, AFP, lymph node metastasis, and Child–Pugh score. The concordance score was 0.71 (95% CI, 0.69–0.73). LMR did not predict PFS.

Conclusions: Pretreatment LMR predicts OS in HCC patients treated with sorafenib. Our OS nomogram, incorporating LMR, can be offered to clinicians to improve their ability to assess

prognosis, strengthen the prognosis-based decision making, and inform patients in the clinic.

Keywords: Lymphocyte, Monocyte, Liver Cancer, Chemotherapy, Overall Survival

PE-107

Surgical Treatment Outcome of Primary Hepatic Sarcoma

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Aims: Primary hepatic sarcoma is rare disease with higher recurrence after surgical treatment. This study analyzed outcomes after surgical resection of patients with primary hepatic sarcoma.

Methods: From 2001 august to 2016 september, 11 patients were pathologically diagnosed after surgical resection as hepatic sarcoma. Patient characteristics and tumor characteristics, treatment, tumor recurrence and patient survival were analyzed.

Results: All patient except 1 was surgically treated with R0 resection. Mean follow up duration was 711 days after surgical resection. Among 11 patients, 5 patients were diagnosed as angiosarcoma, 3 were undifferentiated sarcoma, 1 was biliary cystadenocarcinoma, 1 was embryonal sarcoma and 1 was carcinosarcoma. Mean tumor size was 12.4cm and median tumor number was 1. All patients had recurrence and mean time to recurrence was 282 days. 9 patients get tumor recurrence within 1 years after surgery. These 9 patients are all expired due to cancer recurrence. Only 2 patients (18.2%) are still alive. 1 patient with angiosarcoma received central haptatectomy and got recurrence on liver segment 4 at 5 years later. RFA was done on S4 and he got no recurrence for 6 years. 1 patient with embryonal sarcoma received Rt. hemihepatectomy and got recurrence at abdominal wall at 1 year and 4 months later. After surgical resection and survive for 1 year without recurrence.

Conclusions: Primary hepatic sarcoma has very poor outcome even after proper surgical resection. As known before, only embryonal sarcoma has better outcome, relatively.

Keywords: Liver, Sarcoma

PE-108

Management and Clinical Outcomes of Indeterminate Hepatic Nodules Detected by Preoperative Magnetic Resonance Imaging in Patients with Colorectal Cancer

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Aims: Some liver nodules remain indeterminate despite hepatocyte-specific contrast magnetic resonance imaging (MRI) in patients with CRLM. Our objective was to study the natural course and evaluate possible treatment strategies for indeterminate nodules in patients with colorectal liver metastasis (CRLM).

Methods: We performed a retrospective study of patients who underwent liver resection for synchronous or metachronous CRLM in whom MRI revealed 'indeterminate' or 'equivocal' nodules between January 2008 and October 2018. Patients were followed up until October 2019 or until death (median, 18 months; range, 1–130 months).

Results: The incidence of patients with indeterminate nodules on MRI was 15.4% (60 of 389). Synchronous lesions were found in 60% (n=36) and solitary indeterminate nodules were found in 71.67% (n=43). The sensitivity and specificity of IOUS for detecting indeterminate nodules were 73.68% and 93.75%, respectively, with a positive predictive value of 96.6%. Over half of the patients followed up had benign nodules (58.8%). On comparing characteristics of patients with benign or malignant nodules in the follow up group, the ratio of positive lymph nodes to total number of lymph nodes resected (pLNR) was significantly greater in patients with malignant nodules (P=0.006).

Conclusions: IOUS could be considered as an adjunct to MRI in patients with indeterminate nodules owing to its high positive predictive value. The pLNR could be used to help select which patients can undergo conservative therapy, at least in metachronous CRLM.

Keywords: Equivocal, Indeterminate, Intraoperative ultrasound, Colorectal Liver Metastasis

PE-109

Prediction of Nivolumab Treatment Response with Serum Alpha-Fetoprotein Levels in Patients with Advanced Hepatocellular Carcinoma

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Aims: Second–line therapies including nivolumab, and third-line therapy are available for patients with advanced hepatocellular carcinoma (HCC) who experience sorafenib failure. Unfortunately, the systemic therapeutic response to these drugs cannot be predicted in advance, else, effective subsequent therapies could be optimally planned. Since, there are no biomarkers currently known to predict therapy response and outcomes, we aimed to analyze outcomes of nivolumab by baseline and on-treatment changes of serum alpha-fetoprotein (AFP) level in advanced HCC patients.

Methods: Among 121 patients with advanced HCC who received nivolumab treatment (240 mg fixed or 3 mg/kg intra-

venously every 2 weeks) from May 2016 to March 2020, 62 patients were excluded due to a shorter treatment period (<4 weeks) or insufficient baseline data, and eventually, 59 patients were enrolled in this study. Progression-free survival (PFS) was calculated in the following scenarios, namely, baseline AFP (< or ≥400 ng/mL), AFP response at week 4 of nivolumab treatment expressed as a percentile (< or ≥20% decrease from baseline), and as a relative value (< or ≥200 ng/mL decrease from baseline).

Results: Median PFS was 2.6 months (m) (95% CI, 1.37-3.86) for all enrolled patients. Median PFS in patients with baseline AFP of <400 and ≥400 ng/mL was 3.2 m (95% CI, 1.65-4.75) and 2.3 m (95% CI, 1.64-2.96) (HR, 0.66 [95% CI, 0.38-1.13]; *P*=0.132) respectively. Median PFS in patients with a decreased AFP response of ³20% and <20% from baseline at week 4 of nivolumab treatment was found to be 6.1 m (95% CI, 3.32-8.88) and 1.9 m (95% CI 1.49-2.32) (HR, 0.58 [95% CI, 0.32-1.06]; *P*=0.078), respectively. Median PFS in patients with decreased AFP levels of ³200 and <200 ng/mL from baseline at week 4 of nivolumab treatment was 9.1 m (95% CI, 6.90-11.30) and 1.9 m (95% CI, 1.55-2.25) (HR, 0.27 [95% CI, 0.12-0.61]; *P*=0.002), respectively. Among 28 patients with baseline AFP >400ng/mL, median PFS was significantly longer in patients showing decreased AFP levels of >200ng/mL compared with those who not (9.1m vs 1.8m; HR, 0.32 [95% CI, 0.13-0.77]; *P*=0.012).

Conclusions: Patients with advanced HCC with high baseline values showing marked reduction of serum AFP level at Week 4 after treatment may be associated with longer PFS with nivolumab; however, the conduction of a prospective study with a larger number of patients is warranted for confirmation of results.

Keywords: HCC, Nivolumab, AFP, Treatment response

PE-110

Lenvatinib Is Independently Associated with the Reduced Risk of Progressive Disease Compared to Sorafenib in Patients with Advanced Hepatocellular Carcinoma

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Aims: Recently, lenvatinib showed non-inferiority to sorafenib in terms of overall survival with no new safety issue in a randomized phase 3 study which was conducted at 154 sites in 20 countries. Here, we investigated treatment outcomes and safety of lenvatinib compared to sorafenib and identified independent predictors of poor outcomes including shorter progress-free survival (PFS) and overall survival (OS) in Korean patients with unresectable HCC.

Methods: Patients with advanced HCC treated with lenvatinib or sorafenib at Yonsei Liver Center, Severance Hospital, Yonsei University College of Medicine between October 2018 to October 2019 were considered eligible. The treatment response was assessed using the modified RECIST criteria.

Results: Patients treated with lenvatinib had a significantly lower proportion of previous anti-HCC treatments (47.7% vs. 78.7%; *P*<0.001) than those who treated with lenvatinib. Univariate analysis showed that ECOG 1 (vs. 0), serum albumin, AFP, previous anti-HCC treatments, and lenvatinib (vs. sorafenib) were significant predictors of progressive diseases (all *P*<0.05). On the subsequent multivariate analysis, ECOG 1 (vs. 0) (hazard ratio [HR]=4.721, 95% confidence interval [CI] 1.371-16.259; *P*=0.014), higher AFP level (HR=1.000, 95% CI 1.000-1.000; *P*=0.015), and lenvatinib treatment (vs. sorafenib) (HR=0.461, 95% CI 0.264-0.804; *P*=0.006) independently predicted a higher probability of progressive disease.

Conclusions: Patients treated with lenvatinib shows significantly higher progression-free survival than those patients treated with sorafenib. However, mortality was not significantly different whether patients treated with lenvatinib or sorafenib, which indicated that lenvatinib is non-inferiority to sorafenib in terms of overall survival.

Keywords: Hepatocellular carcinoma, Lenvatinib, Sorafenib

PE-111

Analysis of Recurrence-Free Survival Using Adjuvant Cytokine-Induced Killer Cell Immunotherapy for Hepatocellular Carcinoma

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Aims: Several randomized controlled trial showed that adjuvant immunotherapy with cytokine-induced killer (CIK) cells were used to reduce recurrence in hepatocellular carcinoma as an adjuvant therapy. In this study, we aimed to evaluate the efficacy of adjuvant cytokine-induced killer cell immunotherapy for HCC in a retrospective manner in our hospital.

Methods: This study was a retrospective case series. Overall study period was January 2016 to April 2020. The autologous CIK (created by incubation of patient's peripheral blood mononuclear cells with interleukin 2 and an antibody against CD3) were treated as an adjuvant drug within 2 to 3 months after

curative therapy. Clinical characteristics at baseline and after CIK treatment, and recurrence free survival period were analyzed.

Results: During the study period 14 patients were received in CIK in our hospital. After excluding patients who met the exclusion criteria, 9 of HCC patients were evaluated. Patient's median age was 49.8 (31-67) and 4 of 9 patients were HCC stage I, 3 of patients were state II according to the AJCC staging system (8th edition). Among the patients, chronic viral hepatitis B was the most common case of underlying liver disease and about 44% patients had clinical or radiological evidence of liver cirrhosis. Before receiving adjuvant CIK cell immunotherapy, seven patients were undergone curative surgical resection, one patient received radiofrequency ablation(RFA) and the last patient received transarterial chemoembolization (TACE). The median time of recurrence-free survival (RFS) was 19.2 months. Five patients experienced tumor recurrence by the time of the data from our cut-off date. The five patients who had tumor recurrence were further treated such as TACE, RFA, sorafenib administration. Only one patient had constantly receiving CIK treatments after additional therapy. There was one case of death during the study period, the cause of which was death from liver failure accompanying recurrence of hepatocellular carcinoma.

Conclusions: This retrospective study in our hospital showed that adjuvant immunotherapy with cytokine-induced killer (CIK) cells for HCC patients as an adjuvant therapy, the median time of recurrence-free survival (RFS) was 19.2 months. CIK cells therapy could be a feasible treatment option for patients who underwent curative treatment for HCC. However, more cases were needed in the future as to whether CIK cell therapy contributes to the prognosis and RFS of HCC.

Keywords: Hepatocellular carcinoma, Cytokine-induced killer cells, Recurrence-free survival

PE-112

M2BPGi as a Prognostic Factor for HCC Patients Receiving TACE: Analysis in Comparison with HAP Score

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Aims: Serum Mac-2 binding protein glycosylation isomer (M2BPGi) has been studied as a diagnostic marker for liver fibrosis and cirrhosis in HBV patients. This study aimed to validate the potential of M2BPGi in predicting clinical outcomes of patients with hepatocellular carcinoma (HCC) treated with transarterial-chemoembolization (TACE).

Methods: A total of 226 HCC patients treated with TACE for HCC were enrolled for the study. Serum M2BPGi was measured at baseline using an HISCL kit. ROC analysis was used to determine the cut-off value of M2BPGi for prediction of patient outcomes. Prognostic performance of M2BPGi was assessed in relation to hepatoma arterial-embolisation prognostic (HAP) score. Primary outcome was progression-free survival (PFS). Secondary outcomes included overall survival (OS) and recurrence after complete response (CR).

Results: Median progression-free survival was 13.8 months. Patients with low M2BPGi levels (≤2.82) had significantly better OS and PFS than patients with high M2BPGi levels (>2.82). In multivariate analysis, M2BPGi (cut off 2.82) was an independent variable for PFS and OS. For further evaluation, patients were classified into three groups: high-risk group, high M2BPGi levels and high HAP scores; low-risk group, low M2BPGi levels and low HAP scores; and intermediate-risk group. The low-risk group had significantly better PFS than the high- and intermediate-risk groups, whereas the difference between the high- and intermediate-risk groups was insignificant. The high-risk group showed remarkably poor OS compared to the other two groups. M2BPGi alone was a significant factor for HCC recurrence after achieving CR.

Conclusions: Serum M2BPGi level is a useful prognostic indicator of PFS and OS in HCC patients treated with TACE as well as recurrence, which is not predictable with the HAP score. Combination of M2BPGi with the HAP score provides better identification of patients who benefit from TACE.

Keywords: M2BPGi, Hepatocellular carcinoma, Intraarterial chemotherapy, Prognostic marker

PE-113

Sarcopenia Predict the Outcomes in Patients with Hepatocellular Carcinoma Treated by Trans-Arterial Radioembolization

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Aims: Trans-arterial radioembolization (TARE) is a form of radiation therapy performed by selective intra-arterial injection of microspheres loaded with Yttrium-90 in hepatocellular carcinoma (HCC). Emerging evidence on body composition suggests that sarcopenia might be predictive of outcomes in HCC patients. The aim of this study is to identify prognostic factors for overall survival (OS) and progression free survival (PFS) in patients with HCC undergoing TARE.

Methods: This is a single center retrospective study on consecutive HCC patients undergoing TARE from Jul 2009 to May 2019. Using pre-treatment plain computed tomography imaging, the total cross-sectional area (cm^2) of abdominal skeletal

muscle at the third lumbar vertebra was measured. The skeletal muscle index (SMI) was calculated by normalizing muscle area to patient height.

Results: A total of 82 patients were included in the study (mean age 66 years). 28 patients (34.1%) had portal vein tumor thrombus (PVTT), of whom 20 (24.3%) had PVTT involving main trunk or first-order branches. 47 patients (57.3%) were classified as sarcopenia (low SMI). Median follow-up was 16.2 months (IQR 7.9–35.0). Median 5-year OS was 28.3 months (95% CI 24.2–32.3) and median 12-month PFS was 7.0 months (95% CI 4.8–9.2). In univariate analysis, sarcopenia, presence of PVTT, prior treatment experience, and multifocal tumors were associated with poor 5-year OS (all P<0.05). Multivariate analysis revealed that the only variables independently associated with OS were PVTT (HR, 3.12; 95% CI, 1.64-5.93, P<0.01) and sarcopenia (HR, 2.24; 95% CI, 1.15-4.39, P=0.02). PVTT (HR, 2.81; 95% CI, 1.52-5.18, P<0.01), sarcopenia (HR, 2.69; 95% CI, 1.44-5.03, P<0.01), and large tumor (≥10 cm) (HR, 2.68; 95% CI 1.48-4.86, P<0.01) were independent predictors of PFS in multivariate analysis.

Conclusions: TARE is an effective therapy for patients with advanced HCC. In patients undergoing TARE, Sarcopenia and PVTT are independent predictors of both OS and PFS.

Keywords: Hepatocellular carcinoma, Trans-Arterial Radioembolization, Sarcopenia, Portal vein tumor thrombus

PE-114

How Should We Assign Large Infiltrative Hepatocellular Carcinomas for Staging?

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Aims: Infiltrative gross morphology of hepatocellular carcinoma (HCC) is known to be associated with poor prognosis. To date, there has been no study that fully addressed the potential role of tumor morphology in staging HCC, although it requires further clarification. Therefore, we analyzed the prognostic impact of the infiltrative type HCC by evaluating patients who underwent liver resection for HCC, and attempted to clarify how to assign this HCC subtype in the current staging systems to increase their discriminatory ability.

Methods: A total of 774 HCC patients who underwent curative liver resection were retrospectively reviewed and the prognostic significance of infiltrative type HCC was assessed using the Barcelona Clinic Liver Cancer (BCLC) and American Joint Committee on Cancer (AJCC) staging systems. The infiltrative type HCC is defined as a mass with foci varying in size which fuse to form a larger foci without a distinct margin or a mass with a permeative appearance which blends into the background of the cirrhotic liver with an indistinct margin. The cumulative incidence of OS was determined according to the AJCC T-stage and BCLC staging system and the impact of the infiltrative type HCC on each staging system was evaluated using Kaplan-Meier plots (log-rank test), censoring the patients who were lost to follow-up. The Akaike information criterion (AIC) and concordance index (c-index) were calculated to compare the prognostic powers of each staging systems.

Results: Seventy-four patients (9.6%) had infiltrative HCCs with a higher proportion of multifocal tumors, larger tumors, vessel invasion, increased tumor marker levels, and advanced T-stages than those with nodular HCC (all, P<0.01). Infiltrative morphology was independently associated with lower overall survival (OS), but its impact was significant when the tumor size was ≥4cm (P<0.001). Under current AJCC and BCLC staging criteria, these large infiltrative HCCs were associated with significantly worse OS in early AJCC T-stages (T1b/T2, P<0.001) and BCLC stage A/B (P=0.01) but not in advanced AJCC (T3/T4) and BCLC C (Fig 1 & 2). The reassignment of this subtype to T3 and T4 increased the discriminatory ability of AJCC T-staging with lower AIC values (3086.9 and 3084 vs. 3103.6) and higher c-index (0.69 and 0.69 vs. 0.67), respectively (both, P<0.05) (Table 1). For BCLC staging sequential reassignment of large infiltrative HCC from BCLC A to BCLC B and from BCLC B to BCLC C also improved the prognostic performance.

Conclusions: Large infiltrative type HCC should be assigned to the advanced stages beyond T1 or T2 of the AJCC staging or beyond BCLC stage A or B. We recommend assuming the large unifocal infiltrative type HCCs on surgical specimen as tumors with multiple foci and reassign them from AJCC-T1 and T2 to AJCC-T3, or assuming all large infiltrative HCCs staged AJCC-T1 to T3 as those with macrovascular invasion and reassigning them to AJCC-T4. Second, for BCLC staging, we recommend any large unifocal-looking infiltrative type HCCs staged BCLC-A on imaging studies to be reassigned to BCLC-B while definitely multifocal HCCs initially staged BCLC-B to BCLC-C. This enable finer stratification of HCC patients and provide more accurate prognostic competence.

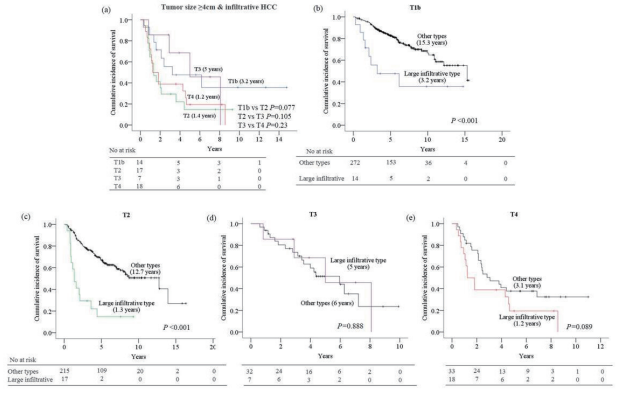

Figure 1.

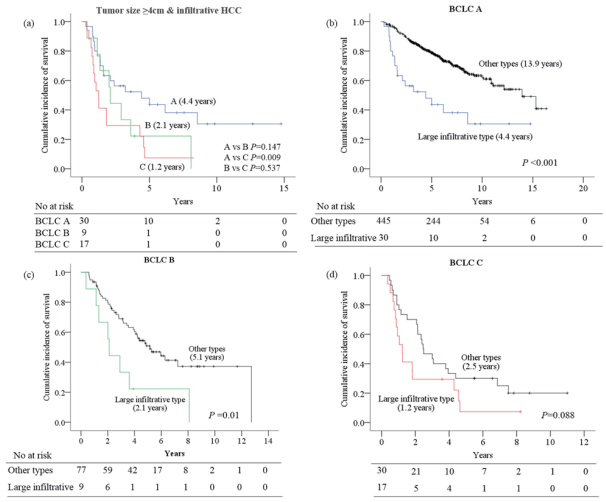

Figure 2.

Table 1. Performance of AJCC 8th T-stage and BCLC stage before and after reassignment of large infiltrative hepatocellular carcinomas

Staging system	AIC	C-index
Original AJCC 8th T-stage	3103.6	0.67 (0.635-0.703)
T3 modified T-stage	3086.9	0.685 (0.651-0.717)*
T4 modified T-stage	3084.0	0.685 (0.651-0.718)**
Original BCLC stage	3085.7	0.664 (0.63-0.697)
BCLC B and C modified	3067.4	0.682 (0.647-0.714) ¶

*P-value 0.014, **P-value 0.022, ¶P-value 0.0042

Keywords: Hepatocellular carcinoma, Infiltrative type, Nodular type, Staging system

PE-115

Entecavir versus Tenofovir in Hepatitis-B Related Hepatocellular Carcinoma Arising in Treatment-naive Chronic Hepatitis B Patients

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Aims: Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are potent nucleoside analogues (NAs) recommended as first-line monotherapies for chronic hepatitis B. There have been some hot debates on the clinical outcomes of the two agents regarding hepatocellular carcinoma (HCC) occurrence or recurrence among chronic hepatitis B patients. The objective of this study was to compare the survival of hepatitis B virus (HBV)-related HCC patients who started ETV or TDF at the time of HCC diagnosis.

Methods: A total of 1,031 consecutive antiviral treatment-naive patients who started ETV (n=516) or TDF (n=515) monotherapy during two months before and after the initial HCC diagnosis between September 2012 and December 2017 were analyzed. Patients who had hepatitis C co-infection or received liver transplantation as the initial cancer-specific treatment were excluded. Overall survival of patients were compared between ETV and TDF groups.

Results: The median age of the study patients was 55 years, and 80.3% were male. Barcelona Clinic Liver Cancer (BCLC) stage 0 and A patients were 42.0%, B for 14.5%, C for 40.8%, and D for 2.7%. Most (85.4%) had Child-Pugh class A. Hepatitis B e antigen-positive patients was 36.3%. There were no differences between ETV and TDF groups in the baseline characteristics. During a median follow-up period of 28.0 months (range: 0.1 – 92.1 months), 441 (42.8%) patients died. Entecavir group and tenofovir group did not show any difference in overall survival (median 28.0 vs 29.0 months, *P*=0.972). When stratified with BCLC stage, the results were similar. By both univariable and multivariable cox regression analysis, the type of NA was not an independent factor for overall survival, while male sex, albumin-bilirubin grade, fibrosis-4 score, serum alpha-fetoprotein, and BCLC stage were revealed to be significant factors.

Conclusions: Among antiviral treatment-naïve patients newly diagnosed with HBV-related HCC, ETV and TDF therapy did not differ for overall survival.

Keywords: Antiviral therapy, Hepatocellular carcinoma, Treatment-naive, Survival

PE-116

The Treatment of HCC with Laparoscopic RFA and Splenectomy

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Aims: In the case of hepatocellular carcinoma (HCC) most frequent cases complicated by the presence of cirrhosis. Therefore treatment of HCC is challenging. Hence, we propose the one of new surgical approaches to reduce the invasiveness and high risk in patients with HCC, esophagogastric varices, and hypersplenism.

Methods: This is a retrospective study among 18 patients with HCC and hypersplenism, who underwent simultaneous laparoscopic-guided radio-frequency ablation and laparoscopic splenectomy with endoscopic variceal ligation. Tumor size was restricted to a single nodule of <2.5-3.0 cm. Characteristics of the patients (cirrhosis etiology, liver function, tumor size, spleen size), surgery (complications, blood loss, time of stay), and follow-up (recurrence and survival) were examined.

Results: The time of operation was 2 hours. The blood loss was 300 mL. Length of stay in a hospital was 10 days. thrombocytopenia and cytopenia recovered quickly after surgery. No cases of conversion to open surgery. Three patients showed worsening liver function, two worsening of ascites after surgery. Four patients suffered from portal vein thrombosis. The 12 months tumor-free survival was 82%, the 24 months tumor-free survival was 70%. According to a literature review, these outcomes

were comparable to those of simultaneous open hepatic resection and splenectomy.
Conclusions: Laparoscopic-guided radio-frequency ablation with laparoscopic splenectomy and endoscopic variceal ligation could be an available technique for patients with HCC <3 cm, hypersplenism, and esophagogastric varices. This approach may help to minimize the surgical risks and results in a fast increase in platelet counts with an acceptable rate of complications.
Keywords: HCC, Liver cancer, RFA, Splenectomy

PE-117

Screening Program of Hepatocellular Carcinoma in Mongolia

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Aims: To screening and diagnosis in early stage of liver cancer in high risk population group
Methods: In our study we used single center patient data. These patients are controlled in screening in early stage of liver cancer in Happy Veritas Clinic and Diagnostic Center. In this center, patients are included for HCC screening, when they have liver fibrosis stage higher than F2 (over 7.2kPa) that indicates higher likehood of developing HCC. Fibrosis stage was measured using a Fibroscan (Fibroscan 502 Touch, Echosens, Paris, France). The total number of patients included for screening was 10682 patients such as abdominal ultrasound and to identify serum AFP every 3 months. 181 patients were included in this study, who had complete set of data and are regularly controlled for screening in early stage of liver cancer. Medical history, results of blood test, liver function tests, AFP, liver fibrosis stage and abdominal ultrasound examination results were collected for each patient.
Results: 181 patients with an average age of 54±11 (range 23-89 years old) were included the study. In the result, causes of liver fibrosis were HCV 59.1%(107), HBV 24.9%(45), HBV/HDV 13.3%(24), HCV/HBV 2%(3), HCV/HBV/HDV 0.6%(1) and without hepatitis viruses 0.6%(1). According to the study F2 stage was 64.6% (117), F3 stage 27.1% (49) and F4 stage 8.3% (15). Increasing fibrosis stage of liver cirrhosis has decreased platelets albumin and total protein level (P<0,001). Liver cancer nodule is detected in 4 patients from 181 patients during the follow-up. Those 4 patients had fibrosis stage F4 in Fibroscan analysis and average level of AFP was 86.
Conclusions: We conclude that patients in F4 stage in Fibroscan analysis have higher risk of developing liver cancer. Therefore, health care providers need regularly screening and testing in early stage of liver cancer in high risk population.
Keywords: Fibroscan, HCV, Stage, Patients

PE-118

Clinical Feature and Prognosis of Multiple Primary Malignancies in Patients with HCC Underwent Surgical Resection

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Aims: Multiple primary malignancies are defined as two or more different malignancies detected synchronously or metachronously in different organs of an individual patient. The aim of the present study was to investigate the clinicopathologic features for the HCC patients with multiple primary malignancies.
Methods: Between May 1997 and July 2016, 1043 HCC patients had been received radical surgical treatment in our institute. Among them 58 (5.6%) cases were diagnosed with extra-hepatic primary malignancies. The clinicopathologic features including Age, Sex, HBs Ag (positive), HCV Antibody (positive), AFP(more than 400ng/ml), tumor size (more than 5cm), multiple tumor number, microvascular invasion, Edmondson grade (grade 3 and 4), cirrhosis (fibrosis stage 4), AJCC staging for HCC (Stage 1). All the data were retrospectively analyzed form the database of our institute which were prospectively collected.
Results: The median follow up time is 53 months in the present study. Of the 58 (5.6%) multiple malignancies patients, 8 were diagnoses synchronously and 50 metachronously; 14 patients' extra hepatic primary malignancies occurred prior to their HCC diagnoses, and 36 after their HCC diagnoses.The 5 years OS rate for multiple and single primary tumor were 77.8% and 66.9%, respectively (P=0.036). The multiple primary tumor patients have the following clinicopathologic features: older mean age, more patients with non-viral background liver, fewer patients with liver cirrhosis and more patients with AJCC stage I for HCC.
Conclusions: The patients with multiple primary tumors have a relatively good prognosis in our institute mostly due to the factors of non-viral background liver and early tumor stage.

PE-119

Development and Validation of Novel Scoring System for the Prediction of Disease Recurrence Following Resection of Colorectal Liver Metastasis

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Aims: The aim of this study was to identify predictive factors for the recurrence of colorectal cancer liver metastasis(CRLM)

and then to develop a corresponding novel scoring system that should improve the sensitivity of predicting recurrence in patients with CRLM.

Methods: A total of 295 consecutive CRLM patients were enrolled in our institution between January 2002 and December 2015. Multivariate analyses were performed to identify the variables associated with disease recurrence and established the novel scoring system based on it.

Results: The scoring system considered seven variables: synchronosity, CA19-9 level, number of liver metastasis, largest size of liver metastasis, resection margin of hepatic lesion, neutrophil-to-lymphocyte ratio and prognostic nutritional index. The area under the curve of ROC was 0.824 (95% confidence interval 0.767–0.882); the sensitivity of our scoring system was 87.9%, specificity was 66.7%, positive predictive value was 20.6%, and negative predictive value was 20.9%.

Conclusions: For patients with CRLM undergoing curative hepatic resection, our novel scoring system would improve the sensitivity for prediction of disease recurrence in Case of CRLM patients.

PE-120

Aspartate Transaminase to Platelet Ratio Index (APRI) and Albumin-Bilirubin Grade (ALBI) Predict Postoperative Morbidity Following Hepatectomy for Hepatocellular Carcinoma A Multicenter Cohort Study

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[1]Eastern Hepatobiliary Surgery Hospital, [2]Pu'er People's Hospital, [3]the Fourth Hospital of Harbin, [4]Liuyang People's Hospital, [5]Ziyang First People's Hospital, [6]Mengchao Hepatobiliary Hospital, [7]The Chinese University of Hong Kong

Aims: Postoperative morbidity following hepatectomy remains high, and understanding its risk factors is important to improve perioperative outcomes. We aimed to identify the role of two non-invasive markers - albumin-bilirubin (ALBI) and aspartate transaminase to platelet ratio index (APRI) - in predicting postoperative morbidity following hepatectomy for hepatocellular carcinoma (HCC).

Methods: A multicenter data of patients undergoing hepatectomy for HCC at 8 centers were retrospectively analyzed. These patients were divided into normal and high groups according to preoperative ALBI and APRI scores. ALBI and APRI's predictive accuracy of postoperative 30-day overall and major morbidity were evaluated by the area under the receiver operating characteristic curve (AUC) and compared with two conventional scores: Child-Pugh grade and model for end-stage liver disease (MELD).

Results: In 2,301 patients, 866 (37.6%) and 400 (17.4%) were in the high ALBI and APRI groups, respectively. There were significant differences of postoperative overall morbidity between the normal and high ALBI groups (26.2% vs. 40.1%, $P<0.001$), as well as between the normal and high APRI groups (29.2% vs. 42.4%, $P<0.001$). The AUCs of the ALBI and APRI scores for predicting overall morbidity are greater than those of Child-Pugh grade and MELD score. Multivariable analyses revealed that ALBI and APRI were independent predictors of overall morbidity in both preoperative and postoperative prediction models. Similar results existed in predicting postoperative major morbidity.

Conclusions: Preoperative ALBI and APRI could predict postoperative 30-day overall and major morbidity following hepatectomy for HCC before or after surgery.

PE-121

Preoperative Controlling Nutritional Status Score in Hepatocellular Carcinoma after Curative Hepatectomy

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Aims: The controlling nutritional status (CONUT) score has been reported to correlate with prognosis of gastrointestinal cancer patients. The aim of this study was to evaluate the value of preoperative CONUT score as a postoperative prognostic marker in patients with hepatocellular carcinoma (HCC) following curative hepatectomy.

Methods: We retrospectively analyzed 94 patients who underwent curative hepatectomy for HCC between Jan 2010 and Mar 2018. Patients were assigned to two groups according to their preoperative CONUT score : high CONUT (≥2) or low CONUT (<2), according the optimal cut-off value. Clinicopathological characteristics, surgical outcome, and long term survival were compared between two groups.

Results: The high CONUT group consisted of 47 patients (50%) and had a poor prognosis with regard to overall survival. ($P=0.044$) The Cox proportional hazard model was used to identify predictors of survival. Gamma GT, blood transfusion, microvascular invasion, CONUT score were identified as prognostic factors.

Conclusions: Preoperative CONUT score can be a useful preoperative predictor for the patients who undergo curative hepatectomy for HCC.

PE-122

Surgical Outcome after Microscopic Incomplete Resection (R1) of Colorectal Liver Metastases in the Era of Agressive Surgical Approach

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Aims: A>= 1-mm margin is standard for resection of colorectal liver metastases(CLRM) . However, microscopic incomplete resection (R1) is not rate because agressive surgical resection has been attempted in multiple and bilobar CLM. in this study, we analyzed surgical outcomes after R1 resection of CRLM.
Methods: From 2005 to 2018, 371 consecutive patients undergoing liver resection for CRLM were included. R1 resection was defined to have Zero tumor free margin at the pathologic report. All patients were divided into R0 (tumor free margin more than 0 mm) and R1 group. Recurrence pattern and disease-free survival were analyzed between the two groups.
Results: A total of 371 patients included in the study. Among them, R1 resection was found in 42 (11.3%) patients. The median age at diagnosis was 59 years (range, 22 to 86). There were 246 (33.7%) men and 125 women (66.3%). The incidence of intrahepatic recurrence was not significantly different between R0 and R1 resection. Similarly, there was no significant difference in term of surgical margin recurrences between patients with R0 and R1 resections (42% [35/84] vs 35% [6/17], respectively, *P*=0.788). When comparing R0 and R1 resection, the 1-, 3-, and 5-year disease-free survival rates was not statistically significant.
Conclusions: R1 resection showed similar marginal recurrence rate and comparable disease-free survival compared to R0 resection. R1 resection should be part of the modern multidisciplinary, aggressive approach to CRLM.

PE-123

Characteristics of Cholangiocarcinoma in India - Experience from a Tertiary Care Centre

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Aims: Cholangiocarcinoma is a rare disease in India with no major studies published till date due to paucity of epidemiological and surgical data. The aim was to evaluate the clinical profile of patients presenting with intrahepatic and peri-hilar cholangiocarcinoma to a tertiary care cancer centre.
Methods: All patients diagnosed with intrahepatic cholangiocarcinoma (IHCC) and perihilar cholangiocarcinoma (PHCC) at Tata Memorial Hospital, Mumbai, between January 2012 to July 2016 were retrospectively analyzed.
Results: A total of 726 patients were evaluated of which 273 patients had IHCC and 358 were diagnosed with PHCC. The median age of presentation for IHCC and PHCC were 57yrs and 56.7yrs. Majority of patients were males – 59% for IHCC and 56.7% for PHCC. Commonest symptoms were pain in abdomen and jaundice with average duration of symptoms being 8 weeks (IHCC) and 9.4 weeks (PHCC) respectively. Most patients with IHCC had metastatic disease (184, 67.9%) on presentation. For patients with PHCC, 50.8% (182) had localized disease, 17% (61) had locally advanced and 24.3% (87) were metastatic. Chemotherapy with palliative intent was offered to 144 patients with IHCC and 60 patients with PHCC. Surgery or chemoradiotherapy could be offered to only 59 patients with IHCC and 128 patients of PHCC. 56 patients with IHCC and 136 of PHCC patients did not take treatment due to socioeconomic reasons.
Conclusions: With less than 15% patients receiving surgery, awareness and early referral with centralization is required to detect disease at a stage where treatment can offer a meaningful survival.

Liver Cancer, Basic

PE-124

Liver Cancer Stem Cell Induction from Induced Pluripotent Stem Cells

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Aims: Liver cancer stem cells represent a small fraction of cells in liver cancer tissues so that studying these cells is very hard. Generation of liver cancer stem cells considered as one of the most important issue in cancer biology research. For this reason, we tried to generate liver cancer stem cells from induced pluripotent stem (iPSCs).
Methods: First of all, CM was collected from confluent culture of Huh7 cells. Then, mouse iPSCs cells without MEF feeder cells were cultured in the presence of 50% CM for 4 weeks. The medium was changed every day with fresh medium containing 50% of CM. Mouse iPSCs cultured is the complete medium with LIF were used as a control.The survived cells (5x105 cells) were suspended in HBSS and injected into the liver of BALB/c nude mice. After 25 days malignant tumor was formed in the liver while benign teratoma was formed by the injection of iPSCs. Tumors were then excised and partly fixed in 10% neutral formalin buffer solution for HE staining and immunohistochemical analysis. The rest of tumors were subjected to rt-qPCR anaylsis and primary culture.
Results: Immunohistochemical analysis with liver cancer associated markers and cancer stem cell marker showed that malignant liver tumor was developed. These results indicate that the primary cells from the malignant tumor are rich in CSCs.

Conclusions: This model will be very important and useful to assess the significant molecular mechanisms necessary to maintain liver cancer stem cells, which will help in defat liver cancer.
Keywords: Liver cancer, Cancer stem cells, Conditioned medium

PE-125

Targeting LAG-3 Reinvigorates Anti-Tumor Function of Intratumoral MAIT Cells in Hepatocellular Carcinoma

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Aims: MAIT cells are major T-cell population in the liver, but whether they contribute to the anti-tumor immunity in hepatocellular carcinoma (HCC) is controversial.
Methods: We characterized intratumoral MAIT cells using MR1-tetramer, compared to the intrahepatic MAIT cells. Phenotypic analyses were performed by flow cytometry, and transcriptome analyses using sorted MAIT cells were performed by RNA sequencing. To evaluate their function, co-culture assays using hepatoma cell lines were performed.
Results: Upon tumor cell-stimulation, MAIT cells produced anti-tumor cytokines and cytotoxic molecules, and could kill the hepatoma cells. Intratumoral MAIT cells had a gene signature which is associated with the T-cell exhaustion and poor patients' survival. Intratumoral MAIT cells more expressed CTLA-4 and LAG-3 compared to the intrahepatic MAIT cells. They also had poor cytokine and cytotoxic molecule production upon tumor cell-stimulation. Interestingly, the relative frequency of $CD8^-$ subpopulation among intratumoral MAIT cells was increased, and this subpopulation significantly expressed LAG-3 compared to the $CD8^+$ subpopulation. The anti-tumor function of $CD8^-$ intratumoral MAIT cells was improved by LAG-3 blockade, resulting in the reinvigoration of the function of total MAIT cell-population.
Conclusions: Our results suggest that MAIT cells and LAG-3 should be considered as cellular and molecular targets for the immunotherapy of HCC, and future experimental and clinical studies are needed.
Keywords: HCC, Immunotherapy, MAIT cells, LAG-3

PE-126

Diffusion-Weighted MR Imaging in Hepatocellular Carcinoma as a Predictor of a Response to Cisplatin-Based Hepatic Arterial Infusion Chemotherapy

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Aims: This study aimed to identify the utility of diffusion-weighted magnetic resonance (MR) imaging with an apparent diffusion coefficient (ADC) map as a predictor of the intrahepatic response of hepatocellular carcinoma (HCC) to cisplatin-based hepatic arterial infusion chemotherapy (HAIC).
Methods: We evaluated 113 consecutive patients with HCC who underwent after gadoxetic acid–enhanced and diffusion-weighted MR imaging were retrospectively evaluated. Significant findings for differentiating the two groups were identified at univariate and multivariate analyses. By using receiver operating characteristic analysis, the optimal cut-off values for quantitative variables were determined. The treatment response was evaluated using modified Response Evaluation Criteria in Solid Tumors. Overall survival times after HAIC were also compared between groups by log-rank tests.
Results: The appropriate cut-off for the tumor-to-liver ADC ratio was determined as 0.741. Of the 113 patients, 51 (45%) presented with a tumor-to-liver ADC ratio < 0.741. Evaluation of the intrahepatic treatment response after 2-3 cycles of HAIC in these 51 patients revealed that 20 patients (39%) experienced an objective response to HAIC. On the other hand, 10 of the 62 patients with a tumor-to-liver ADC ratio ≥ 0.741 (16%) experienced an objective response. Thus, the objective response rate was significantly higher in patients with a tumor-to-liver ADC ratio < 0.741 than in those with a tumor-to-liver ADC ratio ≥ 0.741 (P=0.006). Multivariate logistic regression analysis using parameters including perfusion alteration, percentage of a non-enhancing portion, and tumor-to-liver ADC ratio revealed that a tumor-to-liver ADC ratio < 0.741 (odds ratio 3.03; P=0.015) is a sole predictor of an objective response to HAIC. Overall survival rates were significantly higher in patients with objective responses to HAIC compared with those without ob-

jective responses (P=0.001 by log-rank test).
Conclusions: Patients with unresectable HCC with tumor-to-liver ADC ratio < 0.741 showed a favorable intrahepatic response to HAIC. Therefore, diffusion-weighted MR imaging can take a critical role as a predictor of a response to cisplatin-based HAIC in unresectable HCC.
Keywords: Hepatocellular carcinoma, Diffusion-weighted MR, Hepatic arterial infusion chemotherapy, Cisplatin

PE-127

Synergistic Activity of Paclitaxel and Sorafenib Against Liver Cancer Stem Cells

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Aims: Cancer stem cells (CSCs), also known as tumor-initiating cells (TICs), are suggested to be responsible for drug resistance and cancer recurrence. Current treatments with conventional chemotherapy are not highly efficient against the cancer stem cells (CSCs). The combination of anticancer drugs, of which functions are different from the other, enhances efficiency compared to the mono-therapy because it targets cancer cells in a synergistic or an additive manner. In this study, the effect of paclitaxel and sorafenib on cancer stem cells (CSCs) developed from mouse iPSCs in very low concentration was evaluated.
Methods: To investigate the effect of combination therapy, CSCs were exposed to paclitaxel and/or sorafenib at different concentrations of 1, 2 and 4 nM, respectively. Cell viability was assessed with 3-(4,5-dimethylthiazolyl)-2,5-diphenyltetrazolium bromide (MTT). The same concentrations of the agents were assessed for the effect on the self-renewal potential of CSCs subpopulation by sphere formation ability.
Results: As a result, a combination of sorafenib and paclitaxel significantly reduced the resistance while the CSCs exhibited drug resistance against paclitaxel alone. Also, combination of these agents reduces the self-renewal potential of CSCs when compared to single treatment. Simultaneously, combination significantly suppressed not only the colony formation but also the tube formation of the Cancer stem cells.
Conclusions: These results suggest the combination therapy of paclitaxel and sorafenib in low doses be an attractive approach to target cancer stem cells in the future.
Keywords: Liver cancer, Paclitaxel, Sorafenib

PE-128

Peritumoral Infiltration of T Cells and PD-L1-Expressing Tumor Associated Macrophages as a Potential Predictor of Lenvatinib Response

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Aims: Recently, lenvatinib was demonstrated to be non-inferior to sorafenib in a phase 3 randomized controlled trial in unresectable hepatocellular carcinoma (HCC). In this study, we investigated whether the response to lenvatinib is affected by the immunogenicity of the tumor.
Methods: Between April 2019 and March 2020, 10 patients with intermediate-to-advanced HCC who were administered lenvatinib treatment after liver biopsy were enrolled. Immunohistochemical staining and multi-color flow cytometry were performed with the liver biopsy specimen.
Results: Among 10 patients enrolled, 4 patients showed objective responses (complete response + partial response). Immunohistochemical staining of CD3, CD68, and PD-L1 demonstrated that patients with objective responses showed marked infiltration of T cells and PD-L1-expressing tumor-associated macrophages in intratumoral and peritumoral tissues than those without objective responses. There was a significant difference in the number of infiltrated T cells in responders than in non-responders (P<0.01). For the number of tumor-associated macrophages, there was no significant difference between the responders and the non-responders, although the number of PD-L1-expressing tumor-associated macrophages was significantly higher in responders than in non-responders (P<0.05). Flow cytometry analyses demonstrated the positive correlation of PD-L1 and HLA-DR (P<0.01), suggesting that PD-L1 expression in tumor-associated macrophages in HCC is associated with the capability of antigen presentation of these cells.
Conclusions: Tumor immunogenicity reflected by T cell and PD-L1-positive macrophage infiltration affects the responses to lenvatinib in unresectable HCC. This work was supported by the Scientific Research Fund of the Korean Liver Cancer Study Group. This research was also supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) and funded by the Ministry of Education (NRF-2019R1I1A1A01059642) (P.S.S.). This study was partly supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT)

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Keywords: Hepatocellular carcinoma, Lenvatinib, Tumor response, Immunogenecity

PE-129

Prognostic Molecular Signatures and S100P Expression in Resectable Hepatocellular Carcinoma

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Aims: Although hepatocellular carcinoma (HCC) is often recurred in patients undergoing curative hepatectomy, there are no faithful biomarkers to predict this undesirable events. Recent RNA-based efforts have developed valuable genetic markers or signatures prognostic of cancer outcomes. We aimed to discover molecular predictors of recurrence after HCC resection and to unveil the geno-molecular structure of the resected tumors in a series of Korean patients.
Methods: Based on transcriptomic and genomic data of 206 HCC samples surgically resected at Asan Medical Center, we performed differential gene expression analysis to find quantitative markers associated with early recurrence; and used unsupervised clustering method to classify molecular subtypes. Public RNA-sequencing datasets from Japan (RIKEN) and China (GSE14520) were also used to validate original findings.
Results: The results of differential gene expression analysis showed that S100P was identified as the highest-ranked overexpressed gene in HCCs with early recurrence within 2 years after surgery. This trend was also reproduced in immunohistochemical studies of the original and independent AMC cohorts. On multivariable competing risks modeling, S100P expression independently predicted HCC-specific mortality (adjusted hazard ratio, 1.09; $P<0.05$). Validation in the GSE14520 cohort and *in vitro* experiments confirmed the prognostic value of S100P for HCC recurrence. The c-statics of the S100P mRNA for predicting early recurrence confirmed that it had prognostic utility better than that of serum alpha-fetoprotein. We also identified five discrete molecular subtypes of HCC: the subtype with stem cell features ('AMC-C4') was associated with the worst prognosis both in our series and another two public datasets. S100P was most significantly upregulated in the subgroup C4 ($P<0.05$).
Conclusions: We discovered a promising prognostic biomolecule, S100P, associated with early recurrence after HCC resection, and verified geno-molecular architecture of tumors affecting clinical outcomes particularly in Asian patients. These new insights into molecular mediators would help to tailor care for affected Asians.
Keywords: Liver cancer, Biomarker, Recurrence, Classification

PE-130

MLH1 Single Nucleotide Variant in Circulating Tumor DNA Predicts Overall Survival in Patients with Hepatocellular Carcinoma

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Aims: We aimed to identify novel single nucleotide variant (SNV) in circulating tumor DNA (ctDNA) in patients with hepatocellular carcinoma (HCC).
Methods: Deep sequencing of plasma-derived ctDNA was performed using a panel of 2,924 SNVs in 69 genes from 59 patients with HCC. Validation of frequent SNVs (MLH1, STK11, PTEN, and CTNNB1) identified in ctDNA was conducted using droplet digital PCR (ddPCR) in 62 patients. Additionally, the presence of MLH1 and STK11 SNVs was determined in HCC tissues from 37 patients. Association between the presence of SNVs or the amount of ctDNA and clinical parameters and prognosis was determined in 107 patients.
Results: In 33/59 (55.9%) patients, at least one somatic mutation was detected using targeted deep sequencing of ctDNA. Among 25 SNVs in 12 genes, SNVs in KIT (17%), MLH1 (13%), STK11 (13%), PTEN (9%), and CTNNB1 (4%) were the most frequently observed. Using ddPCR, SNVs were detected in 22/62 (35.5%) patients with a frequency of 19% for MLH1 (chr3:37025749_T>A), 11% for STK11 (chr19:1223126_C>G), 8% for PTEN (chr10:87864461_C>G), and 0% for CTNNB1 (chr3: 41224610_C>T). MLH1 and STK11 SNVs in ctDNA were also detected in DNA derived from tumor tissues from all patients. The combination of the presence of MLH1 SNVs and increased ctDNA predicted overall survival in 107 patients.
Conclusions: MLH1 SNV (chr3:37025749_T>A) detection in ctDNA is feasible and can be used to detect somatic mutations in HCC. Furthermore, the MLH1 SNV in ctDNA predicts prognosis with or without determining the amount of ctDNA in patients with HCC.
Keywords: Hepatocellular carcinoma, Circulating tumour DNA, MLH1, Prognosis

PE-131

Dkk-1 Promotes Angiogenesis through Epithelial-Mesenchymal Transition in Hepatocellular Carcinoma

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Aims: Dickkopf-1(DKK1), a negative regulator of the Wnt/ß-catenin pathway, has been recently found to be up-regulated in hepatocellular carcinoma (HCC). However, the biological function of DKK1 in HCC has not yet been well documented. Our previous *in vitro* data suggest that DKK1 can enhance angiogenesis by endothelial cell, independent of the Wnt signaling pathway. This study aimed to investigate the tumorigenic potential and angiogenic role of DKK1 in mouse model.

Methods: We assessed tumorigenic functions of DKK1 in Hep3B cells expressing endogenous DKK-1 and in DKK1-deficient Hep3B cells created using CRISPR/Cas9 technology. These edited cells were injected subcutaneously in immunosuppressed mice and tumor growth was followed for 6 weeks. With the evidence of tumorigenic potential in DKK1, transgenic mouse models expressing DKK-1 or luciferase were developed using hydrodynamic transfection. Transposons encoding an activated form of human H-RAS were mixed with transposons encoding either DKK1 or luciferase. All mice were monitored at least twice per week and sacrificed when moribund. Subcutaneous tumors and tumor-bearing livers were formalin fixed for hematoxylin–eosin and immunofluoroscence staining.

Results: DKK1-deficient Hep3B xenografts exhibited significantly less growth compared to control Hep3B cells expressing DKK1. In addition, the forced expression of DKK1 with H-RAS through the hydrodynamic transfection formed many tumors in the liver, compared to luciferase liver. We investigated the expression of angiogenesis markers, including CD31, VEGFR2 and mesenchymal markers, including vimentin, fibronectin in the subcutaneous tumors and tumor-bearing livers. Quantity of angiogenic and mesenchymal cells were found to be reduced in the established DKK1 homozygous knockout mice (all $P<0.05$). Taken together, it was confirmed that the expression of CD31 ($P<0.0001$), VEGFR2 ($P<0.0001$), vimentin, and fibronectin ($P<0.0001$) were up-regulated with DKK1 in the mouse liver.

Conclusions: Our findings indicate that DKK1 appears to facilitate angiogenesis, and the progression of HCC through inducing the EMT.

Keywords: DKK1, Angiogenesis, EMT

PE-132

MiR-23b-3p Suppresses Migration, Invasion and EMT by Downregulating CD44 in Hepatocellular Carcinoma

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Aims: Cancer stem cells (CSC) play a key role in cancer invasion and metastasis. Among CSCs, CD44 has known as important modulators of epithelial-mesenchymal transition (EMT) together with transforming growth factor beta1 (TGF-ß1). EMT is epithelial cells lose their polarity and acquire mesenchymal cell migratory characteristics. miRNA could lead to either EMT through the regulation of various transcription factors. This study aimed to investigate the role of miR-23b-3p regulating the EMT, migration and invasion as well as CD44 expression in HCC cell lines.

Methods: We induced EMT by TGF-ß1 treatment or inhibited EMT by TGF-ß1 inhibitors. Also, miR-23b-3p mimic and inhibitor were transfected into HCC cell lines. The expression of EMT-related mRNA and protein were detected by quantitative real-time PCR and western blot. Also, EMT characteristics analyzed with cell migration and invasion.

Results: FACS analysis showed high expression of CD44 in two HCC cell lines with different levels of TGF-ß1 expression. TGF-ß1-negative SNU-354 cells were treated with TGF-ß1 to induce the EMT and TGF-ß1-positive SNU-368 cells were treated with TGF-ß1 inhibitor to induce the MET. The expression of miR-23b-3p was down-regulated during the EMT and up-regulated during the MET. The Inhibition of miR-23b-3p in SNU-354 cells promoted EMT, cell migration and invasion. In contrast, overexpression of miR-23b-3p in SNU-368 cells suppressed EMT, cell migration and invasion. In addition, TGF-ß1 stimulation after miR-23b-3p overexpression induced neither the mesenchymal phenotype nor cell migration. Also, CD44 is a target of miR-23b-3p. CD44 expression was increased in miR-23b-3p inhibitor cells, whereas miR-23b-3p overexpression cells reduced expression of the CD44 in HCC cells.

Conclusions: Overexpression of miR-23b-3p suppressed EMT, cell migration and invasion by targeting CD44. The results suggest that miR-23b-3p may serve as specific biomarkers and therapeutic targets for HCC.

Keywords: Hepatocellular Carcinoma (HCC), miR-23b-3p, CD44, Epithelial-Mesenchymal Transition (EMT)

PE-133

High Nuclear NADPH Oxidase 4 Expression Levels Are Correlated with Cancer Development and Poor Prognosis in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is typically associated with prolonged inflammation in the cirrhotic liver, which results in the transition from chronic inflammation and fibrosis to dysplastic or regenerative nodules or HCC. As we previously reported, the expression of NOX4 in HCC is the highest compared to paired control tissues and the expression of NOX2 is the highest among NOX family genes in HCC. However, our understanding of the association of NOX2 or NOX4 expression with clinicopathological values in HCC is limited. Our study aimed to investigate correlation NOX2 and NOX4 expression levels with clinicopathological factors of HCC patients.

Methods: A total of 134 matched tissue pairs of HCC cells and non-tumor hepatocytes from HCC patients were examined by immunohistochemical staining. Through these analysis, we tried to find the association of NOX2 and NOX4 expression with multiple clinicopathological parameters. Moreover, Immunoblotting in 4 HCC cell lines (HepG2, Hep3B, Huh-7, and SK-Hep-1) and reverse transcription digital droplet polymerase chain reaction (RT-ddPCR) in 20 pairs of HCC and non-tumor tissue samples were also performed to detect NOX4.

Results: Cytoplasmic NOX2 and nuclear NOX4 expression levels were shown by immunohistochemistry to be higher in HCC cells than in nontumor hepatocytes (P<0.001, each). The Western blotting results for NOX4 in 4 HCC cell lines were consistent with the immunohistochemical results. Increased cytoplasmic expression of NOX2 and NOX4 was significantly correlated with liver cirrhosis (P<0.001 and P<0.031, respectively). However, decreased cytoplasmic expression of NOX2 and NOX4 was significantly correlated with advanced pathologic TNM stage (P<0.029 and P<0.007, respectively). Multivariate analysis with clinicopathologic parameters showed that high nuclear and low cytoplasmic NOX4 expression levels are correlated with short overall survival (P=0 .021). Our findings imply that cytoplasmic NOX2 and nuclear NOX4 expression is upregulated during HCC development.

Conclusions: In particular, NOX4 translocation into the nucleus may affect the development and progression of HCC. NOX2 and NOX4 could be diagnostic markers and have therapeutic implications in HCC.

Keywords: NADPH Oxidase 4, NADPH Oxidase 2, Hepatocellular Carcinoma, Prognosis

PE-134

Overexpressions of P21 Activated Kinases and Snail in Patients with Advanced Hepatocellular Carcinoma

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Aims: Epithelial-to-mesenchyme transition (EMT) has been implicated in cancer progression, invasion and metastasis. It is known that P21 activated kinases (PAKs) and Snail are associated with EMT in various cancers. Recent report suggested that Snail's regulation may involve Rac1 signaling. The aims of study were to determine whether PAKs, Snail and Rac1 were overexpressed in patients with advanced hepatocellular carcinoma (HCC) and to identify mechanisms that can effectively inhibit PAKs and Snail *in vitro* study.

Methods: Fresh-frozen HCC samples and their adjacent normal hepatic tissues from 30 patients (men: 73.3%; mean age: 58.0±9.7 years) underwent surgical resection were provided by the Gachon University Gil Medical Center Biobank. Hep3B cells were transfected with control or Rac1-specific siRNAs for 72hrs. The expressions of PAK1, PAK2, Snail, Rac1 and GAPDH in HCC samples compared with adjacent tissues or cells were analyzed by immunoblotting. Cell migration was measured using transwell migration assay

Results: Among 30 patients with HCC, 63.3%, 23.3%, and 13.3% of the patients were stage I, II, and III, based on eighth edition AJCC TNM-staging, respectively. 80% of the patients tested positive for the hepatitis B surface antigen. The PAK1, PAK2, Snail, and Rac1 were all overexpressed in 5.3% of patients with TNM stage I, 42.9% of patients with TNM stage II, and 75% of patients with TNM stage III HCC, respectively (P=0.004). The PAK1, PAK2, and Snail were all overexpressed in 66.7% of HCCs with vascular invasion and in 4.8% of HCCs without vascular invasion (P=0.001). Rac1 knockdown significantly decreased the expression of PAK1, PAK2 and Snail in Hep3B cell. Rac1 knockdown suppressed the migration of Hep3B cells.

Conclusions: Overexpressions of PAKs, Snail, and Rac1 in patients with HCC were associated with advanced tumor stage and vascular invasion. Inhibition of Rac1 might reduce the expression of PAKs and Snail in HCC.

Keywords: P21 activated kinases, Snail, Hepatocellular Carcinoma, Rac1

PE-135

Cancer-Promoting Property of Circulating Exosomal microRNA-720 in Hepatocellular Carcinoma

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Aims: Exosomes are 30-150 nm-sized vesicles that are released from many cell types into the body fluids. Exosomal miRNAs have recently emerged as potentially promising biomarkers in cancers and play an important role in cell to cell communication. The aim of this study is to investigate exosomal miRNAs contributing to progression of hepatocellular carcinoma (HCC).
Methods: Microarray-based miRNA profiling was performed to explore potential markers on the whole blood samples from patients with various liver diseases. Exosomes were extracted using exoquick and miRNA expression was analyzed by qRT-PCR in sera of 45 healthy controls and 153 HCC patients treated with intra-arterial chemotherapy. Biological functions of selected exosomal miRNAs in tumorigenesis and disease outcomes were investigated with a series of *in vitro* experiments and clinical database.
Results: Microarray-based miRNA profiling revealed 10 miRNAs with differential expressions, of which miR-720 was further evaluated, due to its significant role in carcinogenesis and HCC progression. Transmission electron microscopy and immunoblotting for exosomal markers confirmed the isolation of circulating exosomes from the patients and cell culture media. Exosomal miR-720 correlated with tumor size and tumor stage progression. High exosomal miR-720 expression was associated with poor treatment response, overall survival as well as progression-free survival. Exosomes-mediated transfer of miR-720 promoted tumor cell proliferation as well as inhibited apoptosis of HCC cells.
Conclusions: Exosomal miR-720 has an oncogenic role by promoting cell proliferation and inhibiting apoptosis of HCC cells. Our findings suggest that exosomal miR-720 could be a potential prognostic biomarker for HCC.
Keywords: Hepatocellular carcinoma, Exosome, MiR-720, Progression

PE-136

WAVE2 Overexpression and Promoter Hypomethylation Is Associated with Poor Clinical Outcome in Hepatocellular Carcinoma

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Aims: Hepatocellular carcinoma (HCC) is the one of the most common cancers and lethal diseases in the world. *Wiskott-Aldrich Syndrome Protein Family Member 2* (*WAVE2*) overexpression is reported in HCC. However, the regulation mechanism of *WAVE2* and its effect on HCC progression is not well-known. We aimed to explore *WAVE2* regulation mechanism through methylation study and *WAVE2* role on HCC progression through *in vitro* study.
Methods: Methylation status of *WAVE2* was determined through profiling of promoter-region DNA methylation in HCC from The Cancer Genome Atlas (TCGA) data. Validation was performed with bisulfite-specific PCR sequencing and methylation-specific PCR analysis in 20 pairs HCC tissues with corresponding non-cancerous tissues. Targeted inactivation of *WAVE2* using siRNA was performed in HCC cell lines and cell growth and proliferation were examined.
Results: *WAVE2* was significantly overexpressed in HCCs compared to non-tumor tissues and associated with poor prognosis in overall survival and disease-free survival of patients in TCGA data. Also, we found inverse correlation between DNA methylation and gene expression of *WAVE2*, and *WAVE2* was significantly hypomethylated in human HCC compared to non-tumor. Targeted inactivation of *WAVE2* suppressed cell growth and proliferation of HCC cells, and reduced the metastatic potential of HCC cells by selectively modulating epithelial mesenchymal transition regulatory proteins.
Conclusions: We observed that *WAVE2* is significantly overexpressed and hypomethylated in HCC. Also, *WAVE2* up regulation is associated with poor prognosis in HCC patients. *WAVE2* activation might be one of the key mechanisms during liver tumorigenesis and can be a candidate of therapeutic target for HCC.
Keywords: HCC, *WAVE2*, DNA methylation

PE-137

Promising Fe3O4/CdSe Nanocomposites for Rug Delivery in Liver Cancer Treatment

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Aims: Nowadays, magnetic semiconductors nanocomposites have become a new class of materials of great importance promising with new properties and exploiting unique incorporation between materials. For example, one can make use of a variety of spin-related phenomena, not readily available in other materials.
this work concentrates on synthesis of magnetic iron oxide nanoparticles (MNs) and Cadmium Selenide (CdSe) quantum dots (QDs). CdSe QDs have attractive optical properties such as bright fluorescence emission and wide absorption band in the visible region and they possess the ability to act as energy donors through Förster resonance energy transfer (FRET). MNs also are known to have interesting applications in biomedical

field and drug delievery system.

Methods: In the present work, bi-functional magnetic–luminescent nanocomposites with Fe_3O_4 nanoparticles as the cores and CdSe as the shells have been synthesized by a facile direct precipitation method. Transmission electron microscopy (TEM) images revealed that the obtained bi-functional nanocomposites had a core–shell structure. The flower shape has been ascribed to the inhomogeneous growth of CdSe due to the presence of many active sites which turn to be nucleation centers for the CdSe on the surface of the nano-magnetite. The X-ray diffraction (XRD) patterns ensured the cubic spinel structure of the Fe_3O_4 core.

Results: Magnetic measurements indicated that the presence of CdSe in the composite has reduced its magnetic properties. Optical measurements of the Fe_3O_4/CdSe nanocomposites showed that the prepared samples have dual functions, optical tunable band gap similar to the semiconductor quantum dots and magnetic properties due to Fe3O4 nanoparticles. According to the values of Stokes shift of the new hybrid composites, one can suggest that they may be promising in drug delivery (liver cancer treatment). All of the first line of result idicate that all of fabricated samples are so promising in drug delivery system.

Conclusions: Fe_3O_4 nanoparticles has been successfully prepared by the co-precipetation method. The have been investigated via XRD, TEM and VSM. The XRD confirms the formation of the required cubic ferrite without other unwanted phases. The Fe_3O_4has been used as a seed or as a core to grow CdSe nanoshell around. The obtained hybrid Fe_3O_4 nanostructure has flower shape particles. The Fe_3O_4/CdSe nanocomposites has larger quantum yield values thanthose of pure CdSe QDs may be due to the fact that magnetic nanoparticles facilitate the electron holerecombination and enhance the emission from the quantum dots. In other words, the presence of Fe_3O_4 enhances the optical properties of CdSe quantum dots. The prepared nanocomposites have dual functions, optical tunable band gap similar to the semiconductor quantum dots and magnetic properties due to Fe_3O_4nanoparticles. This composite would be considered as dilute magnetic-semiconductor and could be used in spintronics, biosensors, solarcells and biomedical lables which could confirm that these nanoparticles could be a suitable drug delievery tool for many anticancer agent in the future.

Keywords: Magnetite, CdSe, Magnetization, Band gap

PE-138

Identification of Exosomal lncRNA Based Panel as Potential Diagnostic Marker of Early Stage Hepatocellular Carcinoma

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Aims: Currently, a reliable serum biomarker for hepatocellular carcinoma (HCC) has not been established, particularly for very early stage HCC (single tumor < 2 cm). We aimed to investigate diagnostic serum exosomal long non-coding RNA (exo-lncRNA) panel for very early stage HCC.

Methods: Driver oncogenic lncRNA (onco-lncR) candidates were selected by integrative analysis of lncR expression profiles from two different RNA sequencing datasets of human HCC (Catholic_LIHC and TCGA_LIHC). Expressions of selected onco-lncRs in serum exosome were measured using quantitative real-time PCR (RT-qPCR). Diagnostic performances of serum exo-lncRs for early stage HCC were evaluated in the test cohort (N=44) and validation cohort (N=139). The sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) were calculated for candidate lncRNAs and the current HCC biomarker, alpha-fetoprotein (AFP). Serum exo-lncR panels were developed using a logistic regression model, and their diagnostic performance was evaluated.

Results: Six promising driver onco-lncRs, DLEU2, HOTTIP, MALAT1, NEAT1, SNHG1, and TUG1, were identified. were markedly up-regulated in HCC in two different RNA sequencing datasets, and were also known to play important role in various caner by Lnc2Cacner 2.0 database. Among the six candidates, four serum exo-lncRs (DLEU2, HOTTIP, MALAT1, and SNHG1) showed promising performance in the test cohort with area under the receiving operator curve (AUROC) > 0.8. In our validation study, serum exo- MALAT1 could diagnose HCC in all stages (AUROC = 0.908), even in very early stages (AUROC = 0.920), with a greater accuracy than candidate serum exo-lncRs and serum AFP.

Conclusions: In conclusion, exo- MALAT1-based serum panel is a promising diagnostic marker for very early stage HCC.

Keywords: Hepatocelluar carcinoma, Exosomal lncRNA, LncRNA panel, Diagnostic marker

PE-139

Hepatic Artery Chemoembolization for Management of Patients with Advanced Metastatic Carcinoid Tumors

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Aims: Patients with advanced metastatic carcinoid tumors who have disease progression despite conventional therapy are left with few therapeutic options. Hepatic artery chemoembolization (HACE) may play a role in palliating these patients' symptoms.

Methods: Fifteen patients with biopsy-proven advanced bilobar hepatic carcinoid metastases who demonstrated progression of symptoms and/or tumor size despite treatment with somatostatin analogues were treated with intra-arterial chemotherapy and HACE to determine efficacy and safety. Five days of intra-arterial 5-fluorouracil (1 g/m2) were followed by HACE

with adriamycin (60 mg), cisplatin (100 mg), mitomycin C (30 mg), and polyvinyl alcohol (Ivalon); 200 micron to 710 micron). Patients were continued on octreotide at the same dose (150 to 2000 microg subcutaneous q 8 hours) before, during, and after the procedure.

Results: Efficacy of treatment was assessed by comparing pre-treatment and 3-month clinical, laboratory, radiographic, and quality of life parameters. Symptoms were improved in 8 of 12 patients who had diarrhea, 7 of 12 who had flushing, 9 of 12 who had abdominal pain, and in 4 of 7 who had malaise. Elevated tumor markers decreased in all patients. Biochemical markers (mean +/- SE) at 3 months decreased by 60% +/- 6% for 5-HIAA, 75% +/- 10% for chromogranin A and 50% +/- 7% for neuron-specific enolase.

Conclusions: Hepatic artery chemoembolization improves symptoms of carcinoid syndrome, has a high tumor response rate, and improves short-term quality of life in this group of patients with advanced hepatic carcinoid disease.

PE-140

Fixed Dose Combination Therapy Metformin and Quercetin Ameliorates Diethylnitrosamine-Induced Liver Cancer in Rats via Inflammatory Pathway

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Aims: Hepatocellular carcinoma (HCC) is the most mortal cancer (5 year survival under 11%) and HCC is the 3 most frequent cause of cancer related death in male and 6th most common in women. Still, the treatment of HCC is limited. Systemic chemotherapy for HCC, either as single drug therapy or in combination therapy, radiofrequency ablation or recently introduced tyrosine kinase inhibitors, e.g. sorafenib, are some promising options. The aim of the current study was to scrutinize the synergistic chemo-protective effect of metformin (5 mg/kg) in combination with quercetin in diethylnitrosamine (DEN) induced HCC rats.

Methods: Single intraperitoneal injection of DEN (160 mg/kg) was used for the induction of HCC. The rats divided into different groups and received the combination of metformin and quercetin. Hepatic, antioxidant, pro-inflammatory, inflammatory mediators and apoptosis marker were estimated. Morphological and histopathological component of hepatic tissue were estimated.

Results: Combination therapy of metformin and quercetin down-regulated the AFP (83%) level along-with the hepatic nodules. Combination therapy reduced the hepatic parameters AST (74.5%), ALP (68.5%), ALT (73.4%), CEA (43.5%); antioxidant parameter LPO (64.5%), CAT (73.4%), SOD (65.4%), GST (56.3%), GPx (59.4%), respectively. Combination therapy reduced the inflammatory mediators such as COX-2 (65.5%), PGE2 (63.4%), NF-kB (73.4%) and apoptosis marker such as caspase-3 (54.5%) and caspase-9 (65.5%), respectively. Histopathological investigation support the above hepatic cancer effect of combination therapy.

Conclusions: Our result shows that this remarkable combination has remarkable treatment for HCC in rats via inflammatory and apoptosis pathway.

PE-141

Hepatic Stem Cell-Like Subtypes of Hepatocellular Carcinoma Revealed from the Integrative Multi-Omics Analysis Using Developmental Hierarchies

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Aims: Hepatocellular carcinoma (HCC) is lethal malignancy showing high relapse rates after curative resection in early-stage. Aggressive tumor biology in resectable HCC remains unclear.

Methods: Using human fetal liver signatures, Multi-omics dataset from multiple clinical HCC cohorts were analyzed comprehensively to reveal molecular mechanisms for HCC stemness as well as potential biomarkers to enhance therapeutic efficacy for molecular targeted therapy or immunotherapy in stem cell-like HCC subtypes.

Results: The patients predicted to the hepatic stem cell (HS) subtype showed aggressive tumor features including large tumor size, high AFP, vascular invasion, and extrahepatic metastasis as well as worst prognosis with early recurrence even in early-stage. The oncogenic pathways in terms of cell cycle, epithelial-mesenchymal transition, and TGF-beta pathway were highly upregulated in the HS subtype. Higher mutations of TP53, RB1 with PTEN deletion were significantly identified in the HS subtype. We also identified subtype-specific tissue and serum biomarkers. Predicted responders for immunotherapy were significantly lower in stem cell-like subtypes due to higher accumulation of TAM and MDSC. The HS subtype showed potential higher response to multi-tyrosine kinase inhibitors, especially sorafenib and lenvatinib.

Conclusions: Stem cell-like HCC is not only associated with a significantly higher relapse rate after curative resection but also with molecular biology for the aggressive subtype of HCC. We identified subtype-specific serum and tissue biomarkers for the stem cell-like subtypes and precise therapeutic strategies for each subtype regarding immunotherapy and molecular-targeted treatment. Our findings may offer the theoretical foundation of biomarker-based clinical trials for new therapeutic approaches to resectable early-stage HCC patients.

PE-142

Protective Effect of Biofabricated Trianthema Portulacastrum Silver Nanoparticles Against Hepatocellular Carcinoma

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Aims: Over the recent years, nanoparticle approach for targeted drug delivery is considered as a promising therapeutic method to improve the potential of antitumor agents. Since Trianthema portulacastrum (TP) leaves have been utilized as a strong hepatoprotective in Indian traditional medicinal system. Thus current study was designed to biofabricate, characterize and evaluate protective effect of TP extract mediated silver nanoparticles (AgTPNPs) against diethylnitrosamine (DEN) induced hepatocarcinoma in rat model.

Methods: AgTPNPs were synthesized by co-precipitation method and different characterization techniques confirmed the formation of spherical crystalline nanoparticles with size range of 50-80 nm. Liver damage in rats was induced with a single dose of DEN (200 mg/kg) as well as double dose of phenobarbital. Simultaneously, animals were administered with AgTPNPs at two dose levels (10 and 20 mg/kg p.o.) for 16 weeks. At the end of study, serum biomarkers, hematological status, antioxidants enzymes and proinflammatory cytokines were examined to assess the protective effect of AgTPNPs along with histopathological studies.

Results: DEN significantly induced the hepatocellular carcinoma in each group, which was significantly reversed ($P<0.001$) by AgTPNPs in a concentration dependent manner. A significant reduction in level of serum hepatic and non-hepatic marker enzymes, oxidative stress and different inflammatory markers via direct and indirect inhibition of NF-kB expression were observed in rats administered with AgTPNPs.

Conclusions: Collectively, results demonstrated that AgTPNPs potentially ameliorated the damaging effects of DEN induced hepatocellular carcinoma and it can be utilized as an effective nano technology based anticancer approach.

PE-143

miR-4790-3p Promotes the Survival of Hepatocellular Carcinoma Cells by Inhibiting ZNF225 mRNA by Enhancing Autophagy

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Aims: It is a challenge to overcome the low response rate of everolimus in the treatment of patients with hepatocellular carcinoma (HCC). To overcome this challenge, researchers combined everolimus with Ku0063794, the inhibitor of mTORC1 and mTORC2, to achieve higher anticancer effects.

Methods: However, the precise mechanism for the synergistic effects is not clearly determined yet. We first selected miRNAs that showed the most significant variation in expression according to the mono- and combination therapy of everolimus and Ku0063794. Subsequently, we determined the role of specific miRNAs in the anticancer effects of combination therapy against HepG2 cells through overexpressing or inhibiting the specific miRNAs.

Results: Compared to individual monotherapies, everolimus and Ku0063794 combination therapy significantly reduced viability, increased apoptosis, and reduced autophagy in HepG2 cells. The analysis of the miRNA array revealed that the expression of miR-4790-3p was significantly increased following everolimus monotherapy, decreased following Ku0063794 monotherapy, and significantly decreased following combination therapy. ZNF225, a target mRNA of miR-4790-3p, was significantly highly expressed in HepG2 cells following combination therapy.

Conclusions: miR-4790-3p promotes autophagy in HepG2 cells by inhibiting the expression of ZNF225. Everolimus and Ku0063794 combination therapy has superior anticancer effects against HCC cells, in part because it significantly reduces the expression of miR-4790-3p that plays an essential role in increasing autophagy.

PE-144

Activated Human Fetal Mesenchymal Stem Cells Exhibit Antitumor Activity toward Hepatocellular Carcinoma *in Vitro*

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Aims: Hepatocellular carcinoma (HCC) recurrence rate after liver transplantation (LT) consists of 10%-20% and remains the leading cause of cancer-related death. In recent decades there are a lot of studies have shown that cytokine stimulated lymphocytes, containing much of effector cells, from allogeneic donor, have a vigorous anticancer effect. However, a single treatment with activated lymphocytes might lead to limited effects. We aimed to develop a new therapeutic approach for the efficient expansion of such innate components of cellular immunity obtained from the mesenchymal stem cells.

Methods: Human fetal mesenchymal cells were cultured in the presence of cytokines. The phenotype and characterization of

activated cells were identified and the cytotoxicity against tumor was determined.

Results: After being cultured for 17 days the proportion of cell fractions in the expanded cells varied among individuals. The average proportion of $CD56^+CD3^-$, $CD56^+CD3^+$ and $CD56^-CD3^+$ was 15.4% (range, 3.1%-39.7%), 10% (range, 2.2%-37%) and 58.4 (range, 17.9%-91.8%), respectively. The brief pre-activation of expanded cells exhibit enhanced expression of IFN-γ, TNF-α, Granzyme B and TNF-related apoptosis-inducing ligand (TRAIL) on their surface. Furthermore, these cells showed vigorous anticancer ability *in vitro*, at an effector-target cell ratio of 40:1, effector cells destroyed 63% (±10.1) of HCC cell line.

Conclusions: These findings suggest that repeated adoptive immunotherapy using activated human fetal mesenchymal cells might be a promising approach for inducing innate immunity to decrease the incidence of cancer recurrence after liver transplantation.

Liver Cirrhosis, Portal Hypertension with Cx. Clinical

PE-145

Bone Mineral Density Using Computed Tomography as a Useful Predictor for Long-Term Mortality in Patients with Cirrhosis

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Aims: Sarcopenia and osteoporosis are frequent complications in patients with liver cirrhosis. The aim of this study was to investigate the prognostic impact of skeletal muscle mass and bone mineral density in these patients.

Methods: We included retrospectively cirrhotic patients who underwent both computed tomography scans (CT) and hepatic venous pressure gradient (HVPG) measurement between December 2009 and March 2015. Single transverse CT image at the level of the third lumbar vertebra (L3) were used to evaluate skeletal muscle area, visceral and subcutaneous fat. The mean CT attenuation of the trabecular bone of the vertebral body in L4 ($L4_{HU}$) was measured.

Results: A total of 160 cirrhotic patients were enrolled. The mean age of the patients was 52.9 years with men predominating (n=116, 72.5%) and most of the cause was alcohol (62.5%). Forty-nine patients (30.6%) died during a median follow-up period of 39.6 months (range, 3.6–87.6). In multivariate analyses, HVPG (hazard ratio [HR] 1.069, 95% confidence interval [CI] 1.011-1.130; *P*=0.018), Model for End-Stage Liver Disease (MELD) scores (HR 1.081, 95% CI 1.014-1.153; *P*=0.018), presence of sarcopenia (HR 1.859, 95% CI 1.004-3.443; *P*=0.049) and $L4_{HU}$ (HR 1.839 for $L4_{HU}$ < 145 HU, 95% CI 1.013-3.338; *P*=0.045) were independently associated with long term mortality. In patients with low MELD score (<10), HVPG (HR 1.161, 95% CI 1.040-1.296; *P*=0.008) and $L4_{HU}$ (HR 4.173 for $L4_{HU}$ < 145 HU, 95% CI 1.501-11.598; *P*=0.006) were independent predictors of mortality, but and presence of sarcopenia was not significant.

Conclusions: Muscle mass and bone mineral density, together with the known MELD and HVPG, were associated with long-term prognosis in cirrhotic patients. Especially, in low MELD score, low bone mineral density was independently associated with long-term mortality. It is necessary to identify prognostic roles of liver-muscle-bone according to the degree of cirrhosis.

Keywords: Bone Mineral Density, Cirrhosis, Sarcopenia, Prognosis

PE-146

Clinical Usefulness of Serum M2BPGi Levels on Identifying Liver Cirrhosis in Patients with Chronic Liver Disease

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Aims: Mac-2 Binding Protein Glycosylation isomer (M2BPGi) is a novel serological glyco-biomarker for predicting liver fibrosis. However, there was lack of data to use M2BPGi in Korean patients with chronic liver diseases. We aimed to evaluate its role of diagnosing liver cirrhosis (LC) in Korean patients.

Methods: We reviewed medical records for 258 patients that were performed serum M2BPGi in Kosin University Gospel Hospital from January 2016 to October 2018. The diagnostic accuracy of serum M2BPGi values was compared to that of other fibrosis markers, the aspartate transaminase to platelet ratio index (APRI), the fibrosis index based on four factors (FIB-4), and the gamma-glutamyltranspeptidase to platelet ratio (GPR) using receiver operating characteristic (ROC).

Results: The mean (±SD) of age of study patients was 61.2 (±10.6) years and the proportion of male was 73.6%. 103 (39.9%) patients were positive for hepatitis B virus (HBV) and 45 (17.4%) were positive for hepatitis C virus (HCV). 178 (69.0%) patients were diagnosed LC. The mean (±SD) of serum M2BPGi level showed significant differences between LC group (5.06±3.89) and non-LC group (1.77±2.64) (*P*<0.001). The M2BPGi levels correlated with APRI (r=0.444), FIB-4 (r=0.512), GPR (r=0.155), respectively (all *P*<0.001). The area under the curve of serum M2BPGi for prediction of LC (0.798) was higher

than that of APRI (0.714), FIB-4 (0.767) and GPR (0.635), respectively. The cutoff value of serum M2BPGi that maximized the sum of sensitivity (80.3%) and specificity (71.2%) was 1.72. Adjusting for sex, age, alcohol intake, HBV and HCV, M2BPGi level was an independent predictor of LC [adjusted odds ratio (OR): 1.51, 95% confidence interval (CI) 1.30-1.75, *P*<0.001].

Conclusions: Serum M2BPGi could be a reliable non-invasive marker for identifying LC in Korean patients with chronic liver diseases.

Keywords: Liver fibrosis, Cirrhosis, Mac-2 Binding Protein Glycosylation isomer

PE-147

Is MELD Score Enough to Predict Mortality in Cirrhotic Patients Undergoing Hip Fracture Surgery?: The Importance of Post-Operative Evaluation of Kidney Injury Based on ICA Criteria

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Aims: Fracture is increased in cirrhotic patients. And acute kidney injury is important factor to predict the prognosis of cirrhotic patients. We evaluated prognostic factors and analyzed the impact of acute kidney injury (AKI) in cirrhotic patients undergoing hip fracture surgery along with liver function.

Methods: A total of 75 cirrhotic patients with hip surgery were retrospectively enrolled between 2006 and 2017. We compared the clinical characteristics according to stage progression of AKI and evaluated risk factors for in-hospital, 1-year and overall mortality after hip fracture surgery to use baseline charateristics,the cause of cirrhosis, model for end stage liver disease (MELD) score, ICA(International Club of Ascites)-AKI criteria, operation record, the present of cirrhotic complication, and surgical outcome.

Results: Six patients (8%) died after hip surgery during hospitalization. The MELD score at admission was an independent risk factor for in-hospital mortality. (Hazard ratio (HR)1.26, *P*=0.033) MELD score over 15.5 was associated with in-hospital mortality. (sensitivity 100%, specificity 76%).In the deceased patients during hospitalization, the patients with high MELD score, the present of cirrhotic complication and progression of AKI after hip fracture surgery were more frequent. Specially, in a group of stage progression of AKI after surgery (n=12, 16%), higher BMI and MELD score were observed along with worse in-hospital, 1 year and overall mortality than another. Deceased patients in one year and overall period after surgery were 23 patients (30.7%) and 48 patients (64.0%), respectively. The stage progression of AKI was the risk factor for 1year (HR 2.94, *P*=0.015) and overall mortality (HR 2.43, *P*=0.014) as well as MELD score in multivariate analysis.

Conclusions: The stage progression of AKI is a prognostic factor on short term and long term mortality along with MELD score in cirrhotic patients underwent hip fracture surgery.

Keywords: Liver cirrhosis, Acute kidney injury, Hip fracture

PE-148

Age and Height Should Be Considered in the Assessment of Spleen Size in Patients with Compensated Advanced Chronic Liver Disease

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Aims: We investigated the performance of spleen size in predicting presence of varices in patients with compensated advanced chronic liver disease (cACLD), considering the impact of age and height in spleen size.

Methods: Patients with cACLD, defined as liver stiffness (LS)≥10 kPa with transient elastography, who underwent upper gastrointestinal endoscopy and abdominal ultrasound were included.

Results: A total of 1218 patients were included. Mean age was 56.0 years. Mean LS and spleen diameter were 24.2 kPa and 11.3cm, respectively. Varices were combined in 533 patients (43.8%). On multivariate analysis, older age, lower platelet count, lower albumin level, higher LS, and longer spleen diameter were significantly associated with the presence of varices (all *P*<0.05). On multivariate analysis for the factors associated with spleen size, younger age, taller height, alcoholic etiology, lower albumin level, higher MELD score, and higher LS were significantly associated with the longer spleen size. Using these results, formula for predictive spleen size was conducted as follows: Estimated spleen size (cm)=0.029 × height (cm) – 0.019 × age (year) + 6.670. Interestingly, estimated and measured spleen size was comparable in patients without varices (10.5cm vs. 10.4cm, *P*=0.134), while measured spleen size was significantly greater than estimated spleen size in patients with varices (12.4cm vs. 10.3cm, *P*<0.001). The ratio of measured and estimated spleen sizes (MESS ratio) were calculated as follows: MESS ratio=measured spleen size (cm)/estimated spleen size (cm). AUROC of MESS ratio for the prediction of varices was significantly higher than that of measured spleen size (0.729 vs

0.721, *P*=0.005). Optimal cutoff value of MESS ratio was 1.042 with sensitivity, specificity, PPV, and NPV of 73.0%, 61.0%, 59.3%, and 74.4%, respectively.

Conclusions: Younger age and taller height is associated with greater spleen diameter. It should be considered in evaluating performance of spleen size in predicting varices in patients with cACLD.

Keywords: Spleen, Age, Height, Compensated advanced chronic liver disease

PE-149

Diagnostic Usefulness of the Spot Urine Sodium/Potassium Ratio in Cirrhotic Patients with Ascites

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Aims: A low-salt diet is considered important for the control of ascites in cirrhotic patients. The 24-hour (24-h) urine sodium (Na) excretion test is a standard method performed to determine low-salt diet compliance. Considering that measuring 24-h urine Na excretion is a time-consuming method, the spot urine Na/potassium (K) ratio can be alternatively measured. However, whether 24-h urine Na excretion can be alternatively replaced with the spot urine Na/K ratio has not been fully validated yet. Hence, this study aimed to validate whether the spot urine Na/K ratio could replace 24-h urine Na excretion in assessing low-salt diet compliance.

Methods: A total of 192 patients with liver cirrhosis and ascites were screened. We prospectively studied 175 patients who met the inclusion criteria. Furthermore, 24-h urine collection was performed, and 5-mL spot urine was collected in the morning. Subsequently, 24-h urine Na, creatinine (Cr) level, and spot urine Na and K were assessed. A complete urine collection was confirmed based on 24-h Cr excretion levels of 15 mg/kg/day for men and 10 mg/kg/day for women. The area under the receiver operating characteristic (AUROC) curve analysis was performed to evaluate the feasibility of the spot urine Na/K ratio in predicting 24-h urine Na greater than 78 mmol/day.

Results: Out of the 175 patients, 24-h urine samples were completely collected in 57 patients only. Moreover, urine samples were not completely collected in 118 patients because their 24-h urine Cr excretion level was less than the established criteria. There was no significant difference in age, sex, etiology of liver cirrhosis, Child-Pugh class, and Model for End-Stage Liver Disease score between the two groups. In the complete urine collection group, the AUROC curve for the spot urine Na/K ratio in predicting 24-h urine Na greater than 78 mmol/day was 0.874 ± 0.051 (*P*<0.001). In the incomplete urine collection group, the AUROC was 0.832 ± 0.039 (*P*<0.001). Both groups showed similar AUROC values. In the complete urine collection group, the classical cutoff value greater than 1.0 of the spot urine Na/K ratio showed 90.9% sensitivity, 56.0% specificity, 73.2% positive predictive value (PPV), and 82.4% negative predictive value (NPV). The best cutoff value for the spot urine Na/K ratio was 1.5, with 87.9% sensitivity and 80.0% specificity. In all patients, the AUROC was 0.841 ± 0.031 (*P*<0.001), with 94.1% sensitivity, 47.9% specificity, 71.6% PPV, and 85.4% NPV when the cutoff value of the spot urine Na/K ratio was 1.0. Among the studied patients, 131 collected their urine during hospitalization. Complete urine collection did not differ between the inpatient group (34.4%) and the outpatient group (29.5%) (*P*=0.348).

Conclusions: The spot urine Na/K ratio reflects 24-h urine Na, but the AUROC value obtained in this study is lower than that of a previous study. However, drawing conclusions based on the results of the study is difficult considering the large number of patients with incomplete urine collection. Even in hospitalized patients, several incomplete urine collections are observed, making it difficult to accurately check 24-h urine Na. Therefore, a method that more easily identifies low-salt diet compliance in cirrhotic patients with ascites is required in the future.

Keywords: Ascites, Spot urine Na/K, 24 hour urine Na

PE-150

Laparoscopic Liver Resections in Normal and Cirrhotic Livers

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Aims: Liver surgery in patients with underlying liver disease results in higher mortality and morbidity rates compared to patients without underlying liver disease. Laparoscopy seems to have good results in patients with normal liver in terms of postoperative outcomes, but is more challenging in cirrhotic patients. Aim of this study was to evaluate the feasibility of laparoscopic liver resection both in normal and cirrhotic livers, and secondary endpoint was to compare the surgical results.

Methods: We retrospectively evaluated 86 patients who underwent laparoscopic liver resection between January 2001 and November 2016. Candidates for laparoscopic liver resection were divided into two groups according to the presence or absence of an underlying liver disease.

Results: 86 patients (52.4% males, median age 56.1 years) were enrolled, and 37.1% had liver cirrhosis. Hepatocellular carcinoma in hepatitis C virus-related cirrhosis (89.7%) and liver metastases (57.6%) were the main indications for surgery

in patients with cirrhosis and non-cirrhotic livers, respectively. None of the patients died post-operatively. Cirrhotic patients had greater blood loss (100 vs 50 ml; *P*<0.012) and longer hospital stays (6 vs 4 days; *P*<0.031) compared to non-cirrhotics.
Conclusions: Laparoscopic liver resections are safe and feasible procedures in both patients with cirrhotic and non-cirrhotic livers.
Keywords: Laparoscopic liver resections, Cirrhotic livers, Hepatocellular carcinoma, Hepatitis C virus

PE-151

Prognosis and Determinants of Pregnancy Outcome among Patients with Post-Hepatitis Liver Cirrhosis

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Aims: To evaluate maternal, fetal, and neonatal outcomes and their associated risk factors among pregnant women with liver cirrhosis (LC).
Methods: A prospective cohort study was conducted at Regional Clinical Hospital Shymkent, Kazakhstan, between April 1, 2009, and May 1, 2017. Participants included 129 pregnant women with LC (study group), 647 pregnant women without LC (control group 1), and 853 non-pregnant women with LC (control group 2). Univariate and multivariate analyses were performed.
Results: Maternal, fetal, and neonatal complication rates were significantly higher in the study group than in control group 1 (*P*=0.001 for all complications). The rate of hepatic decompensation (HD) was higher in the study group than in control group 2 (63.6% vs 13.6%; *P*=0.001). Maternal mortality was higher in the study group (7.8%) than in either control group 1 (0.2%) or control group 2 (2.5%; *P*=0.001). Variceal bleeding during vaginal delivery was the most frequent cause of maternal mortality. Vaginal delivery and increasing gestational age were the key variables affecting the rate of HD (*P*=0.001 for both).
Conclusions: The presence of LC during pregnancy was associated with high rates of maternal and neonatal complications. Increasing gestational age and vaginal delivery were the most important risk factors for HD.
Keywords: Liver cirrhosis, Post-hepatitis, Fetal, Neonatal

PE-152

The Usefulness of Diffusion-Weighted Imaging in the Characterization of Liver Lesions in Patients with Cirrhosis

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Aims: To evaluate if diffusion-weighted imaging (DWI) is useful in characterizing liver lesions in patients with cirrhosis.
Methods: A retrospective review revealed 37 patients with cirrhosis who had 41 histologically proven hepatocellular carcinoma (HCC) lesions. Another 20 patents with cirrhosis had 29 solid nodules that remained stable for at least 12 months and were deemed to be benign hepatic nodules (BHN). Of the HCC lesions, 14 were well-differentiated (WD HCC), 20 were moderately differentiated, and seven were poorly differentiated histology. For all lesions, two reviewers analysed signal characteristics and made apparent diffusion coefficient value (ADC) measurements.
Results: Visual analysis of DWI was useful in that no HCC was hypointense and no BHN was hyperintense to liver. Visual analysis of DWI was not useful in separating WD HCC from higher grades. There was substantial overlap in ADC values of the HCC and BHN. Among HCC lesions, ADC values of more than 0.99 × 10(-3) mm(2)/s had sensitivity and specificity of 85% and 86% for reviewer 1, and 63% and 64% for reviewer 2 in diagnosing WD HCC.
Conclusions: ADC measurements of BHN were higher than that of HCC, and the ADC values of WD HCC were higher than that of more aggressive grades of HCC. However, quantitative measurements may not help in determining the histological grade of individual cases of HCC.
Keywords: Diffusion-weighted imaging, Hepatocellular carcinoma, Liver cirrhosis, Apparent diffusion coefficient

PE-153

Platelet Count Spleen Diameter Ratio to Predict Esophageal Varices in Mongolian Patients with Liver Cirrhosis

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Aims: Portal hypertension commonly accompanies the presence of liver cirrhosis, and the development of esophageal varices is one of the major complications of portal hypertension. To validate whether the platelet count/spleen size ratio can be used to predict the presence of esophageal varices in Mongolian patients with hepatic cirrhosis.
Methods: This was a cross-sectional study to validate the diagnostic test for hepatic cirrhosis and was performed between 2017 to 2019. Only stable patients were included in the study. Patients with active gastrointestinal bleeding at the time of admission were excluded. All patients underwent screening upper gastrointestinal endoscopy. Biochemical parameters were evaluated, and ultrasound was used to measure the longest diameter of the spleen. The platelet count/spleen diameter ratio was calculated and analyzed to determine whether it can predict the presence of esophageal varices.
Results: A total of 62 patients were included. The mean age was 48.23 ± 14 years; 34 (55%) were men, and 28 (45.0%)

women. Child-Pugh classification, 34 (55%) patients were classified as class A, 22 (36%) as class B, and 6 (9%) as class C. The platelet count/spleen diameter ratio to detect esophageal varices independent of the grade showed using a cutoff value of ≤884.3, had 83% sensitivity, 72% specificity, and positive and negative predictive values of 93% and 41%, respectively.

Conclusions: The platelet count to spleen diameter ratio may be a useful tool for diagnosing EVs in liver cirrhosis noninvasively when endoscopy facilities are not available.

Keywords: Liver Cirrhosis, Esophageal Varices

PE-154

Empirical Treatment with Carbapenem vs Third-Generation Cephalosporin for Treatment of Spontaneous Bacterial Peritonitis: A Multicenter Study

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Aims: Third-generation cephalosporins (TGCs) are recommended as first-line antibiotics for treatment of spontaneous bacterial peritonitis (SBP). However, antibiotics against multidrug-resistant organisms (such as carbapenems) might be necessary. We aimed to evaluate whether carbapenems are superior to TGCs for treatment of SBP.

Methods: We performed a retrospective study of 865 consecutive patients with SBP (275 culturepositive; 103 with TGC-resistant bacterial infections) treated at 7 referral centers in Korea, from September 2013 through January 2018. The primary outcome was in-hospital mortality. We made all comparisons using data from patients whose baseline characteristics were balanced by inverse probability of treatment weighting.

Results: Of patients who initially received empirical treatment with antibiotics, 95 (11.0%) received carbapenems and 655 (75.7%) received TGCs. Among the entire study cohort, there was no difference in in-hospital mortality between the carbapenem (25.8%) and TGC (25.3%) (adjusted odds ratio [aOR], 0.97; 95% CI, 0.85–1.11; *P*=.66). In the subgroup of patients with high chronic liver failure-sequential organ failure assessment (CLIF-SOFA) scores (score of 7 or greater, n=314), carbapenem treatment was associated with lower in-hospital mortality (23.1%) than in the TGC group (38.8%) (aOR, 0.84; 95% CI, 0.75–0.94; *P*=.002). In contrast, among patients with lower CLIF-SOFA scores (n=436), in-hospital mortality did not differ significantly between the carbapenem group (24.7%) and the TGC group (16.0%) (aOR, 1.06; 95% CI, 0.85–1.32; *P*=.58).

Conclusions: For patients with SBP, empirical treatment with carbapenems does not reduce in-hospital mortality compared to treatment with TGCs. However, among critically ill patients (CLIF-SOFA scores ≥7), empirical carbapenem treatment was significantly associated with lower in-hospital mortality than TGCs.

Keywords: Cirrhosis, Ascites, Risk of death, Therapy

PE-155

The Outcome of Thoracentesis versus Pigtail catheter for Hepatic Hydrothorax

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Aims: Hepatic hydrothorax (HH) is a rare complication and associated with poor clinical outcome in patients with cirrhosis. Conservative management for HH includes salt restriction and administration of diuretics, often with percutaneous drainage; thoracentesis, catheter drainage, and chest tube drainage. Therapeutic thoracentesis is a simple that can provide rapid relief of symptoms though it is temporary and repeated. We aimed to evaluate the efficacy and safety the use of pigtail catheters insertion compared to intermittent thoracentesis.

Methods: This multicenter retrospective study included 136 cirrhotic patients with pleural fluid from March 2012 to June 2017. Cirrhosis patients with transudate pleural effusion greater than 500ml are included, other neoplasm and cardiopulmonary disease and infectious condition were excluded.

Results: There were 115 cases of pigtail catheter insertion and 25 cases of intermittent thoracentesis. The mean MELD scores of the enrolled patients were 19.71 ± 7.85 and 21.57 ±8.39, respectively (*P*=0.32). The median catheter dwelling time was 8 days in pigtail catheter group. Spontaneous pleurodesis was occurred in 59 cases (51%) in pigtail group. Bleeding complica-

tion and empyema were occurred in pigtail group. The median hospitalization period was 19 day in pigtail group and 31 day in thoracentesis group (*P*=0.83). The overall 1-year mortality for patients treated with pigtail catheter insertion versus thoracentesis was 40.9% (n=47) and 71.4% (n=15), respectively. There was no difference in survival rate between pigtail catheter group and thoracentesis group (*P*=0.19). Re-admission rate for 1 year did not differ between pigtail catheter insertion group and thoracentesis group (50.1% vs. 37%, *P*=0.38).

Conclusions: Pigtail catheter insertion can safely obviate the need for repeated thoracentesis and may be recommended for management of hepatic hydrothorax.

Keywords: Hepatic hydrothorax, Thoracentesis, Pigtail catheter, Liver cirrhosis

PE-156

Clinical Significance of Relative Adrenal Insufficiency on the Development of Complications and Mortality in Patients with Liver Cirrhosis

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Aims: It is not yet known how much relative adrenal insufficiency (RAI) affects the prognosis of patients with liver cirrhosis. We evaluated the prevalence of RAI in hospitalized patients with liver cirrhosis, and examined their association with prognosis.

Methods: This study included 297 consecutive cirrhosis patients who underwent rapid ACTH stimulation test. RAI was defined by a delta cortisol lower than 9 g/dL and/or a peak cortisol lower than 18 g/dL.

Results: RAI was diagnosed in 183 patients (61.6%) of the 297 patients. The group in RAI (+) had older age, a higher rate with infection, and a deteriorated liver function than the group in RAI (-). In addition, the cause of death from infection was higher in RAI (+) group than RAI (-) group (26.8% vs. 11.8%). The presence of RAI increased significantly the risk of hepatic encephalopathy, acute kidney injury and 3-month mortality. The clinical effect of RAI was further enhanced in the subgroup with relatively higher muscle mass (> ~~)and lower white blood cell count group (< 10,000 μL).

Conclusions: The presence of RAI is relatively frequent in cirrhotic patients with older age, poor liver function and infection In addition, RAI significantly affects the development of complications and the prognosis of liver cirrhosis.

Keywords: Cirrhosis, Infection, Adrenal insufficiency, Prognosis

PE-157

In-Hospital Morality after Surgery in Patients with Liver Cirrhosis: An Analysis from HIRA-NPS of South Korea, 2012–2016

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Aims: Patient of liver cirrhosis have an increased risk of in-hospital mortality after surgery. However, large-scale studies on the prognosis after surgery in these patients are lacking. This study investigated the in-hospital mortality after surgery in patients with liver cirrhosis in current 5 years.

Methods: We used the Health Insurance Review and Assessment Service-National Patient Samples (HIRA-NPS) between 2012 and 2016. In-hospital mortality and hospital stay were analyzed using the data. Mortality rates according to the surgical department were also analyzed.

Results: Of the 1,662,887 patients who underwent surgery, 16,174 patients (1.0%) patients had cirrhosis. In-hospital mortality was significantly higher in patients with cirrhosis than without cirrhosis (8.0% vs. 1.0%). In addition, total hospitalization period (22.6 days vs. 10.2 days) and use of intensive care unit (24.3% vs. 4.8%) were significantly higher in patients with liver cirrhosis. In-hospital mortality after surgery in cirrhotic patients was highest in the otorhinolaryngology surgery (15.7%), followed by neurosurgery (14.8%), thoracic and cardiovascular surgery (13.2%) and plastic surgery (10.2%) compared to the patients without cirrhosis.

Conclusions: Patients with cirrhosis have a significantly higher risk of in-hospital mortality after surgery. A new predictive scoring system for predicting postoperative mortality in these patients is needed.

Keywords: cirrhosis, Surgery, Mortality

PE-158

Clinical Outcomes of Hepatic Veno-Occlusive Disease(VOD)/Sinusoidal Obstruction Syndrome(SOS) after Hematopoietic Stem Cell Transplant(HSCT): Single Center Study

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Aims: Hepatic veno-occlusive disease(VOD), also called sinusoidal obstruction syndrome(SOS), is a potentially life threatening complication primarily associated with hematopoietic cell transplantation(HSCT). VOD/SOS presents with hyperbilirubinemia, ascites, weight gain and painful hepatosplenomegaly. VOD/SOS with multiorgan failure(MOF) is associated with a high mortality rate (>80%). Defibrotide(25mg/kg/day) is approved to treat hepatic VOD/SOS with renal or pulmonary dysfunction post HSCT in the United States.
Methods: Patients who were diagnosed with VOD post HSCT between 2007~2018 were retrospectively reviewed. Patients were diagnosed by Baltimore or modified Seattle criteria or biopsy. Patients received defibrotide or supportive treatment for treatment of VOD.
Results: The total number of transplants between 2007~2018 was 800 and 30 patients were diagnosed with VOD. The incidence of VOD was 4%. 7(30.4%) patients were diagnosed within 21 days post HSCT(early onset VOD), and 23(76.7%) patients were diagnosed after 21 days post HSCT(late onset VOD). Post HSCT 100 day survival rates were 70% among VOD patients(n=30), 85.7% among early onset VOD patients(n=7), and 65.2% among late onset VOD patients(n=23). 8(26.7%) patients developed severe VOD and it occurred late onset after 21days post HSCT. 7 patients among severe VOD patients(n=8) received Defibrotide treatment. Survival at day +100 post-HSCT were 75% for patients with severe VOD and 83.4% for severe VOD patients treated with Defibrotide. Survival at day +100 post-HSCT for VOD patients treated with defibrotide(n=13) and patients treated with supportive care(n=17) were 53.8% and 82.4% respectively. 4(30.7%) patients out of 13 patients who received Defibrotide treatment developed bleeding complications.
Conclusions: The incidence of VOD was 4% and severe VOD developed at late onset(> Post HSCT 21 days). 26.7% of VOD patients developed severe VOD. Defibrotide treatment did not increase day +100 post-HSCT survival rates.
Keywords: Veno-occlusive disease, Sinusoidal occlusive syndrome, HSCT

PE-159

Effect on Liver Transplant Success with Proper Management of Patients on a Waiting List

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Aims: For patients with severe and irreversible acute or chronic liver diseases with no alternative therapy, liver transplantation remains the main option for the treatment of such patients. However, between four main groups (by cause of disease) the appropriate time is difficult to choose the patients on the waiting list for liver transplantation. The aim of this study was to observe the optimal timing for patients depends on categories of disease origin.
Methods: From 2012 among patients who were registered on the waiting list for liver transplantation in the National Register Center of the Republic of Kazakhstan were reviewed in this study and divided for four categories depended on disease cause.
Results: We found that in four major categories of causes such as cirrhosis, fulminant hepatitis, tumors of the liver and genetical damages the firstly the patients with fulmnant hepatitis should be considered for liver transplantation. According to patients with cirrhosis the optimal time when that patients have advanced major complications or coagulopathy. Even MELD score is the main tool to choose the appropriate time for liver transplantation, we found that patient survival was successful with lower MELD score than 15 and that patients could improve there quality of life. In case of patients with tumors the decision depended on the stage of the malignisation in all cases.
Conclusions: The ideal timing for liver transplantation is the time when patient survival is in a high position and all available alternative therapies were not successful.
Keywords: Liver cirrhosis, Waiting list, Treatment

PE-160

Human Fetal Liver Cells as a Bridge to the Liver Transplantation in Patients Waiting for Donors

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Aims: The liver transplantation (LT) a method for treating liver cirrhosis. With a great increase in the death rate of patients with liver disorders, there is a necessity to pursuit alternative therapeutic implement as supportive therapy. Recent studies show outstanding results in therapy using human fetal liver-derived stem cells (FLSC) and can deliver the potential to conservatively manage end-stage liver diseases. The present investigation aimed to study the safety and efficacy of FLSC transplantation.
Methods: 115 patients with liver cirrhosis of different etiologies were included in this study. All patients were on the waiting list and they were divided for 2 groups: received FLSC therapy and no treatment. FLSC was obtained from the fetus after abortion by medical indications and was infused into the periphery. Liver function scores were chosen as endpoints to assess efficacy.
Results: The Child-Pugh score improved in 90 days in the cell therapy group. The model for end-stage liver disease score remained stable in the treated patients, whereas it increased during follow-up in the control group. Bilirubin levels increased among controls, whereas they decreased in the therapy arm during the first 60 days; INR RC differences between groups

reached up to 10%. The changes observed did not persist beyond 90 days. There was marked clinical improvement observed in terms of all clinical and biochemical parameters. Further, there was a decrease in the mean MELD score observed in 6 months of follow-up in all patients.

Conclusions: Transplantation of human FLSC into the periphery improved liver function in patients with advanced cirrhosis in the first 90 days. However, larger studies are necessary to define the role of human FLSC therapy in cirrhotic patients. Treatment by means of human FLSC proposes a potentially helpful modality to liver transplantation in the management of such diseases.

Keywords: Liver cirrosis, Waiting list, Transplantation

PE-161

Portal Vein Thrombosis in Patients with End-Stage Liver Disease on the Waiting List

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Aims: Among the patients with end-stage liver diseases on the waiting list, the portal vein thrombosis (PVT) complicates the liver transplant operation and theoretically disturbs survival. The aim of this research is to find the consequence of PVT on the survival benefit of liver transplantation.

Methods: From January 2015 to February 2019 patients with end-stage liver diseases were treated electively by liver transplantation performance AqtobeMedical Center. Data collection involved the review of age, body mass index (BMI), smoking, and the presence of additional medical disorders, operative complications, postoperative care, surgical infections (SI) and duration of follow-up. Appropriate statistical tests were used. Also by sequential stratification, we estimated the liver transplant survival benefit by MELD score and PVT status.

Results: The occurrence of described PVT among liver transplant recipients was not a predictor of waiting list mortality but was a forecaster of posttransplant mortality. With all of this, transplant advantage was not significantly different for patients with PVT vs. without PVT.

Conclusions: PVT does not disturb waiting list mortality, but it is related with meaningfully advanced posttransplant mortality. Transplant surgeons should sensibly reflect the risks of liver transplantation in clinically stable patients who have PVT.

Keywords: Portal hypertension, Waiting list, Transplantation, end-stage liver disease

PE-162

Meso-Rex Bypass in Treatment for Extrahepatic Portal Vein Obstruction in Children: A Case Report

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Aims: Current management of extrahepatic portal hypertension comprises endoscopic eradication therapy of esophageal varices and conventional shunt surgery. This report assess the early outcome of Mesorex bypass and report their results here.

Methods: Case report: A case of a boy had portal hypertension with hypersplenism and recurrent bleeding from esophageal varices. Preoperative evaluation included blood test, liver function tests, hepatic duplex ultrasonography, computed tomography, computed tomography angiography. The internal jugular vein was used as vein graft in the patient.

Results: The platelet count increased within 4 weeks from a mean of 121.1 x 103 /μL to 150.2 x 103/μL. Ultrasound revealed sufficient perfusion in all shunts (median 32 cm/s). The intrahepatic portal perfusion in segment 4 improved postoperatively.

Conclusions: This study reports the intial result of Mesorex bypass for treatment extrahepatic portal hypertension. The advantageous of technique is restoration of portal flow as porto-systemic shunt. This technique may be used for atresia of portal vein or extrahepatic portal vein obstruction by thrombosis.

Liver Cirrhosis, Portal Hypertension with Cx. Basic

PE-163

Mudeng (Mu2-related Death-inducing gene) Overexpression Accelerates Liver Fibrosis in Carbon Tetrachloride-Induced Cirrhosis

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Aims: Liver fibrosis and its end-stage disease, cirrhosis, are major risk factors for hepatocellular carcinoma. MUDENG (Mu-2 related death-inducing gene, also known as AP5M1) is a gene which encodes a 490 amino acid protein initially reported to be involved in cell death of cytotoxic T cells, in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated anti-apoptotic signaling, and in trafficking of membrane vesicles. Recent advances in TRAIL signaling pathway presents a new target to achieve elimination of activated hepatic stellate cells, thereby reversing fibrosis. In this study, we developed a MUDENG transgenic mouse to further evaluate the role of MUDENG in inducing and potentially alleviating liver fibrosis.

Methods: Eight 8-weeks-old male MUDENG transgenic mice and eight C57BL/6N male mice were injected with carbon tetrachloride (CCl_4) intraperitoneally twice weekly (40 μl/ 20-25 g, 50 μl/ 25-30 g body weight; 1:7 dilution with Olive oil). Livers were

harvested at baseline for control and biweekly after intraperitoneal injection of CCl4. The difference in the percent collagen area at baseline, 2, 4, and 6 weeks of the MUDENG transgenic mice and C57BL/6N mice was evaluated. Opensource software ImageJ (distributed by NIH) was used to calculate the collagen proportionate area of the liver after undergoing picoSirius red staining.

Results: The Ishak fibrosis grade of the MUDENG mice at baseline, week 2, 4, and 6 were 0, 1, 2, and 2, respectively. The Ishak fibrosis grade of the C57BL/6N mice at baseline, week 2, 4, and 6 were 0, 0, 1, and 1, respectively. The collagen proportionate area (CPA) at baseline in MUDENG and C57BL/6N mice were 0.36% and 0.38%, respectively (P=0.77). The CPA at 2 weeks in MUDENG and C57BL/6N mice were 0.91% and 0.67%, respectively (P=0.03). The CPA at 4 weeks in MUDENG and C57BL/6N mice were 2.51% and 1.29%, respectively (P<0.001). The CPA at 6 weeks in MUDENG and C57BL/6N mice were 2.86% and 1.84%, respectively (P<0.001). Greater expression of TGF-ß throughout the life span in MUDENG transgenic mice compared to C57BL/6N was noticed.

Conclusions: MUDENG transgenic mice demonstrates rapid development of fibrosis compared to C57BL/6N mice. Further studies to evaluate the pathways altered by MUDENG overexpression inducing accelerated liver fibrosis should be done.

Keywords: Liver fibrosis, Mudeng, TGF-b

PE-164

Generation of Directly Induced Hepatogenic Cells Derived from Human Fibroblast Using Ultrasound Stimulation

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Aims: Recently, reprogramming technology has emerged as a fascinating tool to generate specific tissue cells. In this study we tested the hypothesis that ultrasound-directed cellular reprogramming can generate fibroblasts into hepatogenic cells.

Methods: We directly induced human dermal fibroblasts (HDFs) into hepatocyte like cells mediated by environmental transition-guided cellular reprogramming (h/entr) using ultrasound. We confirmed the characteristics of h/entr by RT-PCR and qRT-PCR. The effects of h/entr on the activation of hepatic stellate cells were analyzed using conditioned medium (CM). h/entr were transplanted into mice with acute liver fibrosis and the therapeutic effects and mechanism of liver fibrosis were determined.

Results: h/entr exhibited high levels of hepatocyte specific genes and showed increased expression of hepatogenic (HGF, CSF3) and anti-fibrotic (IL-10) factors. h/entr CM suppressed the activation of hepatic stellate cells *in vitro*. Transplantation of h/entr significantly delayed liver fibrosis and improved liver function. Transplantation of h/entr accelerates liver regeneration and human albumin expressing h/entr were detected in the mouse livers.

Conclusions: In conclusion, directly induced h/entr may be a novel and highly effective treatment of liver cirrhosis in clinical application.

Keywords: Liver cirrhosis, Hepatogenic cell, Ultrasound

PE-165

Anti-Fibrotic Effects of Gut-Microbiome on Liver

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Aims: Treatment for liver cirrhosis is intended to slow the progression and deterioration of liver function. Although many studies have shown that microbiome is an important factor in improving liver disease progression through the gut-liver axis, the exact mechanism is still unknown. The microbiome in the gut regulates nutrient metabolism and immune response and interacts closely with the host if the gut microbiome can suppress the progression of liver cirrhosis and analyze clinical data. Therefore, our study aim is to suppress the progression of liver fibrosis due to the modulation of gut-microbiome.

Methods: Liver cirrhosis in mice was induced by DDC (3,5-diethoxycarboncyl-1,4-dihydrocollidine) diet. 6-week-old male C57BL/6J mice were divided into 5 groups (n=10/group; normal, liver fibrosis-induced control, strain X, L. lactis, and UDCA). Strain X group was given the strain X twice a week [10^9 CFU/g, 4-week]. Gene expression was compared and analyzed through mRNA sequencing analysis of mouse hepatic stellate cells in the DDC model.

Results: The Strain X showed improvement in the Staging level and Sirius red areas compared to the fibrosis group induced by the DDC diet (P<0.05). The levels of the liver fibrosis markers TIMP1 (P=0.02), Col1a (P<0.001), and TGF-ß (P<0.001) were decreased in the Strain X group compared with fibrosis models. When HSCs were isolated, expression of TIMP1 (P=0.38) and Col1a (P=0.055) decreased in strain X. Strain X compared to DDC in the mRNA sequencing, the up-regulated gene is Ecm1, Fos, Serpina1e and the down-regulated gene is Cd5l, Cd63, Marco (P<0.03).

Conclusions: Strain X improved fibrosis by modulating the gut microbial composition in a mouse model induced cirrhosis.

Keywords: DDC, Fibrosis, Gut-microbiome, Probiotics

PE-166

Clinical Impact of Exosomal microRNA as a Novel Biomarker of Liver Fibrosis

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Aims: Many approaches have been suggested for the non-invasive diagnosis of liver fibrosis, including the use of serum biomarkers and ultrasound-based elastography, but none has yet replaced liver biopsy. MicroRNAs (miRNAs) have been suggested as potential diagnostic tools for liver diseases. We investigated alterations in the expression of serum exosomal miRNAs with the progression of liver fibrosis and evaluated their clinical applicability as biomarkers.

Methods: This study prospectively enrolled 71 patients who underwent liver biopsy at a large-volume academic hospital in Korea. Exosomes were extracted from serum samples, and next-generation sequencing (NGS) of miRNAs was conducted in patients from different stages of liver fibrosis. Differential expression of miRNAs was quantified using targeted real-time quantitative polymerase chain reaction (RT-qPCR). A model was derived to discriminate advanced fibrosis based on miRNA levels using multivariate logistic regression. The performance of this model was evaluated and compared using area under the receiver operator characteristic (ROC) curve (AUC) and DeLong's test.

Results: NGS data revealed the relationship between exosomal miR-122 expression and liver fibrosis progression. The level of miR-122 decreased as the pathologic fibrosis grade progressed from stage 0 to 4. Patients with biopsy-proven advanced fibrosis had significantly lower levels of exosomal miR-122 (P<0.001) than those without advanced fibrosis. Exosomal miR-122 exhibited a fair performance in discriminating advanced fibrosis with an AUC of 0.77, which improved to 0.86 in combination with fibrosis-4 score (FIB-4) and transient elastography (TE). This value was higher than that reported for any other non-invasive modalities, including TE (AUC of 0.80) or FIB-4 (AUC of 0.57) alone. In a subgroup of patients with a non-viral etiology of liver disease, the performance of exosomal miR-122 as a biomarker improved, evident from the increase in the AUC value to 0.87. In this subpopulation, the combination model of miR-122, FIB-4, and TE showed the best discrimination ability (AUC of 0.90), which was significantly higher than that of TE alone (AUC of 0.83; DeLong's test P=0.046). Inhibition of miR-122 expression increased the proliferation of the human hepatic stellate cell line, LX-2, and upregulated the expression of collagen-1A, a-smooth muscle actin, fibronectin, and transforming growth factor-ß.

Conclusions: Exosomal miR-122 may serve as a novel biomarker for discriminating advanced liver fibrosis, and its accuracy may enhanced in combination with other non-invasive tests such as FIB-4 and TE.

Keywords: Exosome, MicroRNA, Liver fibrosis, NGS

PE-167

Bone Marrow-Derived Mesenchymal Stem Cells Isolated from Patients with Cirrhosis and Healthy Donors Show Comparable Characteristics

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Aims: Autologous or allogeneic bone marrow-derived mesenchymal stem cells (BMSCs) have been applied in clinical trials to treat liver disease. However, there are only a few studies comparing the characteristics of autologous MSCs from patients and allogeneic MSCs from normal subjects.

Methods: Therefore, to identify BMSCs that are more suitable for the treatment of cirrhosis, we compared the characteristics of isolated BMSCs from six healthy donors (BCs) and six patients with cirrhosis (BPs).

Results: In passage 3 (P3), senescent population and expression of p53 and p21 were slightly higher in BPs, but the average population doubling time for P3–P5 in BPs was approximately 65.3 ± 11.1 h, which is 18.4 h shorter than that in BCs (83.7 ± 9.2 h). No difference was observed in the expression of CD73, CD90, or CD105 between BCs and BPs. Adipogenic differentiation slightly increased in BCs, but the expression levels of leptin, peroxisome proliferator-activated receptor γ, and CCAAT-enhancer-binding protein a did not vary between differentiated BCs and BPs. While ATP and reactive oxygen species levels were slightly lower in BPs, mitochondrial membrane potential, oxygen consumption rate, and expression of mitochondria-related genes such as cytochrome c oxidase 1 were not significantly different between BCs and BPs.

Conclusions: Taken together, there are marginal differences in the proliferation, differentiation, and mitochondrial activities of BCs and BPs, but both BMSCs from patients with cirrhosis and healthy donors show comparable characteristics.

Keywords: Mesenchymal stem cells, Cirrhosis, Proliferation, Dif-

ferentiation, Mitochondria, Senescence

PE-168

The State of Anti-Endotoxin Immunity in Chronic Viral Hepatitis and Cirrhosis

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Aims: study the state of the immune response to endotoxins of intestinal microbiocenosis in chronic viral hepatitis (CVH) and viral cirrhosis of the liver (VCL).

Methods: In 49 patients with CVH, 60 - ICP, and 30 healthy individuals (HI), the concentration of serum anti-endotoxin antibodies (AEA), lipopolysaccharide-binding protein (LBP) and the soluble form of the CD 14 differentiation cluster (sCD 14) were determined by enzyme-linked immunosorbent assay (ELISA). Markers of hepatitis B virus (HBV) and C (HCV) were studied in all patients by ELISA and polymerase chain reaction.

Results: The concentration of AEA in KG averaged (8.0 ± 0.4) μg / ml, with CVH - (8.54 ± 1.24) μg / ml, with CP - (10.0 ± 1.1) μg / ml In HBV-positive patients with CP, the AEA level was (11.67 ± 1.33) μg / ml versus (8.0 ± 0.8) μg / ml in HCV-positive. A statistically significant correlation (r = 0.444) was established between elevated AEA and the presence of HBV markers in the blood. With respect to HCV, a similar trend was observed, not reaching statistical significance. The concentration of LPB in CG averaged (13.5 ± 0.9) μg / L, with CVH - (33.2 ± 2.3) μg / L, and with CP - (39.0 ± 1.5) μg / l (χ 2 = 18.0, *P*=0.0001). The concentration of sCD 14 in the CG was (2.7 ± 0.3) μmol / L, with CVH - (4.9 ± 0.1) μg / L, with CP - (5.2 ± 0.2) μmol / L (χ 2 = 15.2; *P*=0.0002). The correlation coefficient between LPB and sCD 14 was at CVH r = 0.35; with CP r = 0.42, which reflects their closer relationship with the progression of the hepatic process, the development of portal hypertension.

Conclusions: In patients with chronic hepatitis C and LC of viral etiology, a significant increase in the markers of anti-endotoxin immunity AEA, LPB and sCD 14 was revealed, which indicates, on the one hand, the severity of endotoxemia syndrome, and on the other, the tension of anti-endotoxin immunity.

Keywords: Intestinal microbiocenosis, Cirrhosis of the liver

PE-169

Isolation of Secretome with Enhanced Antifibrotic Properties from miR-214-Transfected Adipose-Derived Stem Cells

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Aims: Secretome refers to the total set of molecules secreted or surface-shed by stem cells. The limitations of stem cell research have led numerous investigators to turn their attention to the use of secretome instead of stem cells. In this study, we intended to reinforce antifibrotic properties of the secretome released from adipose-derived stem cells (ASCs) transfected with miR-214.

Methods: We generated miR-214-transfected ASCs, and extracted the secretome (miR214-secretome) from conditioned media of the transfected ASCs through a series of ultrafiltrations. Subsequently, we intravenously injected the miR-214-secretome into mice with liver fibrosis, and determined the effects of miR-214-secretome on liver fibrosis.

Results: Compared with that by naïve secretome, liver fibrosis was ameliorated by intravenous infusion of miR-214-secretome into mice with liver fibrosis, which was demonstrated by significantly lower expression of fibrosis-related markers (alpha-smooth muscle actin, transforming growth factor-ß, and metalloproteinases-2) in the livers as well as lower fibrotic scores in the special stained livers compared with naïve secretome. The infusion of miR-214-secretome also led to lesser local and systemic inflammation, higher expression of an antioxidant enzyme (superoxide dismutase), and higher liver proliferative and synthetic function.

Conclusions: MicroRNA-214 transfection stimulates ASCs to release the secretome with higher antifibrotic and anti-inflammatory properties. miR-214-secretome is thus expected to be one of the prominent ways of overcoming liver fibrosis, if further studies consistently validate its safety and efficiency.

PE-170

Anti-Fibrotic Effect of Urushiol (Rhus Verniciflua Stokes) on Thioacetamide-Induced Liver Fibrosis of Mice Model

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Aims: Liver fibrosis constitutes a serious problem worldwide due to its rapidly leads to cirrhosis, and even cancer. However, there is no clear medical treatment other than treating the cause. Urushiol has been known to have anti-inflammatory and anti-oxidative effects on various disease. We investigated the effect of urushiol on liver fibrosis induced by thioacetamide

(TAA).

Methods: Thirty C57BL/6 mice were randomly divided into 3 groups and urushiol was dissolved in vehicle (DMSO) for *in vivo* experiments: (1) control group; (2) TAA (normal saline as solvent, 300 mg/kg/day, 3 times/week, i.p.) + vehicle (gavage). (3) TAA (300 mg/kg/day, 3 times/week, i.p.) + urushiol (0.128 mg/mL/day, 28 times, gavage). These groups were analyzed by immunohistochemical staining, reverse transcription polymerase chain reaction, and microarray.

Results: The TAA + Urushiol group improved the deposition of fibrillar collagen (Sirius Red (%) 1.55 ± 0.25 vs. TAA, $P<0.0001$), Fibrosis stage reduced (1.64 ± 0.20 vs. TAA, $P<0.0001$) and Inflammation activity decreased concurrently (1.17 ± 0.16 vs. TAA, $P<0.0001$). The analysis of mRNA expression showed that Col1a1 (2.30-fold change vs. TAA, $P<0.0001$) and TIMP-1 (1.48-fold change vs. TAA, $P<0.05$), IL-6 (3.03-fold change vs. TAA, $P<0.0001$), JAK2 (0.89-fold change vs. TAA, $P<0.05$), STAT3 (3.26-fold change vs. TAA, $P<0.0001$) downregulated significantly. As shown microarray analysis, downregulation of Col1a1 (1.12-fold change vs. TAA, $P<0.05$), Chka, lipid metabolic process gene (2.21-fold change vs. TAA, $P<0.001$), Pnpla3, patatin-like phospholipase domain containing 3 (1.57-fold change, $P<0.001$) Contrast, Orm2, regulation of immune system process gene (2.28-fold change vs. TAA, $P<0.001$) Saa1, serum amyloid A (2.25-fold changes vs. TAA, $P<0.05$), Saa2 (3.09-fold change, $P<0.001$)

Conclusions: Our results indicated that urushiol has therapeutic effect on liver fibrosis. Although it is needed more clinical research, urushiol can be a potential agent for the treatment of liver fibrosis.

Keywords: Liver fibrosis, Thioacetamide, Urushiol

NAFLD, Clinical

PE-171

Cardiac Relaxation Abnomality Related with Non-Alcoholic Liver Disease in Korea

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Aims: Left ventricle (LV) diastolic dysfunction has been reported in patients with non-alcoholic fatty liver disease (NAFLD). NAFLD is also associated to the metabolic syndrome. The aim of the study is to investigate the effect of on LV systolic and diastolic function using echocardiography measures in patients with or without NAFLD in primary medical center in Korea.

Methods: We examined the medical records of 207 patients who performed medical check-up contained ultrasound from October 2014 to September 2019. We excluded other causes of liver disease such as viral hepatitis, cirrhosis and excessive drinking. Upper abdominal ultrasonography was performed to determine the fatty liver. Complete echocardiographic exams including tissue Doppler imaging (TDI) was performed. The following parameters were assessed by echo Doppler: Ejection fraction (EF; by Simon's method/M-mode), peak velocities for E/A ratio, Decreasing time(DT). Using TDI early diastolic velocity (E') and E/E' ratio of mitral annulus were obtained.

Results: In this study, we retrospectively analyzed 77 patients under the criteria. Diastolic dysfunctions were defined that at least one of the following factors (E/A ratio, DT, E', E/E' ratio) existed. The NAFLD group was found to be a significant risk factor for diastolic dysfunction [93.8% (30/32) vs 71.4% (30/42), $P=0.018$]. LV systolic function by EF was also higher than control groups [18.8% (6/32) vs 2.3% (1/44), $P=0.018$]. E' on TDI were significantly higher compared with the control group (11.4±0.6 vs. 22.2±7.3 cm/s, $P=0.166$). NAFLD was not significantly associated with LV function, adjusted for age, body weight and biochemical markers.

Conclusions: In this clinical data, patients with NAFLD altered LV systolic and diastolic dysfunction. Early diastolic velocity on TDI (Tissue doppler index) was found to be the significant index that could classify the patients with fatty liver. It is nessesary to approach comprehensive aspests such as hypertension, diabetes, and metabolic syndrome as well as liver function.

Keywords: NAFLD, Cardiac Relaxation, Systolic dysfunction

PE-172

Effects of Probiotic Supplementation on Hepato-Protective and Oxidative Stress Indices in Subjects with Diabetes Mellitus: A Randomized Double-Blind Clinical Trial

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Aims: Liver disease is one of the most common and occurs asymptomatically until disease affects a significant part of the organ. Probiotics are live microorganisms promoted with claims that they provide health benefits when consumed adequate amount, health benefits including antidiabetic, anti-inflammatory and antioxidant properties. This study aimed to determine the effects of probiotic supplementation on liver function and oxidative stress biomarkers in Type II Diabetes mellitus (T2DM) patients.Liver disease is one of the most common and occurs asymptomatically until disease affects a significant part of the organ. Probiotics are live microorganisms promoted with claims that they provide health benefits when consumed adequate amount, health benefits including antidiabetic, anti-inflammatory and antioxidant properties. This study aimed to determine

the effects of probiotic supplementation on liver function and oxidative stress biomarkers in Type II Diabetes mellitus (T2DM) patients.

Methods: In a randomized double-blind placebo-controlled clinical trial, 60 Subjects with aged 30–65 years were selected from CTR, Jiwaji University and assigned into two groups; Subjects in the probiotic group received a daily capsule containing Lactobacillus acidophilus, Bifidobacterium bifidium & Saccharomyces boulardii each 0.5 Bn/g and Lactobacillus plantarum, Bacillus clausii each 0.25 bn/g with 125mg FOS. BD for 12 weeks. (Placebo group only 125mg FOS in a capsule). In the baseline and at the end of the study, physical activity levels, and dietary intakes were assessed. Anthropometric parameters, blood glucouse, Liver function markers malondialdehyde (MDA), superoxide dismutase (SOD), reduced glutathione (GSH), and catalase (CAT) activities were measured.Statistical analysis was carried out using a paired t-test and student t- test.

Results: There was no significant difference between the two groups for demographic characteristics, anthropometric parameters at the baseline of study. The mean fasting blood glucose levels were reduced by 16.3%.The probiotic supplementation resulted in a significant improvement in bilirubin by 22.3%, 15.9% ALP 17%,10.2% SGOT 27.2, 22.5%, SGPT 17.9, 17.1% GTT 13.9, 11.9% in subjects taken probiotic placebo capsules respectively. It also observed that the significant increase in GSH (P<0.01), SOD (P<0.01), CAT (P<0.01) and decrease in MDA level (P<0.01). Significant difference was observed between-group for these enzymes activities & other parameters at the end of the study.

Conclusions: Overall, the results demonstrate that probiotics could improve liver function and oxidative stress factors among T2DM patients.

Keywords: Hepato-protective, Probiotics, Oxidative stress, Type II diabetes Mellitus

PE-173

High Visceral Adipose Tissue Index Predicts Advanced Liver Fibrosis in Patients with Biopsy-Proven Non-Alcoholic Fatty Liver Disease

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Aims: Visceral adipose is associated with liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD). Our study is aim to investigate the association between computed tomography-measured visceral adipose tissue index (VATI) and advanced liver fibrosis in patient with biopsy-proven NAFLD.

Methods: We analyzed 178 biopsy-proven NAFLD patients using computed tomography at the level of the L3 vertebra. A receiver operating characteristic curve analysis was performed to evaluate optimal cut-off value (COV) of VATI to predict advanced fibrosis (F3). The optimal COVs of VATI to predict advanced fibrosis were 92.722 cm^2/m^2 in men and 63.445 cm^2/m^2 in women, respectively. Severe non-alcoholic steatohepatitis (NASH) was defined as histologically proven NASH with NAFLD activity score ≥5.

Results: Among the 178 NAFLD patients, advanced fibrosis was diagnosed in 47 (26.4%). The advanced fibrosis patients revealed a higher age (64.6 ± 8.1 vs. 45.7 ± 16.1, P<0.001) and VATI (81.5 ± 26.1 vs. 64.5 ± 26.4, P<0.001). The progression of liver fibrosis was positively correlated with VATI (r = 0.26, P<0.001). On the multivariate analysis, high VATI (odd ratio [OR] 11.39, 95% confidence interval [CI] 2.09–61.95, P=0.005), presence of severe NASH (OR 16.72, 95% CI 2.62-106.92, P=0.003), alanine aminotransferase (OR 0.97, 95% CI 0.95-1.00, P=0.0476), and platelet counts (OR 0.97, 95% CI 0.96-0.99, P=0.006) were associated with advanced fibrosis in Biopsy-proven NAFLD patients.

Conclusions: High VATI independently associated with advanced fibrosis in patients with biopsy-proven NAFLD.

Keywords: Non-alcoholic fatty liver disease, Advanced liver fibrosis, Visceral adipose tissue index

Table 1. Univariate and multivariate analysis of factors associated with advanced liver fibrosis in patients with non-alcoholic fatty liver disease

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.12	1.08-1.16	0.0001			
Sex	3.79	1.80-7.94	0.0004			
Obesity	1.23	0.59-2.58	0.5757			
Diabetes	4.40	2.14-9.02	0.0001			
Hypertension	5.85	2.81-12.15	0.0001			
Severe NASH	3.85	1.92-7.74	0.0002	16.72	2.62-106.92	0.0029
Platelet,	0.97	0.97-0.98	0.0001	0.97	0.96-0.99	0.0059
Albumin	1.06	0.94-1.19	0.3596			
ALT	0.98	0.98-0.99	0.0002	0.97	0.97-1.00	0.0476
GGT	1.00	1.00-1.00	0.7529			
PT-INR	0.91	0.59-1.41	0.6693			
CRP	0.76	0.37-1.56	0.4576			
TC	0.98	0.97-0.99	0.0005			
HDL	0.98	0.95-1.01	0.1873			
LDL	0.98	0.97-1.00	0.0054			
TG	0.99	0.99-1.00	0.0197			
LSMM	0.23	0.05-1.03	0.0553			
SATI (yes vs. no)	1.13	0.57-2.21	0.7320			
VATI (yes vs.no)	6.90	3.28-14.54	0.0001	11.39	2.09-61.95	0.0049

PE-174

Association with Low Skeletal Muscle Mass and Carotid Atherosclerosis in Patients with Non-Alcoholic Fatty Liver Disease

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Aims: Although low skeletal muscle mass (LSMM) and carotid atherosclerosis are associated with non-alcoholic fatty liver disease (NAFLD), respectively, associated with LSMM and subclinical atherosclerosis in patients with NAFLD has not been established. We investigated whether LSMM was associated with carotid atherosclerosis in patients with NAFLD.

Methods: From January 2010 to November 2019, a total 683 ultrasound-confirmed NAFLD patients who performed carotid ultrasound from health promotion center of Yeungnam University Hospital were included in the analysis. LSMM was defined as Appendicular skeletal muscle (ASM) using bioelectrical impedance analysis divided by body mass index (ASM/BMI). Using carotid ultrasound and Doppler, elevated carotid intima media thickness (IMT) (>1cm) and presence of carotid plaque were measured, which are defined as indicators of early atherosclerosis.

Table 1.

	Elevated IMT		Carotid plaque	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
LSMM_BMI in NAFLD patients (yes vs. no)				
Unadjusted	2.95 (1.74-5.02)	<0.001	2.85 (1.51-5.39)	0.001
Age, sex adjusted	2.26 (1.26-4.04)	0.006	2.05 (1.03-4.08)	0.004
Model 1	2.28 (1.27-4.08)	0.005	2.20 (1.10-4.40)	0.026
Model 2	2.28 (1.27-4.08)	0.005	2.90 (1.40-6.04)	0.004
Model 3	2.26 (1.26-4.04)	0.006	2.74 (1.30-5.78)	0.008

LSMM, low skeletal muscle mass; OR, odds ratio; BW, body weight; BMI, body mass index; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; ASM: appendicular skeletal muscle mass.

Model 1: Age, sex, presence of diabetes, and hypertension

Model 2: Further adjusted for presence of obesity, waist circumference, and hyperuricemia

Model 3: Further adjusted for total cholesterol, triglyceride, and high-density lipoprotein, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, homeostatic model assessment-insulin resistance, and high sensitivity C-reactive protein

Results: Of 683 patients with NAFLD, 75 (11.0%) were diagnosed with LSMM. The LSMM group were older (52.9 vs. 49.2 years, *P*=0.011), had higher BMI (29.0 vs. 26.3 kg/m2, *P*=0.001), proportion in presence of insulin resistance (53.3 vs. 33.2%, *P*=0.001), proportion of elevated IMT (33.3 vs. 14.5%, *P*=0.001) compared to non-LSMM group. In patients with NAFLD, the presence of LSMM was associated with elevated IMT (odd ratios [OR] = 2.26 to 2.95, *P*<0.05) and carotid plaque (OR = 2.05 to 2.90, *P*<0.05) using adjusted models for age, sex, diabetes, hypertension obesity, waist circumference, hyperuricemia, lipid profile, aminotransferase, gamma-glutamyl transferase, homeostatic model assessment-insulin resistance, and high sensitivity C-reactive protein. (Figure) In patients with obese NAFLD as a subgroup, the presence of LSMM was associated with elevated IMT (odd ratios [OR] = 2.44 to 3.30, *P*<0.05) and carotid plaque (OR = 2.56 to 3.54, *P*<0.05) using adjusted model.

Conclusions: LSMM may be associated with elevated IMT and presence of carotid plaque in patients with NAFLD, independently classic metabolic factors and insulin resistance.

Keywords: Non-alcoholic fatty liver disease, Low skeletal muscle mass, Carotid plaque, Intima media thickness

PE-175

Comparative Analysis of Efficiency of Ursodeoxycholic Acid and Combination of Vitamin E and Vitamin C in Treatment of Non-Diabetic Non-Alcoholic Steatohepatitis

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Aims: Nonalcoholic steatohepatitis (NASH) is a frequent liver disease that can progress to cirrhosis and for which effective therapy is still lacking. Despite an important role of oxidative stress in the pathogenesis of NASH, antioxidant approaches have not been investigated sufficiently. The aim of the study was to detect the efficacy of vitamin E and vitamin C combination in non-diabetic patients with nonalcoholic steatohepatitis.

Methods: Patients with elevated aminotransferase levels and drinking, less than 40g alcohol/week with NASH diagnose were randomly assigned to receive either UDCA 15 mg/per kg/day (group A) or vitamin E 800 mg/day plus vitamin C 500 mg/day (group B) for 12 months and control group, which did not receive any medical treatment. Lifestyle modification was advised to all groups. The primary study end point was improvement in alanine transaminase (ALT) levels, secondary end points were improvement in steatosis score and improvement in fibrosis score.

Results: 107 patients were included 35 in the group A, 52 in the group B and 20 in control group, 11 patients dropped out, non because of side effects. Baseline characteristics were not significantly different between groups. After 12 months treatment with vitamin E plus C, as compared with UDCA, was associated with a significant reduction of mean alanine aminotransferase (ALT) levels. Similarly, there was significant reduction of both mean steatosis score and fibrosis score.

Conclusions: Vitamin E plus C combination is an effective, safe and inexpensive treatment option in patients with NASH and may be useful to reduce damage from oxidative stress and slow the process leading to cirrhosis.

Keywords: Nonalcoholic fatty liver disease, Nonalcoholic steatohepatitis, Vitamin E, Ursodeoxycholic acid

PE-176

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Efficacy of Biphenyl Dimethyl Dicarboxylate/Ursodeoxycholic Acid (UDEX) on Aminotransferase among the Patients with Chronic Liver Disease Related to Metabolic Syndrome

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Aims: Steatohepatitis related to metabolic syndrome is a chronic liver disease which is prevalent in the patients not only with NASH but also with alcoholic liver disease, and chronic viral hepatitis. However, there is limited data dealing with the effect of hepatotonics for recovery of necro-inflammation and fibrosis in these patients. Therefore, we were intended to evaluate the efficacy of a combined hepatotonic agent in this study population.

Methods: We randomly assigned 33 adults with chronic liver disease with one or more component of metabolic syndrome to receive biphenyl dimethyl dicarboxylate (12.5 mg)/ursodeoxycholic acid (50 mg), or placebo for 24 weeks. The primary outcome was a normalization of ALT (≤40 U/L). Secondary outcomes were the change of controlled attenuation parameter (CAP) and transient elastography (TE), and Chronic Liver Disease Questionnaire (CLDQ) score.

Results: Thirty three patients were randomly assigned to each group. Eight (50%) of 16 patients who received intervention drug showed normalization of ALT compared with one (6%) of 17 patients in the placebo group in ITT analysis (*P*=0.007). In contrast, the change of CAP (-0.96 ± 1.72 dB/m vs. -0.59±1.54 dB/m; *P*=0.529), and TE (-10.75±26.33 kPa vs. -11.76±35.22 kPa; *P*=0.926), and CLDQ score ([median (IQR)] 2.50 (0.00-11.00) vs. 9.00 (4.00-17.00), *P*=0.078) were not significant different between two groups. ALT was significantly changed during the four assessment periods (*P*<0.001), and this change was affected by group (*P*=0.023). The interaction between group and time was also statistically significant (*P*<0.001) (Fig. 1). AST was significantly changed during the four assessment periods (*P*<0.001). However, this change was not affected by group (*P*=0.544) (Fig. 2).

Conclusions: Biphenyl dimethyl dicarboxylate/ursodeoxycholic acid combination reduced ALT in chronic liver disease related to metabolic syndrome. However, there is no evidence supporting that this leads to the improvement hepatic steatosis and fibrosis within 6 months.

Keywords: Chonic liver diease, Metabolic syndrome, Hepatotonic

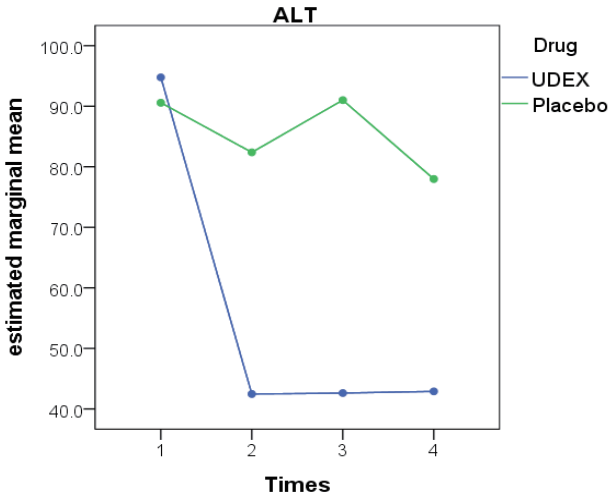

Figure 1. Comparison of change in serum ALT level during the treatment period between intervention and placebo group. ANCOVA for repeated measures showed P=0.010 for Group, P<0.001 for Time, P<0.001 for interaction between Group and Time.

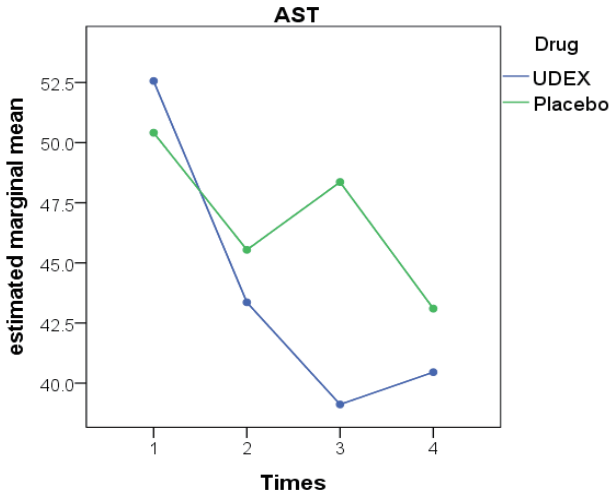

Figure 2. Comparison of change in serum AST level during the treatment period between intervention and placebo group. ANCOVA for repeated measures showed P=0.538 for Group, P=0.001 for Time, P=0.093 for interaction between Group and Time.

PE-177

Machine Learning Models Identify Novel Histologic Features Predictive of Clinical Disease Progression in Patients with Advanced Fibrosis due to NASH

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USA; [4]Radcliffe Department of Medicine, Oxford University, UK; [5]Inova Fairfax Hospital, Falls Church, VA, USA; [6]Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, USA; [7]Virginia Commonwealth University, Richmond, VA, USA

Aims: Fibrosis is the primary determinant of disease progression in patients with nonalcoholic steatohepatitis (NASH), but the prognostic impact of other histological features is unclear. We used a machine learning(ML) approach to identify novel morphologic features and associations with disease progression in NASH patients with F3/4 fibrosis.

Methods: Biopsies from 644 patients screened in phase3 trial of selonsertib (STELLAR-4) were scored by a central pathologist(CP) according to the NASH CRN and Ishak staging systems. The PathAI research platform(PathAI, Boston, MA) was trained a convolutional neural network(CNN) with >68,000 annotations (e.g. steatosis, ballooning, lobular/portal inflammation) collected from 75 board-certified pathologists on images of H&E and trichrome(TC) stained slides. For staging fibrosis, CNN models were trained using slide-level pathologist scores to recognize unique patterns associated with each stage within fibrotic regions of TC images. 202 features were extracted from biopsy images from patients (F3-F4) enrolled in the STELLAR trials. Cox regression was used to identify associations between these features with progression to cirrhosis in F3 patients, and liver-related events (e.g. decompensation, transplantation, death) in F4 patients.

Results: 1526 NASH patients with F3-F4 fibrosis (median age 59 yrs, 73% diabetic, 52% F4) were included. During a median follow-up of 16.5 mos, 14.5% (105/726) of F3 patients progressed to cirrhosis, and over 15.9 mos, 2.8% (22/800) of F4 patients had liver-related events. Progression to cirrhosis was associated with greater area of Ishak 6 fibrosis and portal inflammation (Figure). Similar associations were observed in F4 patients, with hepatocellular ballooning and clinical events. In F3, a greater proportion of area of Ishak 1 fibrosis and steatosis were associated with a reduced risk of progression. In F4, area of steatosis was similarly protective, while proportion of Ishak Stage 1 Fibrosis over Ishak scored area trended towards protective.

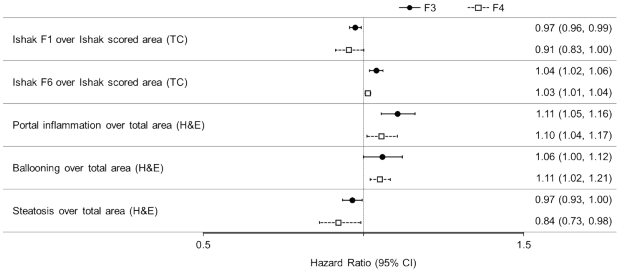

Figure 1. Associations Between ML-Based Morphological Features with Disease Progression in Patients with Advanced Fibrosis Due to NASH

Conclusions: Liver histological evaluation using ML approach identified novel features associated with progression in NASH patients with advanced fibrosis. These data support the utility of ML approaches to evaluation of liver histology as endpoints in NASH clinical trials.

Keywords: NASH, Machine learning, Fibrosis

PE-178

Validation of the Performance of MRE for the Detection of Advanced Fibrosis due to NASH across Multiple Clinical Trials

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Aims: Magnetic resonance elastography(MRE) is a quantitative imaging biomarker for the detection of advanced fibrosis due to NASH. Our aim was to validate the performance of MRE for detection of advanced fibrosis using data from multiple clinical trials.

Methods: Baseline data were pooled on 296 subjects with NASH from seven randomized, phase 2 and 3 trials including ATLAS and STELLAR-3/-4 trials. All subjects underwent 2D MRE and liver biopsy with staging of fibrosis according to NASH CRN classification. Associations between MRE-stiffness, fibrosis stage, noninvasive tests (NITs) of fibrosis (ELF, FibroTest, FIB-4, NAFLD Fibrosis Score [NFS]), and NASH activity (NAFLD Activity Score ≥5 vs <5) were determined. The discrimination of MRE for advanced fibrosis (F3-F4 vs F0-F2) and cirrhosis (F4 vs F0-F3) was evaluated using areas under receiver operating characteristic (AUROC) curves, and cutoffs from literature-based MRE thresholds (3.64 and 4.67 kPa, respectively) and optimal thresholds(defined by the maximal sum of sensitivity and specificity) were determined.

Results: Among 296 subjects, fibrosis stages were F0-1(6%), F2(11%), F3(44%), and F4(40%); median MRE-stiffness was 4.71 kPa(IQR 3.52, 6.35). MRE-stiffness was correlated with fibrosis stage(Spearman ρ =0.60), and other NITs of fibrosis(ρ =0.47-0.52; all P<0.05). The AUROCs(95% CI) of MRE-stiffness for detecting advanced fibrosis and cirrhosis were 0.85(0.80, 0.90) and 0.81(0.76, 0.86), respectively. In general, cutoffs from the literature and optimal cutoffs derived from this dataset had similar performance for classification of fibrosis by 2D MRE. Among subjects with F0-F2 fibrosis on biopsy, those with

MRE-stiffness ≥3.64 kPa (potential misclassification) had higher ELF and FibroSure than those with MRE-stiffness <3.64 kPa (both *P*<0.05). Conversely, among subjects with F3-F4 fibrosis on biopsy, those with MRE-stiffness <3.64 kPa had lower ELF, FibroSure, FIB-4, and NFS compared with those with MRE-stiffness ≥3.64 kPa(all *P*<0.05).

Conclusions: This multi-center, multi-study validation demonstrates the clinical utility of 2D MRE for the detection of advanced fibrosis due to NASH.

Keywords: Magnetic resonance elastography, MRE, Advanced fibrosis, NASH

PE-179

A Critical Appraisal of the Definition of Sarcopenia in Patients with Non-Alcoholic Fatty Liver Disease: Pitfall of Adjusted Muscle Mass by Body Weight

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Aims: Traditionally, sarcopenia has defined as amount of absolute muscle mass adjusted by height in the elderly people. However, relative muscle mass adjusted by weight has used extensively in most non-alcoholic fatty liver disease (NAFLD) studies. Here, we attempted to investigate the pitfall of sarcopenia in NAFLD according to adjustment methods.

Methods: Adult subjects (n=1,343) who underwent a health check-up at the healthcare center were finally included for analysis, except for 682 subjects. Total skeletal muscle (TSM), appendicular skeletal muscle (ASM) and fat measured using the bioelectrical Impedance Analysis (BIA). The weight-adjusted skeletal muscle mass index (wSMI) and height-adjusted SMI (hSMI) calculated by dividing the total ASM by weight or the square of height, respectively. Fatty liver diagnosed by using abdominal sonography.

Results: Prevalence of sarcopenia defined by wSMI in the NAFLD group was significantly higher than in the control group (1.3% vs. 8.8%, *P*<0.001). But there was no difference in the prevalence of sarcopenia defined by hSMI between the control and NAFLD groups (2.0% vs. 0.8%, *P*=0.055). The concordance rate of the two methods was 0.29% (4/1343) NAFLD. Because body weight was most potent independent risk factor for NAFLD in multivariable logistic regression analysis, when we adjusted parameters adjusted by body weight, prevalence of abnormality of almost all parameters increased in NAFLD population. When the bilirubin (or platelet) adjusted by weight, prevalence of abnormal bilirubin (or platelet) increased in NAFLD subjects. However, prevalence of abnormality of non-metabolic parameter (bilirubin or platelet) did not increase in NAFLD, after adjusting by height. Only metabolic parameters showed relationship with NAFLD, after adjusting by height

Conclusions: The concordance rate of sarcopenia defined by wSMI and hSMI was very low. As NAFLD is highly associated with body weight, attention should be given in the case of studying the relationship of NAFLD with sarcopenia adjusted by body weight.

PE-180

Noninvasive Tests of Fibrosis as Markers of Disease Progression in Patients with Non-Alcoholic Steatohepatitis (NASH)

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Aims: Surrogate endpoints that predict complications are necessary for approval of new therapies for NASH. We assessed associations between histologic and noninvasive fibrosis markers with disease progression in NASH.

Methods: Patients with advanced fibrosis (Ishak stages 3-6) due to NASH (NAS ≥3) were enrolled in Phase 3, placebo-controlled trials of selonsertib. Treatment groups were combined for this analysis. Liver fibrosis at baseline[BL] and W48 were staged according to the Ishak classification. Hepatic collagen and a-SMA expression were quantified by morphometry. Noninvasive tests of fibrosis such as LS by TE, ELF and NAFLD Fibrosis Score (NFS) were calculated. Cox regression determined associations between these parameters with disease progression (i.e. progression to cirrhosis in patients with bridging fibrosis and adjudicated clinical events [e.g. decompensation, transplantation, death] in those with cirrhosis), and discrimination was assessed using c-statistics.

Results: 1679 subjects with bridging fibrosis(n=802) or cirrhosis(n=877) were randomized (median age 59 yrs, 60% female, 74% diabetes). During a median follow-up(FU) of 14.3 mos, 16% of subjects (117/748 with W48 biopsies) with bridging fibrosis progressed to cirrhosis. Risk of histological progression was greater with higher BL Ishak stage, hepatic collagen,

a-SMA expression, ELF, NFS, and LS, as well as greater increases in these markers over time(Table). BL ELF(c-statistic, 0.68) and LS(0.70) more accurately discriminated progression to cirrhosis than BL Ishak stage(0.58) and hepatic collagen(0.56; all *P*<0.05). During a median FU of 14.3 mos, 26(3%) cirrhotic subjects had clinical events. BL factors associated with clinical events included higher Ishak stage, hepatic collagen, a-SMA, ELF, NFS, and LS(Table). After adjustment for BL, increases in hepatic collagen, a-SMA, NFS, and LS were associated with an increased risk of events. Prediction of future clinical events was greatest for BL ELF (c-statistic, 0.84 vs. 0.66 for Ishak stage and 0.62 for hepatic collagen; both *P*<0.05).

Conclusions: Clinical disease progression in patients with advanced fibrosis due to NASH is associated with greater fibrosis burden at baseline and larger increases over time, measured histologically or with noninvasive markers. These data support the utility of noninvasive fibrosis markers as endpoints in NASH clinical trials.

Table. Predictors of Disease Progression

Variable*	Bridging Fibrosis (Progression to Cirrhosis)		Cirrhosis (Adjudicated Clinical Events)	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
Ishak stage				
BL 4 vs. 3	1.84 (1.29, 2.64)	0.0008	N/A	N/A
BL 6 vs. 5	N/A	N/A	7.76 (1.83, 32.83)	0.010
Hepatic collagen, %				
BL	1.24 (1.16, 1.32)	<0.0001	1.08 (1.03, 1.14)	0.004
Change from BL	1.20 (1.16, 1.23)	<0.0001	1.05 (1.01, 1.10)	0.020
α-SMA, %				
BL	1.10 (1.05-1.15)	< 0.0001	1.06 (1.01, 1.11)	0.011
Change	1.12 (1.10-1.15)	< 0.0001	1.04 (1.00, 1.09)	0.051
ELF				
BL	2.08 (1.74, 2.49)	<0.0001	3.79 (2.73, 5.26)	<0.001
Change from BL	1.42 (1.10, 1.84)	0.008	1.28 (0.75, 2.19)	0.36
NFS				
BL	1.54 (1.35, 1.74)	<0.0001	2.24 (1.64, 3.04)	<0.0001
Change from BL	1.78 (1.41, 2.24)	<0.0001	3.04 (1.90, 4.88)	<0.0001
LS by VCTE, kPa				
BL	1.07 (1.05, 1.08)	<0.0001	1.06 (1.04, 1.08)	<0.0001
Change from BL	1.04 (1.02, 1.06)	0.0005	1.04 (1.01, 1.07)	0.006

N/A, not applicable.
*Changes from baseline adjusted for baseline value.

Keywords: Noninvasive test of fibrosis, NASH

PE-181

Association between Non-Alcoholic Fatty Liver Disease and Subclinical Hypothyroidism in Pediatric Patients: A Multicenter Study from Korea

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Aims: It is uncertain whether nonalcoholic fatty liver disease (NAFLD) is associated with subclinical hypothyroidism (SH) in pediatric patients. The aim of this study is to investigate the prevalence and related factors of SH in pediatric patients with NAFLD. We also evaluate the association between liver fibrosis and SH.

Methods: In ten hospitals in Korea, medical records were reviewed retrospectively for patients under the age of 18 who were diagnosed with NAFLD and tested for thyroid function from January 2015 to December 2019. The association between NAFLD and SH was analyzed.

Results: 428 patients with NAFLD were included. The prevalence of SH in pediatric NAFLD patients was 13.6% (95% CI: 10.6%-17.1%). In multivariate logistic regression, more severe grades of steatosis on ultrasound and higher APRI (Aspartate aminotransferase (AST) to Platelet Ratio Index) score were associated with increased risk of SH. Using Receiver operating characteristic (ROC) curves, optimal cut-off value of APRI score for predicting SH was 0.6012(Area under the curve; AUC 0.67(*P*<0.001), sensitivity 72.4%, specificity 61.9%, positive predictions 23%, negative predictions 93.5%).

Conclusions: This study showed that the higher degree of liver steatosis and fibrosis, the more likely it is to be accompanied by SH. It is necessary to conduct thyroid function tests for pediatric NAFLD patients.

Keywords: Non-alcoholic fatty liver disease, Subclinical hypothyroidism, Pediatrics

PE-182

Light Dose of Alcohol Drinking and Risk of Fatty Liver: A Nationwide Population-Based Study

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Aims: Many studies defined the dose of alcohol in non-alcoholic fatty liver disease (NAFLD) as less than moderate drinking. Some literatures reported that light alcohol drinking (LAD) prevent the development of NAFLD. In this study, we investigated effect of LAD on the risk of fatty liver (FL).

Methods: The Korean health examinee study (2004-2017) was used. After exclusion of participants above moderate alcohol

drinking and without data of fatty liver index (FLI), 132,523 participants were enrolled. Participants were grouped as life time abstainer (LTA) and LAD group (current and ex-drinker). Current drinkers were further divided into <10 and ≥10 years of alcohol drinking. Ex-drinkers were divided into <10 and ≥10 years of alcohol withdrawal. FL was defined by FLI above 60. The risk of FL between LTA and LAD group was compared.

Results: The mean age and proportion of female were 52.9 ± 8.3 and 74.3%, respectively. The prevalence of FL in LTA (n=78829) and LAD group (n=53694) were 5.86% and 10.06%, respectively (*P*<0.001). Compared with LTA, LAD group had more proportion of male, younger age, obesity, diabetes mellitus, hypertension, and dyslipidemia. In evaluating FL risk, the odd ratio (OR) in LAD group was 1.32(95% CI: 1.25-1.40, *P*<0.001) after adjusting compounding factors (age, sex, body mass index, diabetes mellitus, hypertension, and dyslipidemia). The ≥10 years drinking group [1.69(95% CI: 1.35-2.10), *P*<0.001] had higher OR than that of the <10 years drinking group [1.16(95% CI: 1.00-1.35), *P*=0.06] after adjusting compounding factors. The <10 years withdrawal group [1.49(95% CI: 1.02-2.24), *P*=0.04] had higher OR than that of the ≥10 years of withdrawal group [1.27(95% CI: 0.89-1.81), *P*=0.19] after adjusting compounding factors.

Table 1. Univariate and multivariate analyses producing odds ratio for the risk of NAFLD among light drinker as compared to life time abstainer

The cross sectional association of light drinker (ex and current drinker) and the risk of NAFLD				
		Light drinker(ex and current drinker)	Life time abstainer	p
NAFLD risk	Crude HR [95%CI]	1.79 [1.72-1.87]***	1(reference)	<0.001
	Age, sex HR	1.18 [1.13-1.24]***	1(reference)	<0.001
	Model 1	1.34 [1.26-1.42] ***	1(reference)	<0.001
	Model 2	1.32[1.25- 1.40]***	1(reference)	<0.001
The association of light drinker (ex- drinker) and the risk of NAFLD				
NAFLD risk	Crude HR [95%CI]	2.30[2.12-2.49]	1(reference)	<0.001
	Age, sex HR	1.32[1.21-1.44]	1(reference)	<0.001
	Model 1	1.20[1.07-1.35]	1(reference)	0.001
	Model 2	1.16[1.03-1.29]	1(reference)	0.018
The association of light drinker (current drinker) and the risk of NAFLD				
NAFLD risk	Crude HR [95%CI]	1.73[1.66-1.81]	1(reference)	<0.001
	Age, sex HR	1.18[1.13-1.24]	1(reference)	<0.001
	Model 1	1.38[1.30-1.46]	1(reference)	<0.001
	Model 2	1.37[1.29-1.46]	1(reference)	<0.001

Model1: adjusted for age, sex, body mass index, total Calorie intake, total carbohydrate intake, total protein intake, total lipid intake, regular exercise, stress
Model2: adjusted for age, sex, body mass index, waist circumference, total Calorie intake, total carbohydrate intake, total protein intake, total lipid intake, regular exercise, alcohol ingestion duration, smoking status, diabetes mellitus type 2 history, hypertension history, and dyslipidemia
Abbreviation: NAFLD, non alcoholic fatty liver disease; HR, hazard ratio; 95%CI, 95% confidence interval

Table 2. Univariate and multivariate analyses producing odds ratio for the risk of NAFLD according to duration of alcohol ingestion among ex and current drinker

	Alcohol ingestion duration among ex drinker	Life time abstainer	Ex-light drinker (>10 year of alcohol withdrawer)	Ex-light drinker (≤10 year of alcohol withdrawer)	Life time abstainer	Current light drinker (≤10 year of alcohol ingestion)	Current light drinker (>10 year of alcohol ingestion)
NAFLD+	Crude HR [95%CI]	1 (reference)	2.81 [2.38-3.33] P<0.001	2.35 [2.11-2.62] P<0.001	1 (reference)	0.82[0.75-0.90] P<0.001	2.06[1.97-2.16] P<0.001
	Age, sex HR	1 (reference)	1.18 [0.99-1.40] P=0.05	1.15 [1.02-1.28] P=0.02	1 (reference)	0.91 [0.82-0.99] P=0.04	1.27 [1.21-1.33] P<0.001
	Model 1	1 (reference)	1.21[0.85-1.73] P=0.28	1.44[0.96-2.16] P=0.07	1 (reference)	1.12[0.96-1.30] P=0.14	1.71 [1.38-2.13] P<0.001
	Model 2	1 (reference)	1.2 7[0.89-1.81] P=0.19	1.49 [1.02-2.24] P=0.04	1 (reference)	1.16 [1.00-1.35] P=0.06	1.69 [1.35-2.10] P<0.001

Model1: adjusted for age, sex, body mass index, waist circumference, total Calorie intake, total carbohydrate intake, total protein intake, total lipid intake
Model2: adjusted for age, sex, body mass index, waist circumference, total Calorie intake, total carbohydrate intake, total protein intake, total lipid intake, regular exercise, alcohol ingestion duration, smoking status, diabetes mellitus type 2 history, hypertension history, and dyslipidemia
Abbreviation: NAFLD, non alcoholic fatty liver disease; HR, hazard ratio; 95%CI, 95% confidence interval

Conclusions: Compared to LTA, LAD was the independent risk factor for FL. Especially, LDAD ≥10 years and LDAD withdrawal <10 years were significant risk factor for FL.

Keywords: Fatty liver, Light dose of alcohol, Nationwide study

PE-183

Are there Beneficial Effects of Lifestyle Intervention in Non-Obese Patients with Non-Alcoholic Fatty Liver Disease?

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Aims: Currently, the population prevalence of NAFLD in Asia is around 25%, like many Western countries. Around 8-19% of patients with non-alcoholic fatty liver disease (NAFLD) are non-obese. The benefit of weight reduction in such patients is unclear. We aim to study the efficacy of lifestyle intervention in non-obese patients with NAFLD and to identify factors that predict treatment response.

Methods: A total of 50 community NAFLD patients were randomized to a 12-month lifestyle intervention program involving regular exercise, or to standard care. The primary outcome was to improve NAFLD at Month 12 by Abdominal Ultrasonography. After the program, the patients were prospectively followed until Year 3. The Asian body mass index (BMI) cut-off of 25 kg/m^2 was used to define non-obese NAFLD.

Results: Patients were assigned to the intervention (n=25) and control (n=25) groups. More patients in the intervention

group achieved the primary outcome than the control group regardless of baseline BMI (non-obese: 64% vs. 18%, *P*<0.001; obese: 58% vs. 21%, *P*<0.001). Lifestyle intervention, lower baseline triglyceride, and reduction in body weight and waist circumference were independent factors associated with remission of NAFLD in non-obese patients. Half of the non-obese patients achieved remission of NAFLD with 3-5% weight reduction; the same could only be achieved in obese patients with 7-10% weight reduction. By Year 3, non-obese patients in the intervention group remained more likely to maintain weight reduction and alanine aminotransferase normalization than the control group.

Conclusions: Lifestyle interventions are effective in improving NAFLD in both obese and non-obese patients. Moderate weight loss may be sufficient, especially in non-obese patients.

Keywords: NAFLD, Non-obese, Lifestyle Intervention

PE-184

Long-Term Use of Antibiotics and the Risk of Non-Alcoholic Fatty Liver Disease: A Prospective Cohort Study among Women

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Aims: Gut microbial dysbiosis is associated with the development of nonalcoholic fatty liver disease (NAFLD). Antibiotics can alter the composition of the gut microbiota. However, the association of antibiotic use with the risk of NAFLD has not been clarified in a population at usual risk. We investigated the association of the duration of antibiotic use in different phases of adulthood with the risk of NAFLD.

Methods: This study included 68,644 women in the Nurses' Health Study II cohort without NAFLD at baseline (in 2005). Participants were followed prospectively through 2015. In the 2005 questionnaire, women were asked to indicate the cumulative amount of antibiotic use at age 20–39 years (young adulthood) or 40–49 years (middle adulthood). Cox proportional hazard models were used to estimate multivariable adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs).

Results: Over a total of 534,644 person-years, we documented 1,944 incident cases of NAFLD. Compared to women with no antibiotic use during young adulthood, use of long-term antibiotics for ≥2 months was associated with significantly increased risk of incident NAFLD (multivariable aHR 1.48, 95% CI 1.03–2.11). In analyses focused on middle adulthood, compared to women who did not use antibiotics during middle adulthood, those with both short-term (<2 months) and long-term (≥2 months) antibiotics use had significantly increased risk of incident NAFLD (multivariable aHRs, 1.32 [95% CI 1.01–1.72] and 1.83 [95% CI 1.37–2.45], respectively).

Conclusions: In conclusion, long-term antibiotic use in both young and middle adulthood was associated with a significantly increased risk of developing incident NAFLD. These findings support the potential role of the gut microbiota in the pathogenesis of NAFLD.

PE-185

A Prospective Cohort Study of Red Meat Consumption and Non-Alcoholic Fatty Liver Disease Risk Among Women

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Aims: Previous studies have suggested consumption of red meat might be associated with an increased risk of developing nonalcoholic fatty liver disease (NAFLD). However, large-scale, prospective data regarding red meat consumption in relation to the incidence of NAFLD are lacking, nor is it known whether this association is mediated by obesity.

Methods: This prospective cohort study included 77,795 women in the Nurses' Health Study II cohort without NAFLD at baseline (in 1995), who provided detailed, validated information regarding diet, including consumption of red meat, every 4 years, through 2015. Lifestyle factors, clinical comorbidities and body mass index (BMI), were updated biennially. Cox proportional hazard models were used to estimate multivariable adjusted

hazard ratios (aHRs) and 95% confidence intervals (CIs).
Results: Over 1,444,637 person years of follow-up, we documented 3,130 cases of incident NAFLD. Women consuming ≥2 servings of red meat per day had a 56% higher risk of developing incident NAFLD compared to women consuming ≤1 serving per week (95% CI, 1.26-1.93), after multivariable adjustment. Similarly, significant and positive associations were observed for both unprocessed and processed red meat (both *P*-trend<0.0001). However, after further adjustment for BMI, all associations for red meat, including unprocessed and processed red meat, were attenuated and not statistically significant (all *P*-trend>0.05). BMI was estimated to mediate 66% (95% CI, 41.9%-83.9%; *P*<0.0001) of the association between red meat consumption and NAFLD risk.
Conclusions: Red meat consumption, including both unprocessed and processed red meat, was associated with significantly increased risk of developing NAFLD. This association was mediated largely by obesity.

PE-186

Non-Alcoholic Fatty Liver Disease in Pregnant Women

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Aims: Non-alcoholic fatty liver disease (NAFLD) is considered the commonest liver disease in the last year. The most common risk factor associated with NAFLD is the presence of the metabolic syndrome and type 2 diabetes. There are no studies of NAFLD in pregnant women in Mongolia. We aimed to investigate pregnancy outcomes in NAFLD.
Methods: Pregnant volunteers (n=31) were referred to the obstetric medicine clinic of Dornod Medical center, Dornod, Mongolia. All pregnant had tests for blood chemistries ALT (0-45 u/l), AST (0-35 u/l), cholesterol (349 mg/dl), triglyceride (<453 mg/dl), HBsAg, Anti-HCV, BMI (calculator.net), gestational age and abdominal ultrasound scans using accepted criteria.
Results: The BMI in before pregnancy 1 (3.2%) women as underweight, 16 (51.6%) as normal weight, 7 (22.5%) as overweight and 8 (25.8%) as obese. During the pregnancy BMI were 13 (41.9%) as overweight and 14 (45.1%) as obese, compared to before pregnancy increased percent overweight and obese. The average of BMI before pregnancy was 26.2 ± 5.4 and during pregnancy BMI average 30,39 ± 5.1 (P value 3.5 * 10-5), this was shown to increasing obesity during pregnancy. Nineteen pregnant had fatty liver on ultrasound, in 16 (84.2%) increased than the weight should be, during pregnancy. Among the five patients that developed abnormal liver function test. One patient with hypercholestrinemia, and another one with hyperglycemia.
Conclusions: Ultrasound is a noninvasive and useful diagnostic tool in the detection of NAFLD. Most of pregnant women with NAFLD have normal AST and ALT. This study has shown that having are overweight and obesity increased in pregnant women is associated with increased risks for diagnosis of NAFLD.
Keywords: Nonalcoholic Fatty Liver Disease, Pregnant Women

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Small Dense LDL Level and Non-Alcoholic Fatty Liver Disease: Possibility of a New Biomarker

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Aims: Small dense low-density lipoprotein (sdLDL) is a distinct low-density lipoprotein (LDL) cholesterol subclass that has been reported to be associated with metabolic disease. On the other hand, the relationship between the sdLDL level and the non-alcoholic fatty liver disease (NAFLD) severity is unclear. In this study, the sdLDL level was measured in patients with NAFLD to assess its potential as a biomarker for evaluating NAFLD.
Methods: 126 patients diagnosed with NAFLD at a single referral hospital from January 2018 to August 2019 were enrolled. The lipoprotein profile was analyzed from a blood test of NAFLD patients, and transient elastography (TE, Fibroscan®) was performed to evaluate the degree of NAFLD.
Results: Among the 126 patients, 83 patients that could confirm the lipoprotein profile and TE results were finally enrolled in the study. The controlled attenuation parameter (CAP) value obtained from TE did not show any correlation with the total cholesterol, LDL. But, the sdLDL level showed a significant positive correlation with the CAP value (r=0.237, *P*=0.031), and the sdLDL/LDL ratio also showed a significant positive correlation with the CAP value (r=0.235, *P*=0.032). The liver stiffness (LS) measured by TE and the sdLDL level were positively correlated in patients with NAFLD (rho=0.217, *P*=0.049). The sdLDL/LDL ratio also showed a significant positive correlation with the LS value (rho=0.228, *P*=0.038). In addition, the fatty liver index also showed a significant positive correlation with the sdLDL/LDL ratio (r=0.448, *P*=0.000).
Conclusions: In this study, the sdLDL level measured by a blood test of NAFLD patients showed a positive correlation with the CAP value and LS, which indicate the degree of hepatic steatosis and fibrosis. These results suggest the possibility of the sdLDL level as a new biomarker of NAFLD, but further studies will be needed to support these results.
Keywords: LDL, NASH, Biomarker

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The Association between Non-Alcoholic Fatty Liver Disease and Stroke: Results from The Korean Genome and Epidemiology Study (KoGES)

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Aims: Non-alcoholic fatty liver disease (NAFLD) is associated with various cardiometabolic diseases. However, the association between NAFLD and stroke is not well known. Therefore, this study aimed to characterize the role of NAFLD in the risk of stroke in middle-aged adults based on a prospective cohort study in Korea.

Methods: Using data from a Korean prospective cohort study, we excluded participants with heavy alcohol consumption and history of stroke; hence, 7,964 adults aged 40–69 years were included in this study. According to their fatty liver index (FLI), participants were divided into three groups: <30 (n=4,550, non-NAFLD), 30–59.9 (n=2,229, intermediate), and ≥60 (n=1,185, NAFLD). The incidence of stroke according to the degree of FLI was evaluated using the Cox proportional hazard model.

Results: During the 12-year follow-up period, 168 strokes occurred. A graded association between NAFLD and stroke incidence was observed, i.e., 1.7% (n=76), 2.5% (n=56), and 3.0% (n=36) for non-NAFLD, intermediate, and NAFLD FLI groups, respectively. After adjusting for confounding variables and compared to the risk of stroke in the non-NAFLD group, the risk of stroke in the NAFLD group was the highest (hazard ratio [HR]: 1.98, 95% confidence interval [CI]: 1.17–3.34), followed by the risk of stroke in the intermediate group (HR: 1.41, 95% CI: 0.94–2.21) (p for trend < 0.001). However, the level of aspartate aminotransferase, alanine aminotransferase, or gamma-glutamyltransferase alone did not show any significant association with stroke.

Conclusions: This study demonstrated that the risk of stroke gradually increased with the degree of FLI. Individuals with NAFLD should be properly counseled and monitored for risk for stroke.

Keywords: Non-alcoholic fatty liver disease, Stroke, Fatty liver index, Korean Genome and Epidemiology Study

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Development and Validation of the Non-Alcoholic Fatty Liver Disease Self-Management Questionnaire

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Aims: Non-alcoholic fatty liver disease (NAFLD) is one of common causes of chronic liver disease. The prevalence of NAFLD is increasing with other weight related disease such as obesity, diabetes and metabolic diseases. Self-management is known as a crucial key to improve health outcomes of patients with chronic diseases including NAFLD. However, there is no instrument to measure the level of self-management for patients with NAFLD. This study aims to develop and validate NAFLD self-management questionnaires.

Methods: A 23-item of Non-Alcoholic Fatty Liver Disease Self-Management Questionnaire (NAFLD-SMQ) was initially developed after theoretical and literature review by three phases: (1) Items generation; (2) Evaluation of the items; and (3) Psychometric evaluation. Data collection was from April-November in 2019. Participants were 155 individuals recruiting from S hospital in South Korea. The questionnaire was tested by the construct validity using for exploratory factor analysis.

Results: Items of the questionnaire were generated based on guideline for patients with NAFLD and the Individual and Family Self-Management Theory. A six-factor was extracted from construct validation using exploratory factor analysis: lifestyle management, drinking management, sleep management, health-supplements management, medical treatment compliance, and family support. These factors accounted for 66.2% of total variation, and have an eigenvalue higher than 1 in the scale. The corrected item-total correlation coefficients ranged 0.33-0.59, and all items were significantly correlated with the total score. Cronbach's alpha of the total items was 0.87.

Conclusions: The NAFLD-SMQ was developed through three phases, and the results of EFA were determined to be valid and reliable. Healthcare providers should assess and evaluate the level of self-management to provide tailored interventions based on their care needs. This instrument would provide useful information for healthcare providers who assess self-management level for individuals with NAFLD. In addition, it may be used as the indicator of health outcomes in this population.

Keywords: Non-alcoholic fatty liver disease, Questionnaire development, Self-management, Exploratory factor analysis

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Risk of Dementia in Non-Alcoholic Fatty Liver Disease Subjects: A Nationwide Nested-Case Control Study

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Aims: Nonalcoholic fatty liver disease (NAFLD) is known to be associated with metabolic syndrome in which diabetes is an im-

portant component. Diabetes is also known to be a risk factor for dementia. This study aimed to determine whether NAFLD would be a risk factor for development of dementia in an elderly population.

Methods: This study included 107,369 subjects aged ≥60 years in the Korea National Health Insurance Service-Senior cohort, entered in 2009 and followed up until 2016. NAFLD was diagnosed by calculating fatty liver index (FLI). Subjects were screened for dementia at baseline using a Korean Dementia Screening Questionnaire and dementia was diagnosed using ICD-10 codes. Controls were randomly selected at a ratio of 1:5 from individuals who were at risk of becoming the case subjects at the time of selection.

Results: From 107,369 subjects, 68,898 stroke and dementia free subjects without chronic hepatitis B or C or excessive alcohol drinking were evaluated. Having NAFLD, determined by FLI was associated with increased risk of dementia development (AOR [adjusted odd ratio] 1.521; 95% CI [confidence interval] 1.003-2.306). The increased risk of dementia in NAFLD subjects was independent of type 2 diabetes (AOR 1.362; 95% CI 1.067-1.739).

Conclusions: In this population based study, having NAFLD increased risk of dementia, independent of diabetes.

Keywords: Nonalcoholic fatty liver disease, Dementia, Population based study, Metabolic syndrome

PE-191

Clinical Characteristics of Non-Alcoholic Fatty Liver Patients with Antinuclear Antibody Positivity

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Aims: For the diagnosis of nonalcoholic fatty liver disease (NAFLD), autoantibodies are tested to exclude autoimmune liver disease, and clinical significance of the autoantibodies found in NAFLD patients was not clear. The aim of this study were to investigate the positive rate of antinuclear antibody (ANA) in NAFLD patients, and to compare clinical characteristics between ANA-positive and ANA-negative group of NAFLD.

Methods: We retrospectively enrolled patients who have diagnosed as NAFLD and underwent ANA test between 2003 and 2019 in a Korean tertiary hospital by searching the clinical data warehouse. After exclusion of autoimmune diseases and combined alcoholic liver diseases, clinical characteristics of ANA-positive group were compared to those of ANA negative group using 1:1 Propensity matching.

Results: Among 966 NAFLD patients (464 males and 472 females), the ANA positive rate was 10.6% . ANA positive group (n=99) showed higher mean age (55.9 years vs. 50.2 years, *P*=0.0002), and higher proportion of female (64.6% vs. 48.7%, *P*=0.0028), lower albumin (4.4g/dL vs 4.5g/dL, *P*=0.0210), and higher globulin level (3.0g/dL vs 2.9g/dL, *P*<0.0001), higher fibrosis score of FIB-4(1.8 vs 1.4, *P*<0.0001), APRI(0.6 vs 0.5, *P*=0.0272), and NFS(-1.3 vs -1.6, *P*=0.0123), and higher value in transient elastography (7.3kPa vs. 6.0kPa, *P*=0.0295) than ANA negative group. After propensity matching based on age and sex between ANA positive group and ANA negative group, ANA positive group showed higher in mean globulin level (3.0g/dL vs. 2.8g/dL, *P*=0.0034), IgG level (1342 mg/dL vs. 1237 mg/dL, *P*=0.0379), higher FIB-4 score(1.8 vs 1.6, *P*=0.0358), and higher value in transient elastography (7.3kPa vs. 5.8kPa, *P*=0.0408).

Conclusions: The ANA positivity in NAFLD was 10.6%, and it was related to higher level of immunoglobulin and higher degree of fibrosis. Further study on the mechanism of autoantibody production and progression of NAFLD is warranted.

Keywords: NAFLD, ANA

PE-192

Characteristics of Asymptomatic Patients with an "Elevated Serum Alpha-Fetoprotein Level" and Its Relationship with Hepatic Steatosis and Visceral Adiposity

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Aims: Alpha-fetoprotein (AFP) is a well-known biomarker of liver cancer and liver injury. However, apparently healthy individuals having AFP elevation on heath check-ups were encountered in clinics. Their clinical features and cause of AFP elevation were not clear. Thus, we aim to investigate the clinical characteristics of the patients with an "elevated AFP level" (>7 ng/mL cutoff), and its relation with body fat deposition in terms of hepatic steatosis and visceral adiposity.

Methods: Patients having a diagnostic code of "elevated AFP level" (R772) were searched from 2009 to 2018 in a tertiary hospital. After excluding patients with any malignancies, liver cirrhosis, or viral hepatitis, 146 patients were included in the case group. As a control group, age and sex-matched 146 hepatic hemangioma (<3cm) patients were selected. Among the subgroup of case (n=49) and controls (n=49) who underwent liver CT, hepatic fat and visceral fat were measured using the pre-contrast CT image.

Results: The case group showed a mean age of 48.7 years, male proportion of 64.4%, and a higher mean serum AFP level (12.76 ng/mL) than the control (2.85 ng/mL). The case group showed a higher prevalence of dyslipidemia (21.2 vs 3.4%,

P<0.001) and hypertension (11.6 vs 4.8%, *P*=0.033), but a lower body mass index (BMI) (22.68 vs 23.85 kg/m^2, *P*=0.003) than the control. Total-bilirubin level was higher in the case group (0.8 vs 0.5 mg/dL, *P*<0.001), but other laboratory results were similar to the control group. Hepatic fat measured by Hounsfield units of 8 regions of liver segments and visceral adiposity index in the subgroups of case and control were not different (59.40 vs 61.76, *P*=0.158 and 28.53 vs 27.32 cm^2/m^2, *P*=0.788, respectively).

Conclusions: Asymptomatic patients with an elevated AFP level showed a higher prevalence of hypertension and dyslipidemia despite lower BMI than controls. Its relationship with abnormal fat metabolism warrants further study.

Keywords: Alpha-fetoprotein, Hepatic steatosis, Visceral adiposity, Hypertension, Dyslipidemia

PE-193

Early Responders to Liraglutide 3.0 mg as Adjunct to Diet+Exercise from the SCALE Maintenance Trial

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Aims: The SCALE Maintenance trial randomized adults with obesity (BMI>30 kg/m2) or overweight (BMI>27 kg/m2) + comorbidities who lost >5% of initial body weight (BW) during a 4-12 week low calorie diet (1200-1400 kcal/day) run-in period (mean weight loss [WL]: 6.0%) prior to randomization to liraglutide 3.0 mg or placebo as an adjunct to diet and exercise

Methods: This post-hoc analysis of SCALE Maintenance compared outcomes in liraglutide 3.0 mg early responders vs. early non-responders (definition: ERs vs. ENRs; >4% vs. <4% WL at week 16 post-randomization). Efficacy outcomes are observed means or proportions for those completing 56 weeks treatment. The safety analysis set is used for adverse events (AEs).

Results: Mean characteristics at randomization (n=212) for liraglutide 3.0 mg were: 46 years old, 84% female, BMI 36 kg/m2. Of those completing 56 weeks treatment, (n=159); 118 (74.2%) were ERs to liraglutide 3.0 mg and 41 (25.8%) ENRs. At week 56, mean WL was -9.2% in ERs vs. +0.3% in ENRs in addition to run-in WL. 89.8% of ERs maintained run-in weight loss (or lost further weight) during 56 weeks vs. 41.5% of ENRs. The percentage of those who regained all run-in WL by week 56 was 0.0% for ERs vs. 14.6%, 0.0% and 0.0% for ENRs. Percentage achieving >5%, >10% or >15% WL at week 56 was 66.9%, 43.2% and 18.6% for ERs vs. 14.6%, 0.0% and 0.0% for ENRs. ERs had greater change in mean waist circumferrence: -7.3cm vs. +0.3cm in ENRs. Serious AEs were 4.4% vs. 0.0% and GI AEs 78.1% vs. 60.4% for ERs vs. ENRs, respectively

Conclusions: Among those who completed 56 weeks treatment on liraglutide 3.0 mg. a greater additional WL of -9.2% was observed for ERs vs. +0.3% for ENRs, with a similar proportion experiencing AEs.

Keywords: Liraglutide 3.0 mg, Obesity, Weight management, GLP-1RA

PE-194

Three "DS" – Elements for Successful Weight Loss Outcomes: Role of Healthcare Professionals

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Aims: In people with obesity (PwO), body weight loss of ≥5% is generally considered to be clinically meaningful. Some PwO do receive treatment and guidance from healthcare professionals (HCPs), but there remains a substantial unmet medical outcomes and weight maintenance need. To identify aspects that might contribute to a successful weight loss outcome (WLO; ≥5% body weight loss maintained for ≥1 year), we investigated the characteristics and experience of PwO with and without successful WLOs using data from the ACTION-IO study (NCT03584191).

Methods: An online survey was completed by adults with obesity and HCPs in 11 countries: Australia, Chile, Israel, Italy, Japan, Mexico, Saudi Arabia, South Korea, Spain, UAE and UK. A successful WLO was defined as ≥5% body weight loss in the past 3 years maintained for ≥1 year.

Results: A total of 14,502 PwO completed the survey. General characteristics were similar between those who had a successful WLO (n=1,559; 11%) vs those who had not (n=12,943; 89%): 53% vs 52% were male; the mean age was 49 vs 48 years; the mean number of comorbidities was 2.0 vs 1.8. The mean number of serious weight loss attempts was 4 for both groups. However, more PwO who had a successful WLO weighed themselves every day (20%) compared with those

who had not had a successful WLO (10%). In terms of interactions with HCPs, more PwO who had a successful WLO had discussed weight (58%) with an HCP within the past 5 years than those who did not have a successful WLO (53%). In addition, more PwO who had a successful WLO compared with those who did not had been diagnosed with obesity (42% vs 35%) and had subsequent direction through the scheduling of a follow-up appointment (25% vs 21%).

Conclusions: A 3D approach from HCPs (diagnosis, discussion and direction) appears to be a key element in facilitating a successful WLO. Neither gender, nor age, nor number of weight loss attempts was associated with a successful WLO.

Keywords: Obesity, Chronic disease, Awareness, Weight management

PE-195

Risk Factors Associated with Significant Liver Fibrosis in Patients with Non-Alcoholic Fatty Liver Disease Using Magnetic Resonance Elastography

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Aims: Magnetic resonance elastrography (MRE) is a noninvasive method to assess liver fibrosis in chronic liver disease. This study aimed to investigate the risk factors for liver fibrosis, assessed by MRE, in patients with nonalcoholic fatty liver disease (NAFLD).

Methods: A cross-sectional study was conducted in 641 patients with NAFLD based on a cohort from Kangbuk Samsung Hospital health screening programs 2015-2018. Liver stiffness measurement (LSM) was evaluated using 2-dimensional real-time MRE. Significant liver fibrosis was defined as LSM ≥2.97 kPa. We investigated significant liver fibrosis and its risk factors in patients with NAFLD.

Results: The mean age was 50.8 years and male was 546 patients (85%). The proportions of hypertension, diabetes mellitus, and metabolic syndrome were 30%, 17%, and 34%, respectively. The mean value of LSM in MRE was 2.44 ± 0.40 kPa. Of 641 patients, significant liver fibrosis (LSM ≥2.97 kPa) was observed in 41 patients (6.4%). The multivariable analysis showed that significant liver fibrosis was associated with body mass index ≥27.5 kg/m^2 (odds ratio [OR], 3.18; 95% confidence interval [CI], 1.56–6.46; *P*=0.001), Fibrosis-4 (FIB-4) index ≥1.3 (OR, 2.35; 95% CI, 1.15–4.80; *P*=0.020), metabolic syndrome (OR, 2.69; 95% CI, 1.26–5.75; *P*=0.010), and diabetes mellitus (OR, 4.55; 95% CI, 2.27–9.15; *P*<0.001).

Conclusions: High levels of BMI and FIB-4 index, metabolic syndrome, and diabetes mellitus were the risk factors for significant liver fibrosis in patients with NAFLD.

Keywords: Nonoalcoholic fatty liver disease, Liver fibrosis, Magnetic resonance elastography

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Correlation between Serum Vitamin D Level and Hepatic Steatosis Index in Patients with Non-Alcoholic Fatty Liver Disease

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Aims: Vitamin D deficiency is commonly seen in patients with non alcoholic fatty liver disease (NAFLD). However there is no previous study to explore the correlation between serum vitamin D and hepatic steatosis index (HSI) in NAFLD patients. This study is to find out correlation between serum vitamin D and HSI.

Methods: Eighty NAFLD patients were included in our study. NAFLD was diagnosed by abdominal ultrasonography. Statistical analysis was done by using SPSS software

Results: Mean age of our study population was 50.2 ± 12.71 years. Mean serum vitamin D level and HSI were 19.61 ± 8.14 ng/ml 38.16 ± 6.08 respectively. 53.75% NAFLD patients were suffering from vitamin D deficiency. Grade I fatty liver was seen in majority of NAFLD patients. Serum vitamin D did not show any significant correlation with hepatic steatosis index (*P*=0.965; r value= 0.005). Multivariate linear regression analysis showed only age (*P*=0.001) and smoking (*P*=0.019) were significantly associated with serum vitamin D level.

Conclusions: Grade I fatty liver are common in NAFLD patients and majority of NAFLD patients are suffering from vitamin D deficiency. There is no significant correlation between serum vitamin D level and Hepatic steatosis index in patients with NAFLD diagnosed by ultrasonography.

Keywords: NAFLD, Vitamin D level, Hepatic steatosis Index, Correlation

PE-197

Prebiotics' Plus Probiotics' Effect on the Patients with Non-Alcoholic Fatty Liver Disease

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Aims: Non-alcoholic fatty liver disease (NAFLD) is a very common disorder caused by a build-up of fat in the liver, often affecting overweight or obese people. Intestinal microbiota has been proved to play a role in the pathogenesis and development of obesity and NAFLD. The aim of the study was to explore the impact of probiotics' plus prebiotics' (synbiotics) on the patients with NAFLD.

Methods: We studied 79 patients in total. Control group with placebo was included. A mixture of 6 probiotic agents (Bifidobacterium bifidum, Bifidobacterium longum, Lactobacillus fermentum, Lactobacillus plantarum, Lactobacillus acidophilus, E-Coli M-17) and an auxiliary prebiotic component: fructooligosaccharide 50 mg. was prescribed to 41 patients (I group) with elevated aminotransferase and serum triglyceride (TGs) levels for 16 weeks versus 38 patients (II group) who were given placebo. Overall, in the patients alcohol consumption accounted for less than 30g/day. Lifestyle modification was advised for both groups. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), TGs, Body Mass Index (BMI), ultrasonographic grades of fatty liver were assessed in the end of the trial.

Results: Totally, 73 patients completed the study (6 dropped out in the I group). In the first group there was a significant reduction in the serum aminotransferase levels (*P*=0.001) and TGs levels (*P*=1.0) comparing the placebo group. (*P*=0.998 and *P*=0.993, respectively). BMI reduction and improvement in ultrasonographic grading was more remarkable in synbiotics' group.

Conclusions: Synbiotics showed good results in 16 weeks in the treatment of NAFLD along with lifestyle modificitanion.

PE-198

Race Does Not Affect the Performance of Noninvasive Tests for the Discrimination of Advanced Fibrosis due to Non-Alcoholic Steatohepatitis(NASH)

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Background: Routinely available noninvasive tests of fibrosis (NITs) can be used to identify patients with advanced fibrosis due to NASH, but their performance may vary by race. Our aim was to evaluate the effect of patient race on the diagnostic performance of NITs using data from the global phase 3 STELLAR studies of selonsertib.

Methods: The STELLAR studies (NCT03053050 and NCT03053063) enrolled patients with bridging fibrosis (F3) or compensated cirrhosis (F4) due to NASH (NAFLD Activity Score [NAS] ≥3). Baseline liver biopsies were centrally read using the NASH Clinical Research Network classification and NITs, including the NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index, Enhanced Liver Fibrosis (ELF) test, and liver stiffness by transient elastography (LS by TE) were measured. The performance of these tests to discriminate advanced (F3-F4) fibrosis by self-reported patient race was evaluated using areas under the receiver operating characteristics curves (AUROCs) with 5-fold cross-validation repeated 100x. Results for White and Asian patients are presented; data for other races (5% of patients screened) are excluded.

Results: Among 3202 patients screened for the STELLAR studies with evaluable liver histology, 24% were Asian and 71% were White. The median age was 58 years in both groups; 47% of Asians and 57% of Whites were female (p<0.0001). The prevalence of F3-F4 fibrosis was 67% in Asians and 72% in Whites (p=0.01). AUROCs for each of the NITS for the discrimination of advanced fibrosis were similar between Asian and White patients (Table). In general, literature-based thresholds for the NITs had similar sensitivity and specificity among the specific racial subgroups.

Conclusion: In these large, global phase 3 trials, the diagnostic performance of routinely available NITs for the discrimination of advanced fibrosis due to NASH was acceptable and similar between Asian and White patients.

Table. Diagnostic Performance of NITs to discriminate advanced fibrosis (F3-F4) in Asian and White patients screened for the STELLAR studies

NIT	AUROC (95% CI)*	Cutoff	% (95% CI)			
			Sensitivity	Specificity	PPV	NPV
NFS						
White (n=1710)	0.73 (0.73, 0.73)	>0.676	40 (37, 43)	87 (83, 91)	93 (91, 95)	25 (22, 28)
Asian (n=581)	0.75 (0.74, 0.75)		33 (29, 38)	92 (86, 96)	94 (89, 97)	28 (23, 32)
FIB-4						
White (n=2225)	0.78 (0.78, 0.78)	>2.67	33 (30, 35)	93 (91, 95)	93 (91, 95)	34 (32, 36)
Asian (n=732)	0.80 (0.79, 0.80)		48 (44, 53)	90 (85, 93)	91 (87, 94)	44 (39, 49)
ELF						
White (n=2259)	0.79 (0.79, 0.79)	>11.3	19 (17, 21)	98 (96, 99)	96 (93, 98)	31 (29, 34)
Asian (n=745)	0.81 (0.81, 0.81)		24 (20, 28)	96 (93, 98)	93 (87, 97)	37 (34, 41)
LS by TE						
White (n=1244)	0.79 (0.79, 0.80)	>11.4	77 (74, 79)	68 (60, 75)	94 (92, 96)	30 (26, 35)
Asian (n=427)	0.82 (0.81, 0.82)		73 (68, 78)	77 (67, 84)	91 (87, 94)	48 (40, 56)

*AUROC and 95% confidence interval (CI) were based on repeated 5-fold cross-validation (CV) 100x.

NAFLD, Basic

PE-199

The Effects of Fermented and Non-Fermented Soymilk (Glycine max) Beverage on Superoxide Dismutase Activity in Liver Tissue of Hyperlipidemic Rats (Rattus Norvegicus)

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Aims: Hyperlipidemia and oxidative stress are risk factors for various diseases such as cancer and increase the risk of liver stenosis. Reactive oxygen species arising from oxidative stress in hyperlipidemic conditions can cause liver cell damage. Superoxide Dismutase is a natural antioxidant in the body to fight oxidative stress. Soybeans have long been known to have good effects on health. Soybeans contain oligosaccharides which are good for the growth of probiotic bacteria. Probiotics can reduce lipid levels and have antioxidant activity. The aim of this study was to determine the effect between ferments and non-fermented soy drinks on superoxide dismutase activity in hyperlipidemic rat liver tissue.

Methods: The subjects are male Wistar (Rattus norvegicus) strain rats 2-3 months with body weight 200-300 grams divided into 4 groups (K+, K-, P1, and P2). Group of K+, P1, and P2 were given quail egg yolk for 2 weeks with a dose of 5 ml while group of K- were only given fed ad libitum. For the next 2 weeks, P1 group was given non-fermented soymilk (5 ml), and fermented soymilk (5 ml) for P2 group. All rats terminated to taken the liver tissue to measure the level of superoxide dismutase activity. All data were statistically analyzed with one way ANOVA. Values were considered significant at $P<0,05$.

Results: Mean of superoxide dismutase activity (expressed in percent (%)) in rats was 68,75 ± 1,68 in K- group, 16,08 ± 1,33 in K+ group, 41,79 ± 1,33 in P1 group and 57,81 ± 2,38. The One-Way ANOVA test showed significant differences in superoxide dismutase activity between group with $P<0,001$ and Bonferroni Post Hoc test $P<0,001$.

Conclusions: Fermented and non-fermented soymilk has a significant effect of increasing superoxide dismutase activity in hyperlipidemic rat liver tissue. Fermented soymilk has a higher superoxide dismutase activity compared to non-fermented soymilk.

Keywords: Fermenetd soymilk, Hyperlipidemia, Liver, Non-fermenetd soymilk, Superoxide dismutase activity

PE-200

Beneficial Effects of Vitamin E on Liver Fibrosis an A Non-Alcoholic Steatohepatitis (NASH) Rodent Model

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Aims: Nonalcoholic steatohepatitis (NASH) is a major form of chronic liver disease and is becoming the leading indication for liver transplantation. In addition to being a major contributor to death from liver disease, NASH imposes a substantial economic burden on health care systems in developing countries. Vitamin E is a potent antioxidant, anti-inflammatory that has been shown to reduce oxidative stress in diabetic patients. We investigated the effects of Vitamin E in preventing liver fibrosis in a rodent model of NASH.

Methods: Adult Sprague-Dawley rats were fed a choline-deficient high-fat diet and exposed to diethylnitrosamine for 6 weeks. The NASH group (n=10) received vehicle and the Vitamin E group (n=10) received 10 IU/kg/day by gavage. A control group (n=4) received only standard diet and vehicle. Following treatment, animals were sacrificed and liver tissue was collected for histologic examination, mRNA isolation, lipoperoxidation analysis and analysis of mitochondrial function. Genes related to fibrosis (MMP9, TIMP1, TIMP2), oxidative stress (HSP60, HSP90, GST), and mitochondrial biogenesis (PGC1a) were evaluated by real-time quantitative polymerase chain reaction (RT-qPCR). Liver mitochondrial oxidation activity was measured by a polarographic method, and cytokines by enzyme linked immunosorbent assay (ELISA).

Results: Vitamin E treatment restored mitochondrial function and reduced lipoperoxidation levels, collagen deposition by nearly 76% compared to the NASH group. Vitamin E upregulated PGC1a and MMP9 and reduced TIMP1 and TIMP2 mRNA and IL-6 and IL-10 protein expression. There were no significant differences in HSP60, HSP90 and GST expression.

Conclusions: Vitamin E modulated PGC1a expression, improved mitochondrial respiration and prevented collagen deposition. It may, therefore, be useful in the treatment of liver fibrosis in NASH.

Keywords: Nonalcoholic steatohepatitis, Vitamin E, Mitochondrial biogenesis, Oxidative stress

PE-201

Circulating Levels of Proinflammatory Cytokines in T2DM Patients with Non-Alcoholic Fatty Liver Disease

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Aims: Type 2 diabetes mellitus (T2DM) is associated with chronic inflammation and oxidative stress, implicated in the patho-

physiology of non-alcoholic fatty liver disease. Oxidative stress plays an important role in the development of vascular complications in type 2 diabetes. Oxidant derived tissue injury occurs when production of oxidants or reactive oxygen species (ROS) exceeds local antioxidant capacity. Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL-6) and various growth factors in hepatic cells modulate the local response are responsible for liver injury.

Methods: 10 ml of fasting venous blood was collected from the anticubital vein in a plain, fluoride and EDTA vacutainers. The blood sample was centrifuged and stored at 4^0 C for biochemical and immunological investigations. The study group consisted of n=50 healthy individuals (Group I), n=25 Type II Diabetic without NAFLD (Group II), n=25 Type II diabetic with NAFLD (Group III) of either sex aged between 50-65 years. The diagnosis of NAFLD was done by ultrasonographic examination of liver. Serum levels of inflammatory markers (IL-6 & TNF-α), antioxidants (Glutathione reductase), plasma malondialdehyde (MDA), hs-CRP were estimated.

Results: Concentration of inflammatory molecules such as TNF-α 9.32±1.08, 14.04±1.42 and 36.56±10.50; IL-6 9.24±1.20, 14.14±1.50 and 36.76±11.56; hs-CRP 0.90±1.10, 1.96±0.50 and 2.18±0.90 was significantly elevated in Group III. GSH were significantly lower in both the groups of Diabetic with and without NAFLD when compared to controls. 7.10±0.58, 6.90±0.70 and 5.80±0.80. Mean value of total MDA 2.32±0.98, 8.68±2.50 and 9.80±2.72 was significantly more in Group III as compared to Group I and Group II.

Conclusions: Results of the present study indicates that inflammatory markers and oxidative stress are increased with decreased antioxidant defense levels in patients with NAFLD in T2DM.

Keywords: T2DM, Cytokines, NAFLD, Antioxidants

PE-202

Expression Analysis of Immune Markers in Non-Alcoholic Steatohepatitis Identifies Activated Macrophages as Key Mediators of Inflammation and Fibrosis Progression

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Aims: The pathophysiology of non-alcoholic steatohepatitis (NASH) is multifactorial and not yet completely understood; however, innate immunity is a major contributing factor in which liver-resident macrophages (Kupffer cells) and recruited macrophages play a central part in disease progression. In this study, we aimed to demonstrate that activated macrophages are as key mediators of inflammation and fibrosis progression in NASH livers.

Methods: Ninety-four, snap-frozen benign liver tissues with various chronic liver diseases in the different fibrosis stages (0: n=17, 1: n=12, 2: n=12, 3: n=25, 4: n=28) were subjected to the expression analyses. Gene expression analysis was performed using the nCounter PanCancer Pathway Panel (NanoString Technologies, Seattle, WA, USA). Liver biopsy was performed for NASH livers with various fibrosis stages. Immunohistochemistry and multicolor flow cytometry were performed with the biopsy specimen. Mouse model of NASH-induced liver cirrhosis was established using high-fat, high-cholesterol (HFHC) diet with intraperitoneal streptozocin injection. All statistical analyses in this study were performed using the open source statistical programming environment R language (version 3.4.3).

Results: Gene expression analysis with 94 patient liver samples using the nCounter PanCancer Pathway Panel identified that expression level of IL12B, SOCS1, and STAT1, which are robustly expressed in activated macrophages, was higher in the livers with advanced fibrosis (stage 3 and 4) than those with low-grade fibrosis (stage 1 and 2) or no fibrosis (P<0.001). Immunohistochemical staining demonstrated that the number of CD68+ macrophages increases as the fibrosis progresses in NASH livers (P<0.05). Flow cytometry using liver biopsy specimen demonstrated that macrophages in the livers with advanced fibrosis show higher expression of HLA-DR and PD-L1, suggesting that these macrophages contribute not only to the inflammation and fibrosis, but also to dismantling anti-tumor immune surveillance in fibrotic NASH livers. Mice fed with HFHC diet with intraperitoneal streptozocin injection developed NASH, liver cirrhosis, and hepatocellular carcinoma, and the number of activated macrophages increased as the disease progressed.

Conclusions: Our data using expression analysis of immune markers showed that activated macrophages are key mediators of inflammation and fibrosis progression in NASH livers. This study was supported by The Research Supporting Program of The Korean Association for the Study of the Liver and The Korean Liver Foundation. This study was also supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (2020R1A2C3011569).

Keywords: Non-alcoholic steatohepatitis, Gene expression, Macrophage, PD-L1

PE-203

Clinical Significance of Serum Exosomal miRNA in Liver Fibrogenesis of Non-alcoholic Fatty Liver Disease

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Aims: Fatty liver disease in non-significant amount of alcoholic drinker (Non-alcoholic fatty liver disease (NAFLD)) is on the rise worldwide as obesity and diabetes increase. Among histologic changes, the degree of liver fibrosis is the most important factor for predicting long term outcomes. Although liver biopsy is the gold standard for diagnosis, it is difficult to be done in routine clinical practice due to the risk of serious complications and variabilities of sampling and interpretation. The aim of this study was to explore clinical significance of serum exosomal miRNA in liver fibrogenesis of NAFLD patients.

Methods: A total of 41 biopsy-proven NAFLD patients were included. Exosomes were isolated from serum samples and exosomal miRNAs were analyzed with GeneChip miRNA 4.0 array (Affymetrix, U.S.A). Expression levels of miRNAs in liver tissues of the same patient who had been tested for serum exosomal miRNA were analyzed. To define the role of miRNA in liver fibrogenesis, hepatocytes or stellate cells were transfected with miRNA of interest.

Results: NAFLD patients with significant fibrosis (Group 1) were older than those with non-significant fibrosis (Group 2). The percentage of patients who had metabolic syndrome was higher in Group 1. In addition, Group 1 patients had lower platelet counts and prolonged PT INR. A total of 86 serum exosomal miRNAs showed significant differences in expression between the two groups. Of these, 42 miRNAs showed significantly higher expression while 44 miRNAs showed significantly lower expression in Group 1 than in Group 2. MiR4668-5p, 3613-3p, 8075, 619-5p, 1184 showed higher expression levels in Group 1 than in Group 2. When human stellate cells (LX2 cells) were transfected with miR4668-5p inhibitors or miR4668-5p mimics, TGF-b, collagen1A1, and a-SMA mRNA expression levels were significantly decreased by miR 4668-5p inhibitors. However, their expression levels or significantly increased after transfections with miR4668-5p mimics.

Conclusions: Serum exosomal miRNAs showed significantly altered expression in NAFLD patients with significant fibrosis. Although additional researches are required, serum exosomal miRNA might have a diagnostic value for advanced fibrosis or serve as therapeutic targets for liver fibrogenesis in NAFLD patients.

Keywords: NAFLD, MiRNA, Fibrogenesis

PE-204

Comparisons between Long-Term Simple Diet- and Diet with Chemical-Induced Animal Model for Non-Alcoholic Steatohepatitis

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Aims: Few models adequately induce both metabolic dysregulation and non-alcoholic steatohepatitis (NASH) with advanced fibrosis that reflect human disease. Recently, a long-term diet (rich in fructose, palmitate, cholesterol: FPC)-induced model, and a western diet plus chemical-induced model have been proposed. The aim of this study was to evaluate which model is more suitable for metabolic dysregulation or hepatic inflammation with fibrosis

Methods: C57BL/6N mice were fed normal chow diet for 28 weeks (G1, n=5), FPC diet with 55% glucose/45% fructose solution for 28 weeks (G2, n=5), and FPC diet with 55% glucose/45% fructose solution plus CCl_4 [0.2 μl (0.32 μg)/g of body weight] for 12 weeks (G3, n=5). Pathologic evaluations for NASH and fibrosis were made based on the NASH CRN score. Hepatic fibrotic contents were quantified by Sirius red staining.

Results: Significant change of body weight was observed between G1 for 28 weeks (⊿10.7±2.1) and G2 (⊿20.7±3.9, *P*=0.001). However, there was no difference between G1 for 12 weeks and G3. Alanine aminotransferase was higher in G2 (351.5±218.9 IU/L, *P*=0.007) and G3 (243±93.5, *P*=0.023) than G1 (30.2±2.1). Total cholesterol (267.2±88.0 vs. 116.7±19.8 mg/dL, *P*=0.017) and low-density lipoprotein (123.5±41.0 vs. 30.8±14.5 mg/dL, *P*=0.005) in G2 were higher than G3. NAS score in G3 was higher than G2 (7.2±0.8 vs. 4.8±1.1, *P*=0.005). Fibrosis score in G3 was higher than G2 (1.8±0.8 vs. 0.8±0.4, *P*=0.046). Sirius red stain (%) in G3 were higher in G2 (4.43±0.53 vs. 2.31±1.36, *P*=0.012).

Conclusions: In the long-term FPC diet-induced model, metabolic dysfunction such as dyslipidemia was apparent, but the induction of NASH and fibrosis was insufficient. In FPC diet plus chemical-induced model, lipid profile changed relatively little, but was suitable for induction of NASH and fibrosis. Therefore, it seems to be important to select a suitable model according to the purpose of the study.

Keywords: NASH, Animal model, FPC Diet, Ccl4

PE-205

MiR-22-3p Alleviated Hepatic Lipogenesis via Inhibiting the SIRT1-PPAR Gamma Signal Pathway in Non-Alcoholic Fatty Liver Disease

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Aims: Non-alcoholic fatty liver disease (NAFLD) is a metabolic-related disorder ranging from simple steatosis to more severe forms, but the exact mechanism of progression remains unknown. MicroRNAs(miR), a class of small noncoding RNAs, are implicated in controlling a variety of biological processes. The aim of this study is to investigate the regulatory and protective role of miR-22-3p in NAFLD progression.
Methods: Both *in vitro* and *in vivo* models of NAFLD were generated by treating HepG2 and Huh-7 cells with palmitic acid (PA) and by feeding mice a high-fat diet (HFD), respectively. HE and Oil Red O staining were used to examine liver tissue morphology and lipid deposition, respectively. qRT-PCR (quantitative real time polymerase chain reaction) was used for investigate expression of miR, SIRT1, and proteins involved in lipogenesis
Results: HFD-mice hepatic tissues and PA-treated HepG2 and Huh-7 cells presented excess lipid production. Both *in vitro* and *in vivo* NAFLD model displayed decreased miR-22-3p and SIRT1 expression as evidenced by qRT-PCR. Overexpression of miR-22-3p induced downregulation of FAS, PPAR gamma and SREBP-1c via upregulation of SIRT1 expression. Reduction of hepatic lipid accumulation was observed by Oil red O staining.
Conclusions: In this study, miR-22-3p had a role in ameliorating hepatic lipogenesis by regulation of SIRT1 signal pathway in NAFLD model. The overexpressed miR-22-3p protects hepatocytes from lipid metabolism and suppresses hepatic lipogenesis, suggesting as a potential target for the therapeutic strategy of NAFLD.
Keywords: Non-Alcoholic Fatty Liver Disease, Lipogenesis, MicroRNA, SIRT1-PPAR gamma

PE-206

The Relationship between Total Cholesterol (TC) Levels and Lipid Fraction Area of Liver Tissue in the Dyslipidemic Rats (Rattus Norvegicus) Model after Intervention of Probiotic Beverage from Date Palm and Kefir Milk

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Aims: Dyslipidemia is often associated with the occurrence of fatty liver disease. One of the signs of dyslipidemia is an increase in total cholesterol (TC) levels, while fatty liver disease is characterized by the accumulation of lipids in hepatocytes. The purpose of this research is to know the correlation between TC and lipid fraction area of liver tissue in the dyslipidemic rats (Rattus norvegicus) model after the intervention of probiotic beverage from date palm and kefir milk.
Methods: This study used a quasi-experimental method with post-test only control group design. This research was conducted in the laboratory of physiology, Universitas Islam Indonesia (UII) for 2 months. This research used male Wistar strain rats aged 1-2 months with BW of 100-150 grams. Rats were divided into three groups. All groups were given fed ad libitum for 2 months. In the first month, the first group and third group were given 5 ml/200 gram BW/day quail egg yolks (G1 and G3), while the second group was not given the quail egg yolks (G2). In the second month, the third group was given 5 ml/200 gram BW/day probiotic beverage from date palm and kefir milk. At the end of the research, rats were terminated.
Results: The mean of TC (mg/dL) in G1, G2, and G3 consecutively were 70.91 ± 3.21, 174.71 ± 3.25, and 125.67 ± 4.69. The mean of lipid fraction area (%) in G1, G2, and G3 consecutively were 0.95 ± 0.17, 1.50 ± 1.34, and 1.43 ± 0.53. The result showed there is a normal correlation between TC and lipid fraction area of liver tissue with r 0.541 (normal positive correlation) and no significant difference with $P>0.05$ ($P=0.069$).
Conclusions: TC and lipid fraction area of liver tissue in dyslipidemic rats after the intervention of probiotic beverage from date palm and kefir milk have a normal correlation with no significant difference.
Keywords: Fatty Liver, Total Cholesterol, Lipid Fraction Area, Probiotic Beverage

PE-207

The Effect of Non-Fermented and Fermented Soymilk (Glycine Max) on Liver Malondialdehyde Levels in the Dyslipidemic Rats (Rattus Norvegicus)

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Aims: Liver is an organ that plays an important role in lipid metabolism. The accumulation of lipids can increase the level of reactive oxygen species (ROS). Malondialdehyde (MDA) can be used as a marker of oxidative stress. If this occur continuously, it will increase the risk of non alcoholic fatty liver disease. There were few studies have compared the effect of non-fermented and fermented soymilk on dyslipidemia. The purpose of this research is to compare the effect of non-fermented and fermented soymilk on liver MDA levels of dyslipidemic rats.
Methods: This study used a quasi-experimental method with

post-test only control group design. This research was conducted in the laboratory of physiology, Universitas Islam Indonesia (UII) for 4 weeks. This research used male Wistar strain rats aged 1-2 months with BW of 100-150 grams. Rats were divided into four groups. All groups were given fed ad libitum for 4 weeks. In the first two weeks, first group, third group, and fourth group were given 5 ml/200 gram BW/day quail egg yolks (G1, G3, and G4), while second group was not given the quail egg yolks (G2). In the second two weeks, third group (G3) were given 5 ml/200 gram BW/day non fermented soymilk, while fourth group (G4) were given 5 ml/200 gram BW/day fermented soymilk. In the end of the research, MDA levels on liver were measured. ANOVA with bonferroni post-hoc test was used in statistical analyzing.

Results: Mean of MDA level (nmol/gr) were 1,96 ± 0,34 for G1; 9,70 ± 0,24 for G2, 4,60 ± 0,27 for G3, and 3,38 ± 0,32 for G4. Statistical analyzing shown that there were significant differences of MDA levels among the groups (P=0.00).

Conclusions: Both non fermented and fermented soymilk had the potency to reduce MDA levels (P=0.00), but fermented soymilk can reduce the MDA level on liver better than non-fermented soymilk.

Keywords: Dyslipidemia, Soymilk, Liver Malondialdehyde, Fermented and Non-Fermented

PE-208

Complementary Liver Histological Effects of Mitochondrial Function Enhancer HSG4112, a Synthetic First-in-Class Small Molecule, and Semaglutide in a Diet-Induced and Biopsy-Confirmed Obese Mouse Model of Non-Alcoholic Steatohepatitis

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Aims: HSG4112, a synthetic new chemical entity, is a first-in-class oral small molecule in clinical development for obesity. In preclinical studies, HSG4112 as mitochondrial function enhancer has been demonstrated to increase energy expenditure and decrease chronic low-grade inflammation, resulting in reduced adiposity and robust weight loss. As these therapeutic effects are highly relevant for the management of non-alcoholic steatohepatitis (NASH), we aimed to compare the therapeutic effects of HSG4112 and semaglutide (GLP-1 receptor agonist) in a diet-induced obese (DIO) and biopsy-confirmed mouse model of NASH.

Methods: Male C57BL/6JRj mice were fed AMLN diet high in trans-fat, fructose and cholesterol for 35 weeks. Only animals with liver biopsy-confirmed steatosis (score ≥2) and fibrosis (stage ≥F1) were included and stratified into treatment groups according to baseline body weight and liver collagen-1a1 deposition. DIO-NASH mice received vehicle (PO, QD), HSG4112 (50 or 100 mg/kg, PO, QD), or semaglutide (30 nmol/kg, SC, QD) for 10 weeks. Endpoints included within-subject changes in body composition, NAFLD Activity Score (NAS) and fibrosis stage as well as terminal quantitative liver histology and transcriptome analysis.

Results: HSG4112 and semaglutide induced similar reductions in body weight (20%) and whole-body fat levels (10-12%) in DIO-NASH mice. These metabolic effects were accompanied by significantly reduced plasma levels of liver injury markers (ALT, AST, ALP). Notably, in contrast to semaglutide, HSG4112 did not reduce any food intake and improved NAS by a different mode of action. Accordingly, HSG4112 specifically attenuated lobular inflammation while semaglutide reduced steatosis severity. Both compounds significantly reduced fibrogenesis activity associated with suppressed stellate cell activation and lowered collagen mRNA expression.

Conclusions: HSG4112 showed robust anti-obesity and anti-NASH efficacy, especially with reduced liver inflammation and fibrogenesis, in DIO-NASH mice with biopsy-confirmed liver pathology. While its efficacy was comparable to that of semaglutide, HSG4112 did not reduce food intake, further demonstrating its energy expenditure-enhancing effect. These findings suggest HSG4112 as a potent novel drug for the treatment of NASH.

Keywords: NASH, NAFLD, Mitochondria, Clinical-stage drug

Liver Transplantation

PE-209

Outflow Vein Venoplasty of Left Lateral Section Graft for Living Donor Liver Transplantation in Infant Recipients

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Aims: The size of the orifice of the left hepatic vein (LHV) trunk in left lateral segment (LLS) grafts is often too small for direct anastomosis. Several methods were developed to enlarge the graft and recipient hepatic vein orifices. This study describes our surgical techniques for secure hepatic vein reconstruction in infant recipients and analyzes their patency outcomes.

Methods: Twelve infants undergoing pediatric living donor liver transplantation (LDLT) were selected during a 2-year study peri-

od between January 2018 and December 2019. Surgical techniques and vascular complications of graft hepatic vein outflow in these recipients was analyzed.

Results: Mean recipient age was 12.5 ± 4.5 months, mean body weight was 9.4 ± 1.0 Kg, and mean graft-recipient weight ratio was 2.84% ± 0.60%. Primary diseases were biliary atresia in six patients, metabolic disease in two, hepatoblostoma in two, and acute liver failure in two. Eight LLS grafts were harvested through an open method, and four LLS grafts were harvested through a laparoscopic method. A small superficial LHV branch was present in five of 12 LLS grafts and used to widen the graft hepatic vein orifice. Incision-and-patch venoplasty was performed in 10, incision venoplasty in 1 and no venoplasty in 1. All four LLS grafts harvested through laparoscopic approach required circumferential vein patch because of very short hepatic vein stump. No patient experienced graft hepatic vein-associated vascular complications.

Conclusions: This refined surgical technique with incision-and-patch venoplasty for LLS grafts can reduce the risk of hepatic vein outflow obstruction in recipients receiving LLS grafts.

Keywords: Left hepatic vein, Unification venoplasty, Stenosis, Pediatric transplantation

PE-210

Prognosis of Split Liver Transplantation Compared with Whole Liver Transplantation in Adult Patients: Single-Center Results Under the Korean MELD Score-based Allocation Policy

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Aims: Split liver transplantation (SLT) has been occasionally performed in Korea. This study compared the incidence and prognosis of SLT with liver transplantation (WLT) in adult patients

Methods: Between June 2016 and November 2019, 242 adult patients underwent a total of 256 deceased donor liver transplantation (DDLT) operations. SLT was performed in 7 patients (2.9%).

Results: The mean age of SLT donors was 29.7±7.4 years, and the mean age of recipients was 55.7±10.6 years, with the latter having a mean model for end-stage liver disease score of 34.6±3.1. Mean split right liver graft weight was 1228.6±149.7 g and mean graft-recipient ratio was 1.97±0.39. Of the seven SLT recipients, Korean Network for Organ Sharing (KONOS) status was one in status 1, one in status 2 and five in status 3. The graft (P=0.72) and patient (P=0.84) survival rates were comparable in the SLT and WLT groups. Following propensity score matching, graft (P=0.61) and patient (P=0.91) survival rates remained comparable in the two groups. Univariate analysis showed that pretransplant ventilator support and renal replacement therapy were significantly associated with patient survival, whereas KONOS status category and primary liver diseases were not. Multivariate analysis showed that pretransplant ventilator support was an independent risk factor for patient survival.

Conclusions: Survival outcomes were similar in adult SLT and WLT recipients, probably due to selection of high-quality grafts and low-risk recipients. Prudent selection of donors and adult recipients for SLT may expand the liver graft pool for pediatric patients without affecting outcomes in adults undergoing SLT.

Keywords: Deceased donor, Organ donor shortage, Extended right liver graft, Whole liver graft

PE-211

Association between Pretransplant Serum Soluble PD-1 Level and Prognosis Following Liver Transplantation in Patients with Hepatocellular Carcinoma

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Aims: The study aimed to assess the prognostic influence of pretransplant serum soluble programmed death protein 1 (sPD-1) in patients undergoing liver transplantation for treatment of hepatocellular carcinoma (HCC).

Methods: Data from 229 patients with HCC who underwent living donor liver transplantation between January 2010 and December 2015 were retrospectively evaluated. Stored serum samples were used to evaluate sPD-1 concentrations.

Results: Tumor recurrence, overall survival, and HCC-specific survival rates were 25.5%, 94.3%, and 96.0% at 1 year; 40.8%, 78.2%, and 80.7% at 3 years; and 44.5%, 75.4%, and 77.9% at 5 years, respectively. Prognostic analysis using pretransplant serum sPD-1 with a cutoff of 93.6 μg/mL (median value of the study cohort) did not have significant prognostic influence on HCC recurrence, HCC-specific patient survival and post-recurrence patient survival (P≥0.26). Prognostic analysis using sPD-1 with a cutoff of 300 μg/mL showed marginally higher tumor recurrence (P=0.069), similar HCC-specific patient survival (P=0.25) and higher post-recurrence patient survival (P=0.045). Multivariate analysis revealed that Milan criteria were prognostic for HCC recurrence and HCC-specific patient survival, but pretransplant sPD1 with a cutoff of 300 μg/mL did not become an independent prognostic factor.

Conclusions: The results of this study demonstrate that pretransplant serum sPD-1 did not show significant influences on post-transplant outcomes in patients with HCC, although there was be some potential prognostic influences from very high expression of serum sPD-1. Further large-scale, multicenter studies are necessary to clarify the role of serum sPD-1 in LT recipients.

Keywords: Hepatocellular carcinoma, Recurrence, Tumor biology, Prognosis

PE-212

Fates of Retained Hepatic Segment IV and Its Prognostic Impact in Adult Split Liver Transplantation Using an Extended Right Liver Graft

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Aims: When splitting a liver for adult and pediatric graft recipients, the retained left medial section (S4) will undergo ischemic necrosis and the right trisection graft becomes an extended right liver (ERL) graft. We investigated the fates of the retained S4 and its prognostic impact in adult split liver transplantation (SLT) using an ERL graft.

Methods: This was a retrospective analysis of 25 adult SLT recipients who received split ERL grafts.

Results: The mean model for end-stage liver disease (MELD) score was 27.3±10.9 and graft-recipient weight ratio (GRWR) was 1.98±0.44. The mean donor age was 26.5±7.7 years. The split ERL graft weight was 1181.5±252.8 g, which resulted in a mean GRWR of 1.98±0.44. Computed tomography of the retained S4 parenchyma revealed small ischemic necrosis in 16 (64.0%) patients and large ischemic necrosis in the remaining 9 (36.0%) patients. No S4-associated biliary complications were developed. The peak liver enzyme levels were higher in the large S4 ischemic necrosis group (P≤0.002). The mean GRWR was 1.87±0.43 in the 9 patients with large ischemic necrosis and 2.10±0.44 in the 15 cases with small ischemic necrosis (P=0.28). The retained S4 parenchyma showed gradual atrophy on follow-up imaging studies. The amount of S4 ischemic necrosis was not associated with graft (P=0.59) or patient (P=0.24) survival. A MELD score >30 and pretransplant ventilator support were associated with inferior outcomes.

Conclusions: The amount of S4 ischemic necrosis is not a prognostic factor in adult SLT recipients, probably due to a sufficiently large GRWR.

Keywords: Deceased donor, Donor shortage, Extended right liver graft, Whole liver graft

PE-213

Refined Surgical Techniques to Improve the Patency of Cryopreserved Iliac Artery Homografts for Middle Hepatic Vein Reconstruction during Living Donor Liver Transplantation

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Aims: A cryopreserved iliac artery homograft (IAH) has not been considered suitable for middle hepatic vein (MHV) reconstruction during living donor liver transplantation (LDLT), primarily due to the low patency from its small diameter. We revised our surgical techniques for MHV reconstruction using an IAH to improve its patency.

Methods: This study analyzed the causes of early conduit occlusion and developed revised techniques to address this that had clinical application.

Results: The potential risk factors for early conduit occlusion were the small IAH size, small graft V5/V8 opening, and small recipient MHV-left hepatic vein stump. These factors were reflected to our revised surgical methods which included endarterectomy of the atherosclerotic plaque, unification of the internal and external iliac artery branches for large V5, and branch-patch arterioplasty for large V8. IAH endarterectomy was applied to 8 patients and resulted in a 1-month occlusion rate of 37.5%. Branch unification technique was applied to 5 patients and a 1-month occlusion rate of 20.0% was obtained. Branch-patch arterioplasty was applied to 5 patients leading to a 1-month occlusion rate of 40.0%. The overall patency rates of the IAH-MHV conduits in our 18 patients were 66.7% at 1 month, 38.9% at 3 months, and 33.3% at 1 year.

Conclusions: Our refined MHV reconstruction using an IAH improved short-term MHV conduit patency, but did not effectively prevent early conduit occlusion, particularly with a small- or medium-sized IAH. Individualized reconstruction designs during LDLT operation are needed when an IAH is used for a modified right liver graft.

Keywords: Arteriopasty, Iliac vein graft, Hepatic venous congestion, Endarterectomy

PE-214

Reuse of Liver Allograft from a Brain-Dead Recipient: A Case Report

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Aims: We report our first case of deceased-donor liver transplantation (LT) using a reuse liver graft after the first LT
Methods: The recipient was a 38-year-old female with fulminant hepatic failure from toxic hepatitis.
Results: She had a history of herb intake and her liver function deteriorated progressively. She was enrolled as the Korean Network for Organ Sharing (KONOS) status 1 and the model for end-stage liver disease score was 34. The donor was a 42-year-old male patient who fell into brain death after LT for alcoholic liver cirrhosis. Donation of multiple organs including the transplanted liver graft was performed 10 days after the first LT operation. Since the liver graft appeared to be normal and frozen-section liver biopsy showed only mild fatty changes, we decided to reuse the liver graft. A modified piggy-back technique of the suprahepatic inferior vena cava reconstruction was used. Other surgical procedures were comparable to the standard deceased-donor LT procedures. The explant liver pathology revealed submassive hepatic necrosis, which was compatible with toxic hepatitis. The peak of serum liver enzyme levels were aspartate transaminase 1,063 IU/L and alanine transaminase 512 IU/L at posttransplant day 3. Since the pretransplant general condition of the recipient was very poor, hospital stay was prolonged and she was discharged 51 days after LT operation. She is currently doing well for 3 years to date.
Conclusions: Experience in our case and the literature review suggest that a reuse liver graft can be regarded as one of the marginal grafts which can be transplantable to the LT candidates requiring urgent LT.
Keywords: Brain death, Graft reuse, Graft relay, Recipient death

PE-215

Technical Refinement of Prosthetic Vascular Graft Anastomosis to Recipient Inferior Vena Cava for Secure Middle Hepatic Vein Reconstruction in Living Donor Liver Transplantation

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Aims: Hemashield vascular grafts has been used for middle hepatic vein (MHV) reconstruction during living donor liver transplantation (LDLT). We occasionally encounter outflow disturbance of MHV conduit at the anastomotic stump of the middle-left hepatic vein (MLHV) trunk. To mitigate the disturbance, we carried out a series of studies regarding hemodynamics-compliant MHV reconstruction.
Methods: This study comprised of three parts: Part 1: Determining the causes of outflow disturbance; Part 2: Computational simulative analysis; and, Part 3: Clinical application of our refined technique. The types of Hemashield conduit-MLHV stump reconstruction were end-to-end anastomosis (type 1), side-to-end anastomosis (type 2), and oblique cutting of the conduit end and patch plasty (type 3).
Results: In Part 1 study, the reconstruction types were type 1 in 23, type 2 in 25, and type 3 in 2. Significant anastomotic stenosis was identified in 7 (30.4%) in type 1, 6 (24.0%) in type 2, and none (0%) in type 3. The size of MLHV stump was the most important factor for anastomotic stenosis. Through Part 2 study, technical knacks were developed as follows: the conduit end was cut in a dumb-bell shape and a vessel patch attached; and then sutured bidirectionally from the 9 o'clock direction. In Part 3 study, these knacks were applied to 5 patients and none of them experienced noticeable anastomotic stenosis
Conclusions: Our refined technique to perform conduit-MLHV stump anastomosis appears to reduce the risk of anastomotic outflow disturbance for relatively small MLHV stump.
Keywords: Prosthetic vascular graft, Middle hepatic vein, Anastomosis, Hepatic venous congestion

PE-216

Patients with Underlying Liver Disease without "Fibro-Cirrhosis" Should Be Carefully Managed to Improve the Survival Outcome in Pediatric Liver Transplantation: A Single Center Experience

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Aims: Although liver transplantation (LT) has become the standard for treatment of end-stage liver disease in children, there are still some complications that adversely affect the post-transplant outcome. The aim of this study is to identify the risk factors affecting the outcomes in pediatric LT.
Methods: Data from pediatric patients who underwent primary LT at Seoul National University Hospital from March 1988 to December 2018, were retrospectively analyzed. Liver disease without "fibro-cirrhosis" was defined as explanted liver showing fibrosis regardless of grade or cirrhosis, or as underlying disease causing progressive liver injury and eventually leading to fibrosis or cirrhosis.
Results: There were 255 pediatric LT patients and their 1-, 5-, and 10-year overall survival rates were 90.5%, 88.4%, and 87.8%, respectively and the 1-. 5-, and 10-year graft survival rates were 87.8%, 86.2%, and 84.9%, respectively. Multiple variate analysis identified that liver disease without fibro-cirrhosis as underlying disease (P=0.024) and PELD≥30 (P=0.036) were risk factors of overall survival and body weight <6kg (P=0.028), liver disease without fibro-cirrhosis as underlying disease (P=0.041), and postoperative hepatic artery complication (P<0.001) were risk factors of graft survival. Liver disease

without fibro-cirrhosis was the only factor independently associated with hepatic artery complication (*P*=0.003).

Conclusions: More caution is recommended in pediatric LT patients liver disease without fibro-cirrhosis to improve the survival outcome as well as patients with high PELD or low body weight. Hepatic artery complication was the only surgical complications affecting on the graft survival outcome especially in patients having liver disease without fibro-cirrhosis.

Keywords: Pediatric liver transplantation, Graft survival, Liver cirrhosis, Hepatic artery

PE-217

The Outcome of Primary Liver Transplantation from Deceased Donors in Children with Body Weight 10 kg or Less

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Aims: The aim of this study was to analyze the outcome in terms of patient and graft survival and to search for factors affecting this outcome

Methods: Between March 2002 and November 2017, 42 children with body weight 10 kg or less had a primary liver transplantation from deceased donors in our unit. Overall, one-, three-, five-, and 10-yr primary patient and graft survival rates were 73%, 71%, 66%, 63% and 59%, 56%, 53%, 48%, respectively. Fifteen of 42 (36%) children died and in the remaining 14 (33%), the first grafts failed and they were retransplanted. Cox regression analysis revealed that a need for retransplantation and urgent transplantation were important predictors for patient survival (*P*=0.04 and *P*=0.001, respectively). To assess whether the need for retransplantation can be influenced, all study variables were compared between surviving grafts and failed grafts

Results: Cox regression analysis showed that only donor/recipient (D/R) weight ratio proved to be independent predictor for graft survival (*P*=0.004). After comparison of graft survival with the long rank test according to different D/R weight ratios (3.0-7.0), the cut-off point for significantly different graft survival approached 4.0. In summary, patient survival in children with body weight < or =10 kg is determined by urgent transplantation and the need for retransplantation.

Conclusions: Graft loss and retransplantation in small children can be prevented by adequate size matching of donor and recipient whereby a D/R weight ratio <4.0 seems to offer the favorable outcome

Keywords: Liver transplantation, Retransplanted, Graft, Urgent transplantation

PE-218

Comparison of Laparoscopy-Assisted and Open Donor Right Hepatectomy

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Aims: Laparoscopy-assisted hepatectomy is a new minimally invasive approach for graft harvesting in living donors. Only a few liver transplant centers have introduced this surgical procedure.

Methods: A prospective case-matched study was conducted on 25 consecutive donors who underwent laparoscopy-assisted donor right hepatectomy (LADRH) between March 2011 and July 2017 at our transplant center. These donors were matched 1:1 according to age, gender, and body mass index with 25 donors who underwent open donor right hepatectomy (ODRH).

Results: LADRH was successfully performed in all 25 of the donors. Donor complications, estimated blood loss, and operative time were similar between the groups. Hospital stay and periods of analgesic use were significantly shorter in the LADRH group [7.0±1.4 (LADRH) vs. 8.7±2.4 (ODRH), p=0.003, and 2.4±1.0 (LADRH) vs. 3.2±1.0 (ODRH), p=0.011, respectively). The total in-hospital cost is higher with LADRH, primarily due to the additional material costs for LADRH. Finally, there were no differences in graft size, graft survival, or recipient complications between the two groups.

Conclusions: The results of this study show that LADRH is a feasible and safe procedure compared with ODRH. Although higher material costs for laparoscopic assisted procedures are inevitable, LADRH may have an advantage over ODRH by causing less pain and facilitating earlier recovery. Efforts can be made to improve the technical success of LADRH for some overweight donors.

Keywords: Assisted hepatectomy, Graft, Laparoscopy-assisted, Open donor right

PE-219

Surgical Management of Biliary Complications Following Living Donor Liver Transplantation

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Aims: Biliary complications (BC) account for much of the morbidities seen after living donor liver transplantation (LDLT). Surgical reconstruction might be necessary after the failure of endoscopic or percutaneous procedures.

Methods: Between December 2002 and November 20016, a total of 76 LDLTs were performed. Six patients were excluded from statistical analysis because of early graft or patient loss.

Results: Of 70, 26 (37.1%) developed BC; 12 (46.2%) were successfully managed by non-surgical procedures, three (11.5%) died from BC-related sepsis, one (3.8%) died from BC-unrelated causes, and 10 (38.5%) underwent surgical reconstruction. Of those 10, four patients had single duct reconstruction, five patients had double ducts reconstruction, and reconstruction was abandoned in one patient because of hepatic artery thrombosis. After a median follow-up period of 4.5 yr (0.1-6), seven (70%) remained well with no recurrent biliary problems, and three (30%) had recurrent BCs that were managed either conservatively or by retransplantation. Patients who underwent surgical reconstruction had significantly fewer hospital admissions, less need for invasive procedures, and shorter cumulative hospital stay (P<0.05).

Conclusions: In our experience, BCs after LDLT were frequently resistant to non-surgical procedures. Surgical reconstruction is associated with fewer hospital admissions and less need for invasive procedures leading to reduced resources utilization.

Keywords: Liver transplantation, Endoscopic and percutaneous procedures, Graft, Retransplantation

PE-220

Effect of Calcineurin Inhibitors in the Outcome of Liver Transplantation in Hepatitis C Virus-Positive Recipients

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Aims: There is a paucity of good studies evaluating the impact of calcineurin inhibitors on posttransplantation outcome in hepatitis C virus (HCV)-infected liver transplant (LT) recipients.

Methods: We sought to determine whether there are differences on posttransplantation survival and histologic recurrence in HCV-LT recipients based on initial immunosuppression (IS) by conducting a prospective study comparing tacrolimus (Tac) versus cyclosporine-based IS in patients undergoing LT between 2001 and 2007. Protocol liver biopsies were performed.

Results: Baseline characteristics (demographics, liver function at LT, genotype distribution, donor, surgery, and IS except for the type of calcineurin inhibitor) did not differ between groups. Severe disease (defined as bridging fibrosis, cirrhosis, cholestatic hepatitis, or allograft loss or death because of recurrent disease in the first year) was present in 67 of 253 (26.5%) and was equally distributed in the CsA and Tac groups (27% vs. 26%; P=0.68). Two thirds of protocol biopsies performed at 1 year showed some fibrosis without differences between CsA and Tac groups (75% vs. 70%). Advanced fibrosis (bridging fibrosis and cirrhosis) was diagnosed in 30% CsA and 24.5% Tac patients (P=NS). No differences in survival at 1 and 7 years were observed (83% and 67% vs. 78% and 64%, respectively, P=0.4).

Conclusions: In summary, in patients undergoing LT for HCV-related liver disease, posttransplantation outcome is not related to the calcineurin inhibitor used.

Keywords: C virus-positive recipients, Calcineurin inhibitors, Liver transplantation, Graft

PE-221

Microbiologic Investigation of Patients Before Living-Donor Liver Transplant

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Aims: Chronic infections can cause serious complications and create morbidity and mortality for affected patients during immunosuppressive therapy in the posttransplant period. Here, we studied the microbiologic screening results of patients before living-donor liver transplant.

Methods: The microbiologic screening results of 25 patients during 2016 at NSRC(Astana, Kazakhstan) before LDLT were prospectively analyzed. Sputum samples, swabs from throat and nose, and urine samples were collected for quantitative microbiologic examination. Identification of isolates and antibiotic susceptibility testing were performed using the Vitek 2AS.

Results: Of the patients, 16(64%) were female and the average age was 46.8±2.2 years. Of 97clinical samples collected, 80samples(82.4%) showed bacterial growth. A total of 88-isolates to 15-different species was isolated. The greatest number of bacteria was isolated from throat swabs(35.2%). Of 88 isolates, 70isolates(79.5%) were gram-positive, with a-hemolysis streptococci being the major isolate(39.7%). Coagulase-negative staphylococci were found in 13.6% of isolates, Staphylococcus aureus in 11.3%, and both Klebsiella pneumoniae and Streptococcus pneumoniae in 10.2%. Results of antibiotic susceptibility testing showed that the resistance rate of Staphylococcus aureus to oxacillin was 10%. About 87.5%of isolates of Klebsiella pneumoniae were resistant to inhibitor-protected penicillin, 85.7% to quinolones, and more than 60% to cephalosporins and aminoglycosides groups of antibiotics.

Conclusions: Microbiologic monitoring of recipients before living-donor liver transplant showed higher prevalence of opportunistic pathogens. These results suggest establishing quality preoperative preparations with a view to possible improvements in the health status of intended recipients and elimination of factors that could adversely affect the transplant and cause complications during the postoperative period

Keywords: Microbiologic Investigation, Liver transplantion, Prevalence of opportunistic pathogens, Graft

PE-222

Sorafenib for Recurrent HCC after LT Has Better Treatment Outcomes Compared to Sorafenib in Advanced HCC without LT

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Aims: Sofarenib has been used for advanced hepatocellular carcinoma (HCC) over the last decade. However, the efficacy of sorafenib in recurrent HCC after liver transplantation (LT) compared to the non-LT settings has not been elucidated. Moreover, factors affecting sorafenib efficacy in the LT group have not been extensively clarified.

Methods: Between 2008 and 2019, a total of 832 HCC patients (790 in the non-LT group and 42 in the LT group) treated with sorafenib were consecutively enrolled in our study. Primary outcome was overall survival (OS) in the non-LT and LT groups. Secondary outcomes were objective response rate (ORR), disease control rate (DCR) and time to progression (TTP). Subgroup analyses according to metastasis, liver function and intrahepatic tumor burden were also examined.

Results: Overall, the median follow-up duration was 152.5 days. The LT group had younger age, better Child-Turcotte-Pugh (CTP) scores, smaller intrahepatic tumors and lower AFP levels than those of the non-LT group. The LT group showed significantly better OS (16.8 vs. 7.1 months, $P<0.001$, respectively) than the non-LT group. Moreover, the LT group had significantly longer TTP, higher ORR and DCR than in the non-LT group. The superior efficacy of sorafenib in the LT versus non-LT groups was corroborated in detailed sub-group analyses stratified by metastasis or CTP class A. However, in patients with small or no intrahepatic tumor, there were no significant differences in OS, TTP, ORR and DCR between the two groups.

Conclusions: Sorafenib in transplant patients is more effective and provide better outcomes than in non-transplant patients. Intrahepatic tumor burden as well as underlying hepatic function is a crucial determinant for the effectiveness of sorafenib.

Keywords: Sorafenib, Liver transplantation, Hepatocellular carcinoma, Metastasis, Tumor size, Liver function

PE-223

Metformin Combination with Tacrolimus Attenuate GVHD Severity in Mice by Modulating Treg and Th17 Imbalance

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Aims: Tacrolimus is one of important immunosuppressant (IS) to reduce rejection after liver transplantation (LT). Metformin is not only antidiabetic drugs but also immune modulatory drugs via several pathways including Signal transducer and activator of transcription 3 (STAT3) signal. In this study, we examined the effect of metformin with tacrolimus in immune microenvironment including regulatory T cells (Treg) *in vitro* and vivo analysis.

Methods: We performed *in vitro* analysis and vivo analysis with mouse to examine the immune modulatory effect of combination therapy with metformin and tacrolimus. Regulatory effect of T cells by combination drug in T cell activation condition and allo-response *in vitro* was determined by flow cytometry and enzyme-linked immunosorbent assay (ELISA). Also we analyzed the *in vitro* Treg stability. Metformin and tacrolimus was treated in the graft versus host disease (GVHD) model following MHC-mismatched bone marrow transplantation, and the effects *in vivo* were determined.

Results: *In vitro* allo-response condition, combination of metformin with tacrolimus much more decreased the proliferation of allo-responsive T cell compared to metformin and tacrolimus monotherapy in mice and human system. Moreover, combined treatment significantly decreased the level of pro-inflammatory marker such as TNF-α and IL-6. In T cell activation condition, the activation of Th1 and Th17 cells in normal and GVHD mouse model decreased by combination of metformin and tacrolimus compared to tacrolimus monotherapy. Combined treatment also decreased IL-17 and IFN-γ level in supernatant form mouse and human T cell. *In vivo* metformin and tacrolimus treatment in GVHD mice ameliorated the clinical severity and histological inflammation in target tissue.

Conclusions: Our preliminary study suggests that metformin may give additional immune modulatory effect by increasing Treg and decreasing pro-inflammatory markers compared to tacrolimus mono-therapy.

Keywords: Metformin, Tacrolimus, GVHD, Liver transplantation, Regulatory T cell, Th17 cell

PE-224

Upper Midline Incision Is Enough to Do Living Donor Right Hepatectomy

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Aims: Pure laparoscopic donor hepatectomy has become more popular because of the donor's demand for cosmetic and functional concern. However, laparoscopic approach has not been performed in almost living right donor hepatectomy (LDRH) because this is more technically demanding and is associated with increased donor morbidity. Instead, several studies have described LDRH using upper midline incision (UMI) to reduce donor morbidity. Herein, we describe our experience with small UMI as a standard procedure for LDRH.
Methods: We retrospectively reviewed the outcomes of 444 living donor right hepatectomy (LDRH) at our institution from January 2010 to June 2019; 124 donors received LDRH using UMI (UMI group), whereas 320 donors underwent LDRH using J shaped incision. (J shaped group) We began to use small UMI during LDRH since 2016 and now, this incision has been standard procedure for LDRH regardless of graft type, body mass index, graft weight or vascular variation. Patient demographics, intraoperative parameters, laboratory data and postoperative complications, were compared between the 2 groups.
Results: The mean size of the UMIs is 12.9cm (ranged from 11 to 16cm) and the overall complication rates did not differ significantly between the 2 groups. Most postoperative parameters are not different between the 2 groups but postoperative hospital stay and operation time in UMI group were significantly lower than those in J shaped group. In multivariate logistic regression analyses, only large graft (>900g) and severe hepatic steatosis (≥15%) were significant risk factors for difficult operation but not related to type of incision. Moreover, in high risk group for operation (donors with large graft or severe graft steatosis), neither the operation time nor intraoperative blood loss in UMI group were higher than those in J shaped group.
Conclusions: LDRH could be safely performed under small UMI and this UMI could be considered as standard procedure during LDRH.
Keywords: Upper midline, Incision, Right hepatectomy, Living donor

PE-225

Hepatitis B Immunoglobulin Prophylaxis for Prevention of De Novo Hepatitis B Infection from Hepatitis B Core Antibody-Positive Donors

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Aims: Recently, hepatitis B core antibody (anti-HBc) positive liver grafts are used as extended criteria donor organs. However, prophylaxis methods to prevent de novo hepatitis B virus (HBV) infection after liver transplantation (LT) are still controversial. Thus, the purpose of our study is to evaluate the risk and outcomes of receiving anti-HBc positive grafts with prophylactic hepatitis B immunoglobulin (HBIG) monotherapy.
Methods: All adult patients who underwent LT at Samsung Medical Center in Seoul, Korea, between January 2001 and December 2018 were gathered from a prospectively maintained database and reviewed retrospectively. HBV patients received the combination treatments with antiviral prophylaxis and HBIG. Prophylactic HBIG monotherapy was given for patients without HBV receiving grafts from anti-HBc positive donors.
Results: A total of 1355 patients underwent LT during this period. Among them, 457 (33.7%) were anti-HBc positive and 898 (66.3%) were anti-HBc negative donors, who underwent follow-up for a median time of 5.7 years. Perioperative outcomes (mortality in 30 days, complications and postoperative ICU stay period) were similar between the two groups. Also, there were no significant difference in the 1-, 5-, 10- and 15-year patient survival rates between the anti-HBc positive (87.5%, 73.5%, 67.7% and 61.2%) and the anti-HBc negative groups (88.5%, 77.7%, 70.7% and 69.6%, *P*=0.080). All of the 117 recipients who were HBsAg negative and received anti-HBc positive grafts were given prophylactic HBIG monotherapy. Only one patient (0.9%, 1/117) developed de novo HBV during follow-up. There were 972 HBsAg-positive patients and 348 (35.8%) received anti-HBc positive grafts. The risk of HBV recurrence was similar between 2 groups (*P*=0.308). The donor anti-HBc status did not have a significant influence on the long-term survival or the risk of de novo or recurrent HBV infection after LT.
Conclusions: De novo HBV was very rare especially with HBIG prophylaxis in non-HBV patients received anti-HBc positive liver graft. There was no significant influence of anti-HBc positive grafts on the perioperative and long-term outcomes after LT.
Keywords: Hepatitis B core antibody, De novo hepatitis B virus infection, Hepatitis B immunoglobulin

PE-226

A Comparison Study of Liver Regeneration in Laparoscopic versus Open Right Hemihepatectomy for Adult Living Donor Liver Transplantation

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Aims: This study aims to compare differences between laparoscopic donor right hemihepatectomy (LDRH) and open donor right hemihepatectomy (ODRH) in the quality of the operation, postoperative complications, and liver regeneration measured via volumetry.
Methods: This study included 119 patients who underwent living donor right hemihepatectomy at Samsung Medical Center from January 2016 to December 2017. We compared several

aspects of LDRH and ODRH and analyzed the results using the independent t-test, chi-square test and Fisher's exact test.

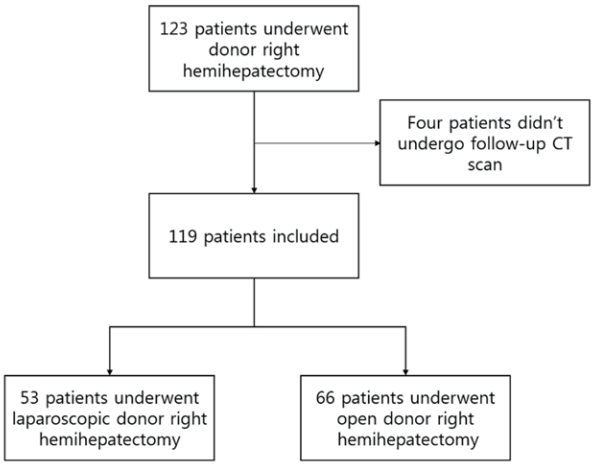

Figure 1. Flow chart of patient enrollment

Results: Among 119 enrolled patients, 66 patients (55.5%) underwent open surgery, and 53 patients (44.5%) underwent laparoscopic surgery. The mean operation time was significantly shorter for ODRH (290.57 ± 54.04 minutes) than LDRH (312.28 ± 53.5 minutes) (*P*=0.031). Estimated blood loss was significantly less in LDRH (258.49 ± 119.99 ml) than ODRH (326.52 ± 157.68 ml) (*P*=0.011). The remnant liver recovered to 83.35 ± 10.71% of the preoperative estimate whole liver volume (pre-EWLV) in the ODRH group and 84.04 ± 8.98% of the pre-EWLV in the LDRH group (*P*=0.707). The percentage of increased estimated liver volume to postoperative estimate remnant liver volume (post-ERLV) was 137.62 ± 40.34% in the ODRH group and 130.56 ± 36.78% in the LDRH group, and there was no statistically significant difference between the two groups (*P*=0.326). An analysis of postoperative complications showed no significant differences.

Table 1. Demographics and characteristics of right liver donors for LDLT

	Open (n=66) Mean ± SD	Laparoscopic (n=53) Mean ± SD	*p* value
Age (years)	35.70 ± 12.71	32.79 ± 11.92	0.205
Sex (male)	36 (54.5%)	25 (47.2%)	0.424
BMI	23.64±2.68	23.49±2.79	0.776
HTN	1 (1.5%)	1 (1.9%)	1.000
DM	0	1 (1.9%)	0.445

BMI, Body mass index, HTN, Hypertension, DM, Diabetes mellitus

Table 2. Operative characteristics of adult living donor right hemihepatectomy

	Open (n=66) Mean ± SD	Laparoscopic (n=53) Mean ± SD	*p* value
Operative time (min)	290.57±54.04	312.28±53.5	0.031
Estimated blood loss (ml)	326.52±157.68	258.49±119.99	0.011

Table 3. Analysis of liver regeneration assessed by the estimate volumetry of CT scan after adult living donor right hemihepatectomy

	Open (n=66) Mean ± SD	Laparoscopic (n=53) Mean ± SD	*p* value
Pre-EWLV (cm^3)	1194.96±237.60	1163.51±213.30	0.454
Post-ERLV (cm^3)	424.36±96.84	433.49±125.49	0.655
FERLV (cm^3)	985.18±22.97	974.93±27.01	0.772
Liver regeneration ratio (%)	83.35±10.71	84.04±8.98	0.707
Increased volume ratio (%)	137.62±40.34	130.56±36.78	0.326

CT, Computed tomography, *Pre-EWLV*, Preoperative estimate whole liver volume, Post-ERLV, Postoperative estimate remnant liver volume, *FERLV*, Future estimate remnant liver volume, *Liver regeneration ratio*, (FERLV/pre-EWLV) x 100(%); *Increased volume ratio*, {(FERLV - post-ERLV) / post-ERLV} x 100(%)

Table 4. Complications after adult living donor right hemihepatectomy

	Open (n=66) Mean ± SD	Laparoscopic (n=53) Mean ± SD	*p* value
Bleeding	0 (0.0%)	0 (0.0%)	-
Wound complication	9 (13.6%)	2 (3.8%)	0.109
Biliary complication	1 (1.5%)	5 (9.4%)	0.087
Fluid collection	2 (3.0%)	2 (3.8)	1.000
Others	1 (1.5%)	0 (0.0%)	1.000
Total complication	12 (18.2%)	9 (17%)	1.000

Conclusions: LDRH is safe, and there is no significant difference in hepatic regeneration compared with ODRH. Therefore, LDRH can be applied for living donation of liver.

Keywords: Living donor right hemihepatectomy, Laparoscopic donor right hemihepatectomy, Liver transplantation, Liver regeneration, Volumetry

PE-227

Splenic Artery Embolization as a Treatment of Hypersplenism in Patients After Liver Transplantation

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Aims: Hypersplenism (thrombocytopenia, leukopenia, anemia) syndrome and ascites frequently occur after liver transplantation. These situations can be treated by open splenectomy. Splenic artery embolization (SAE) has been practiced as an alternative surgical method with low risks and short time.

Methods: From January 2013 and December 2019, frothy-five liver transplants were performed. Five of these patients subsequently received splenic artery embolization - 12, 8, 6 and 2 months after transplant. 3 patients who had been diagnosed with primary biliary cirrhosis (PBC) and 2 patient with hepatitis B virus-related liver cirrhosis. Indications for splenic artery embolization (ascites, splenomegaly) were based on clinical and ultrasonographic investigation and laboratory findings. SAE was performed via a percutaneous femoral artery approach under local anesthesia. Transcatheter splenic artery branch occlusion

was performed by deploying occlusion material.
Results: In all patients, ascites and platelet levels decreased after SAE. In 2 patient with leukopenia, white blood cell count normalized. After embolization, 1 patient had severe abdominal pain requiring analgesia medication, and 2 patients had fever that lasted 3 days. Patients were discharged 7 to 14 days after embolization. One patient developed a perisplenic abscess without fever 1 month after discharge, and the abscess was drained using an ultrasound-guided percutaneous procedure.
Conclusions: One of the safe and effective method for treating hypersplenism and ascites is SAE. Advantages is a minimally invasive and short-time performance method in orthotopic liver transplant recipients and an alternative to open splenectomy.
Keywords: Splenic Artery, Embolization, Hypersplenism, Liver Transplantation

PE-228

Pharmaceutical Medicine

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Aims: Surgical site infection (SSI) is a common and postoperative complication in patients who underwent solid organ transplant and it makes extensive healthcare burden. So far, the pooled prevalence and microorganisms causing SSI among liver transplantation has not been reported well. This evidence-based systematic literature review and meta-analysis aimed to find the pooled prevalence of SSI.
Methods: A systematic literature search on PubMed/Medline, Embase was conducted to identify the study determining the prevalence of SSI among patients who underwent liver transplantation, published from inception to May 2020. We calculated pooled prevalence (%) with 95% confidence interval (CI) with a random-effect model. A meta-analysis was performed using "meta" package through R 3.5.0. software.
Results: A total of fifteen studies with 5,952 study subjects were included in this analysis. The rate of SSI was ranged between 9.0% and 96.4%. The pooled prevalence of SSI was 27.0% (95% CI: 16.09 to 40.01%) with high degree of heterogeneity (I^2 = 99%, heterogeneity-P<0.01). The included studies reported a higher percentage of organ-space SSI (70.2%), followed by incisional, superficial, and deep SSI. The incidence rate of SSI was ranged from 0.34-10.3 episodes per 100 transplantation. Staphylococcus aureus (76.5%) was the most common pathogen identified, followed by Coagulase-negative staphylococci (35.0%) and Escherichia coli (21.25%).
Conclusions: The current result suggests the overall prevalence of SSI infection was high. However, due to a high degree of heterogeneity, resulting a considerable amount of clinical uncertainty regarding the prevalence of SSI among patients who underwent liver transplantation. Therefore, studies are required to confirm the present findings.
Keywords: Liver transplantation, Surgical site infection, Patient outcomes, Prevalence

PE-229

Program of Transplant Organization to Coordinate the Development of Organ Donation in Kazakhstan

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Aims: In recent years organ transplantation has become a well-established procedure for the management of renal, liver, cardiac, and respiratory failure. In spite of that, a shortage of organs still remains a serious problem for the full development of these therapeutic approaches in Kazakhstan.
Methods: The first kidney transplantation was performed in Kazakhstan in 1979, approximately 40 years ago. The operation itself was technically successful, but the lack of immunosuppression caused graft rejection, and the patient died after a few days.
Results: Due to government policy, an organized organ transplant program started more than 4 years ago and the program was supported by the Ministry of Health. During this period a well-designed program of transplant organization has been established. In Kazakhstan, each potential donor hospital has a transplant coordinator who is responsible for the whole process of organ procurement. Eleven transplant centers work currently in Kazakhstan, and 557 transplantations have been performed up to the middle of the year 2015. We found that renal, liver and cardiac transplants increased since the coordination program started.
Conclusions: We conclude that this program was successful in Kazakhstan and organ donation, procurement, and transplantation would become commonplace events to solve the problem of the organ donor shortage.
Keywords: Transplant coordination, Transplantation, Organ donation

PE-230

Renal Outcomes in Patients with IgA Nephropathy Undergoing Liver Transplant: A Retrospective Cohort Study

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Aims: End-stage liver disease (ESLD) is the most common cause of secondary immunoglobulin A nephropathy (IgAN). Multiple mechanisms have been proposed to explain the association between liver disease and IgAN. Although some mechanisms are expected to reverse in patients after liver transplant, the long-term renal prognosis is unclear for these patients.
Methods: This observational retrospective cohort study examined the renal outcomes of 14 patients who had IgAN with end-stageliver disease and subsequently underwent either liver transplant alone or combined liver and kidney transplant at a single tertiary care center.
Results: Of the 7 patients who underwent liver transplant alone, hematuria persisted in 2, 4 had progressive loss of kidney function with worsening proteinuria in 3 but only 1 reached end-stage renal disease posttransplant. Among 7 combined liver and kidney transplant recipients, 1 had histologic and 1 had histologic and clinical recurrence of IgAN without kidney allograft loss.
Conclusions: IgAN in patients with advanced liver disease does not necessarily resolve after liver transplant but has overall favorable renal outcomes.

PE-231

Pediatric Liver Transplantation in University Medical Center

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Aims: The ideal ratio between liver transplant graft mass and recipient body weight is unknown, but the graft probably must weigh 0.8% to 2.0% recipient weight. When this ratio > 4%, there may be problems due to large-for-size transplant, especially in recipients < 10 kg. This condition is caused by discrepancy between the small abdominal cavity and large graft and is characterized by decreased blood supply to the liver graft and graft dysfunction. We evaluated our experience with large-for-size grafts.
Methods: We retrospectively evaluated 12 orthotopic pediatric liver transplants that were performed from 2012-2019 in our center.
Results: There were 8 patients < 10 kg who had living-donor living transplant with graft-to-body weight ratio > 4%. In 2 patients, the abdomen was closed with a Bogota bag. In 4 patients, reoperation was performed due to vascular problems and abdominal hypertension, and the abdomen was closed with a Bogota bag. All Bogota bags were closed in 2 weeks. After closing the fascia, 2 patients had vascular problems that were diagnosed in the operating room by Doppler ultrasonography, and only the skin was closed without fascia closure. No graft loss occurred due to large-for-size transplant. There were 2 patients who died early after transplant (sepsis, 1 patient; brain death, 1 patient). There was no major donor morbidity or donor mortality.
Conclusions: Large-for-size graft may cause abdominal compartment syndrome due to the small size of the recipient abdominal cavity, size discrepancies in vascular caliber, insufficient portal circulation, and disturbance of tissue oxygenation. Abdominal closure with a Bogota

PE-232

Pediatric Liver Transplantation Outcomes in UMC

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Aims: Liver transplantation is the only life-saving intervention for patients with end stage liver disease. LDLT donors are typically healthy adults who do not derive any medical benefit from the procedure for themselves. Donor death is the most serious complication after LDLT, with estimated mortality at 0.28 to 1.0 percent, however, the exact risk cannot be precisely quantified due to the lack of a centralized database measuring donor outcomes.
Methods: We retrospectively reviewed the medical records of 15 LDLT recipients who underwent the procedure using a left liver graft between October 2013 and January 2018 in the Department of Surgery. Donor age, sex, and the degree of hepatosteatosis were compared between the groups. Recipient age, sex, body mass index (BMI), and transplantation indications were also compared between the two groups. We measured the recipients' Child-Turcotte-Pugh (CTP) and PELD scores in both groups to compare the preoperative disease severity. Although the general donor age recommendation in our institution is 18-55 years of age, the donors in this study were 19-48 years old.
Results: The anatomical structure of the vasculature and biliary tree and liver consistency were evaluated using abdominal CT, ultrasonography, and magnetic resonance cholangiopancreatography (MRCP). A frozen section liver biopsy to evaluate the degree of hepatosteatosis was performed in all of the donors during the operation. All of the hepatic grafts were perfused and preserved with iced HTK solution.
Conclusions: LDLT using elderly donors could induce more serious complications and higher mortality rates than those at using younger donors.

PE-233

Importance of Synchronised MRCP and Intraoperative Cholangiogram (IOC) in Living Donor Liver Transplantation (LDLT): Indonesian Single Centre Experience

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Aims: LDLT are obtained from MRCP and IOC. Bile leakage as one of the important complications can be minimised by detail acknowledgment of biliary anatomy by combining MRCP and IOC. This study aims to review donors' biliary anatomy and the

impact of the acknowledgment to technique and duration.
Methods: This single centre retrospective study included 46 adult-to-pediatric and 7 adult-to-adult LDLTs performed in Cipto Mangunkusumo Hospital from 2010-2019. All patients were performed MRCP then synchronised with IOC. All results were classified by Huang Classification. Demographic data, surgical technique, duration, and radiologic discrepancy were collected.
Results: There are 34 cholangiographies out of 53 LDLTs. No biliary complications detected. Forty-nine donors underwent left-lateral sectionectomy and 4 right hepatectomy. Operative duration ranged from 270-600 minutes. The frequency of each type on MRCP/IOC are as follows: Huang A1 40,5%/35,1%; Huang A2 37,8%;37,8%; Huang A3 13,5%/18,9%; Huang A4 5,4%/8,1%; and Huang A5 2,7%/0. Huang A1 has the shortest operative duration and the least blood loss (70cc). Huang A3 has the longest operative duration with the most blood loss (900cc). Discrepancy were found in 6 patients of which 2 underwent longest operative duration and lost the most blood.
Conclusions: Synchronised MRCP and IOC decrease operative duration therefore associated with better outcome. Low discrepancy showed that surgeon does not require nephrotoxic contrast media used in IOC hence reducing surgical duration except for rare cases like Huang A4 and A5 to avoid ligation of major intrahepatic duct.

PE-234

A Randomized Control Trial of Left Hepatic Arterial Anastomosis with Graft Right Hepatic Artery Versus Anastomosis with Right Hepatic Artery and Its Impact on Biliary Complications

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Aims: It has been pointed out that LHA may not be suitable in all cases. This randomized control trial was conducted to assess whether anastomosis with LHA could be carried out in all the assigned cases and whether the outcome was comparable to anastomosis with RHA of the recipient.
Methods: Inclusion criteria:·Living related right lobe adult to adult ABO compatible liver transplantation·Patients planned for duct to duct anastomosis·Single artery in donor graft for anastomosis on preoperative imaging Exclusion criteria:·Retransplantation·Patients with sclerosing cholangitis or far apart ducts requiring two biliary anastomoses or bilioenteric anastomosis as suggested by preoperative imaging·ABO incompatible·Pediatric liver transplant·Multiple arteries
Results: The arterial lumen of the recipient and donor arteries, size mismatch was significantly more in the RHA group. (15% Vs 72%, p-value – 0.03). the early morbidity and mortality was similar in both the groups. Late strictures among survivors were noted more commonly in the RHA group (29.7% vs. 22.7%). Bile leak, mortality, and incidence of late-onset biliary strictures were less common in the LHA group, though the difference was not statistically significant.
Conclusions: Anastomosis of the graft artery in a right lobe graft with recipient LHA is feasible in the majority of the cases. The use of LHA was associated with fewer biliary complications in the long term as compared to RHA.

PE-235

Living Donor Hepatectomy Using Minimal Incision: An Experience of Consecutive 63 Cases by a Single Surgeon

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Aims: Living donor hepatectomy (LDH) is performed widely as a part of living donor liver transplantation. The type and length of incision have been considered important because of the quality of life, such as the cosmetic effect. We describe herein the minimal incision for LDH to evaluate the safety and feasibility.
Methods: We enrolled 63 consecutive cases of donor hepatectomy using a subcostal or upper midline minimal (9-12cm) incision depending on graft type and size between Jul and Dec in 2019 at a single center. Donor demographics, preoperative data, and postoperative outcomes were analyzed.
Results: The mean age of the donors was 32.8 ± 10.3 yrs, and 32 (50.8%) donors were male. The mean operation time was 400.5 ± 69.5 minutes and the mean hospital stay was 9.4 ± 3.7 days. The graft types comprised 52 (82.5%) of the modified right lobe, 6 (9.5%) of the modified extended right lobe, and 5 (7.9%) of the extended left lobe. The portal vein types were I, II, and III in 59 (93.7%), 1 (1.6%), and 3 (4.8%), respectively. The bile duct types were A, B, C1, and C2 in 46 (73.0%), 8 (12.7%), 3 (4.8%), and 6 (9.5%). There were one (0.02%) case of bile leakage, and one (0.02%) case of abdominal wall bleeding postoperatively.
Conclusions: LDH using minimal incision was a safe and feasible option showing an acceptable incidence of complications despite anatomical variations.

PE-236

Biliary Complications after Single- and Dual-Graft Living-Donor Liver Transplantation Using a Right Posterior Section Graft from a Donor with a Type III Portal Vein Variation

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Aims: When the donor's left lobe volume is <30%, donor selection for the right posterior section graft (RPSG) is based on the type III portal vein (PV) anatomical variation. Herein, we validated the selection of a donor with a type III PV variation for RPSG to prevent biliary complications (BCs) after single-graft (SG) and dual-graft (DG) living-donor liver transplantation (LDLT).
Methods: The clinical data of recipients and donors with a type III PV variation for LDLT using an RPSG performed between January 2004 and June 2018 were retrospectively collected and analyzed to determine the occurrence of BCs.
Results: The 26 LDLTs performed using an RPSG, including 20 DG LDLT cases, accounted for 0.6% of all LDLT cases (n=4,292). BCs developed in 6 recipients (23.0%), including biliary stricture in 4 (15.3%) and bile leakage in 2 (7.6%). No vascular complications occurred. The RPSG volume was significantly smaller in recipients with BCs than in those without BCs (400.8±79.9 vs. 504.1±96.5 ml, *P*=0.015). The bile duct types were A, B, C1, C2, and D in 6 (18.8%), 5 (15.6%), 3 (9.4%), 13 (40.6%), and 5 patients (15.6%), respectively. All the RPSGs had a single-orifice bile duct. The bile duct size of the RPSG was relatively smaller in recipients with BCs than in those without BCs (2.8±1.0 vs. 3.6±1.4 mm, *P*=0.237).
Conclusions: When using an RPSG for SG and DG LDLTs, the selection of a donor with a type III PV variation can be feasible to prevent BCs.

PE-237

Biliary Complications following Liver Transplantation within Three Years' Experience

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Aims: The aim of this study was to review the major biliary tract complications after liver transplantation.
Methods: Medical records of 30 liver transplant recipients during 2016 October to 2019 December period at Hepatobiliary and Pancreatic Surgery department, Yangon Specialty Hospital have been evaluated retrospectively. Among the post-transplant complications, biliary tract complications including biliary leakage and biliary stricture are common. Number of bile duct openings of graft, the type of biliary reconstruction performed at the time of liver transplant, type of biliary complications and their managements were reviewed in this study
Results: In this three years' retrospective study, biliary complications were the most frequent post-op complications of liver transplant patients. 8 out of 30 patients faced with biliary complications range from early anastomotic leak to late stricture and obstruction in the extra hepatic or intrahepatic biliary system. 6 cases with biliary complications treated with Endoscopic Retrograde Cholangio (ERC) dilatation and stent implantation, one case with bile leak treated with per cutaneous drain and one case with ischemic biliary stricture case needed re-transplantation.
Conclusions: Biliary tract complications following liver transplantation are relatively common and continue to be a challenging aspect in the management of such patients. These complications require several other endoscopic, per cutaneous and surgical procedures that increase the morbidity, mortality and reduce the quality of life of these patients.

PE-238

Early Experiences of Liver Transplantation in a Newly Opened Hospital

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Aims: Since the first human liver transplantation (LT) performed in 1963, LT has been most effective treatment for end-stage liver diseases and for selected patients with hepatic neoplasms. Herein we will report early experience of liver Transplantation in a newly opened hospital on April, 2019.
Methods: We have been operated eight LT from June, 2019 to December, 2019. In clinical features of recipients, mean age was 50.5 ± 7.7 (years), six male and two female, the causes of LT were one autoimmune liver cirrhosis (LC), three alcoholic LC and four HBV-LC with HCC. MELD score (mean) was 16.9 ± 13.2, GRWR(%) was 1.07 ± 0.22, operative time(mean) was 661 ± 161.9 minutes. Two transplanted graft was extended left lobe, five grafts were modified right graft and one was cadaveric donor whole liver graft. All bile duct reconstruction was conducted by duct to duct anastomosis. Mean post-operative hospital day was 25.6 ± 9.8 (days), and there was some morbidity.
Results: In features of seven living donors, mean age was 29.7± 11.3 (years), six male and one female, post-operative hospital day was 15.3 ± 5.6 (days), and there was two minor bile leakage but no mortality
Conclusions: A multidisciplinary approach with surgical, anesthetic, radiologic and medical departments, and wide range of administrative supports, which can be provided with institutional and foundational support, is crucial. We thought that the multidisciplinary teamwork including thorough preparation for

LT is most important for which first started the liver transplant in a newly opened hospital.

PE-239

Outcome of Pediatric Liver Transplantation and Risk Factor Affecting Overall Survival: Using Two Korean National Registry Data

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Aims: Children are not just small adults and the results might be somewhat different from the adult LT. The aim of this study is to evaluate the national cohort of pediatric LT patients and analyze the risk factor for mortality.

Methods: Two national registry data were used. One is the Korean Network Organ Sharing (KONOS) of the Korea Centers for Disease Control and Prevention, a mandated national registry started in 2000 but the prospective variables are limited. The other one is the Korean Organ Transplantation Registry (KOTRY), a nationwide organ transplantation registration system, includes many variables but started in 2014. Prospectively collected data of 802 pediatric LT patients between February 2000 and December 2015 from KOTRY and 76 pediatric LT patients between May 2014 and December 2017 were retrospectively reviewed.

Results: The 1-, 2-, 5-, and 10-year patient survival rates from KONOS data were 89.5%, 87.5%, 85.7%, and 84.8%. The 1-month, 1-, and 2-year patient survival rates from KOTRY were 92.1%, 89.4%, and 87.2%. There was no significant survival difference between the two registry data. KONOS data of 802 children showed that the mean age was 3.9 years and there were 359 (44.8%) male. Biliary atresia was the leading indication (n=357; 44.5%). KOTRY data of 76 children showed that the mean age was 59.4 months and there were 33 (43.4%). Risk factor for mortality was analyzed using KOTRY data. Hepatic artery complication after liver transplantation was the only risk factor of overall mortality (P<0.001).

Conclusions: Long-term pediatric patient survival after liver transplantation is satisfactory.

PE-240

Oncologic Outcomes of Alcohol Induced HCC after Liver Transplantation

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Aims: Alcohol is a well-known oncogenic substance that many people still have abused. Alcohol can make liver not only cirrhosis but also hepatocellular carcinoma (HCC). More and more patients who have HCC undergo liver transplantation (LT) these days. However, there was no report to research the oncologic outcomes of LT for those patients.

Methods: The data from 470 patients with HCC who underwent LT were retrospectively collected and analyzed. We compared oncologic outcomes between alcoholic and non-alcoholic HCC patients.

Results: Out of 470 HCC patients, 20 patients had alcoholic HCC before LT. There were no differences in Milan criteria proportion and AFP level between the groups. The mean MELD score of the groups was not different. Living donor LTs were performed in 70% of non-alcoholic group and 80% of alcoholic group, which was no significantly different. RBC transfusion and operation time were not different during the operations. However, recurrence-free survival rates of alcoholic HCC group was worse than non-alcoholic group (3yr RFS; 58.9% vs 85.7% respectively, P=0.032).

Conclusions: Alcohol induced HCC patients showed worse recurrence-free survival after LT than non-alcoholic HCC patients. Further study will be needed to clarify the cause of these results.

PE-241

A Novel Approach to the Management of Hepatic Artery Intimal Dissection During Living Donor Liver Transplantation

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Aims: Hepatic artery intimal dissection (HAD) followed by hepatic artery thrombosis (HAT) is serious complication of liver transplantation. There is paucity of information in literature on the management options for HAD encountered during surgery. In this study we describe a new classification and technique for the management of HAD during living donor liver transplant (LDLT).

Methods: Based on the longitudinal extent of intimal dissection, HAD was classified into 4 types. Management was based on the availability of adequate length of hepatic artery and availability of alternate source of inflow. The dissected hepatic artery itself was used for arterial anastomosis in cases with preserved flow in the dissected artery and paucity of an alternative sources of arterial inflow. The technique of using the dissected artery is based on close approximation of tunica intima to media with the first two sutures of the arterial anastomosis. Patients with HAD were compared with those without HAD for evaluation of risk factors for intimal dissection.

Results: 47 (2.4%) patients developed HAD during surgery. 22 (46.7%) patients had type II dissection for whom the other (right or the left) undissected hepatic artery was used for anastomosis. 20 (45%) patients were found to have major (type III or IV) dissection. The dissected artery was used for anastomosis in 9

of (45%) of these patients. Post-operative HAT developed in only one out of the 9 patients. Pre-existing portal vein thrombosis (PVT) and prior trans arterial embolization (TAE) were found to be major risk factors for development of intimal dissection.

Conclusions: Classification

PE-242

Antiviral Therapy Increases the Risk of Bacterial Infections in HCV-Infected Cirrhotic Patients Awaiting Liver Transplantation: A Retrospective Study

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Aims: Recurrence of hepatitis C after liver transplantation (LT) is universal and may cause premature graft loss. We evaluated the efficacy and safety of antiviral therapy in HCV-infected patients with decompensated cirrhosis awaiting LT.

Methods: Fifty-one patients underwent treatment with peginterferon-alfa-2a and ribavirin. A control group of 51 untreated individuals awaiting LT were matched by age, Child-Pugh and MELD scores and time on the waiting list.

Results: Case and control patients were comparable for all relevant variables. Fifteen treated patients (29%) had undetectable HCV-RNA at the time of transplantation and 10 (20%) achieved SVR. Early virological response and non-1 genotype were the strongest predictors of viral clearance. There was a higher incidence of bacterial infections in treated patients vs controls, particularly in Child-Pugh B-C individuals (17 vs 3 episodes) (log-rank=0.0016). Importantly, the incidence of spontaneous bacterial peritonitis (SBP) in patients who were not receiving norfloxacin prophylaxis (n=83) was significantly higher in the treated group than in controls (log-rank=0.01).

Conclusions: Our data demonstrate that antiviral treatment prevents hepatitis C recurrence in 20% of HCV-infected patients. However, treatment should be recommended with caution in individuals with poor liver function who do not receive norfloxacin prophylaxis for SBP, since it increases the risk of bacterial infections.

PE-243

Venous Anatomic Variants Encountered During Liver Transplantation

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Aims: Adequate knowledge of hepatic vascular particularities is mandatory before preparing the patient for liver transplantation, significant anatomical variants being present in certain cases.

Methods: We present two cases in which venous malformations were seen. In the first case supranumerary hepatic veins (two inferior hepatic veins originating from segments 5 and 6) were encountered at the donor; in the second case type Ib Abernethy malformation has been described preoperatively at the receiver.

Results: The first case necessitated performing a supplemental anastomosis between the two inferior hepatic veins, the resulting structure being directly reinserted in the inferior cava vein; the second case had been diagnosed with unresectable liver adenomatosis in the presence of an aberrant portal vein draining directly into the inferior cava vein; the patient was successfully submitted to living donor liver transplantation using a left hemiliver.

Conclusions: The presence of venous abnormalities should be carefully investigated in both donor and receiver among cases submitted to living donor liver transplantations; modifications encountered in both donor and receiver might significantly influence the further technical details.

PE-244

Portal Vein Thrombosis During Liver Transplantation: The Risk of Extra-Anatomical Portal Vein Reconstruction

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Aims: This study is designed to analyze the risk and benefit of extra-anatomical portal vein reconstruction during liver transplantation of patient with portal vein thrombosis.

Methods: Patients who underwent liver transplantation between 2008 to 2018 were reviewed. Portal vein thrombosis was graded according to the Yerdel system. Risk factor for portal vein complication-free, graft and overall survival were analyzed with multivariate Cox regression.

Results: Seventy out of 1180 patients had portal vein thrombosis. Number of patients who underwent extra-anatomical reconstruction were 3 (13.0%), 3 (15.0%), and 6 (50.0%) with grade II, III and IV thrombosis, respectively. Grade III patients with extra-anatomical reconstruction (HR=10.212, CI=2.475-42.133, *P*=0.001), grade IV with both anatomical (HR=16.991, CI=5.224-54.740, *P*<0.001) and extra-anatomical reconstruction (HR=12.262, CI=2.698-50.666, *P*=0.001) were risk factors for portal vein complication-free survival. Grade IV thrombosis with both anatomical (HR=4.296, CI=1.059-17.430, *P*=0.041) and extra-anatomical reconstruction (HR=7.777, CI=2.461-24.571, *P*<0.001) were risk factors for graft failure. Extra-anatomical reconstruction for both grade I to III (HR=3.638, CI=1.155-11.453, *P*=0.027) and grade IV thrombosis

(HR=4.798, CI=1.773-12.982, *P*=0.002) were risk factors for survival.

Conclusions: Grade IV thrombosis and extra-anatomical reconstruction were related to poor prognosis. Therefore, thorough evaluation and planning is required for patients with portal vein thrombosis.

PE-245

Venous Outflow Congestion is Related to Poor Recurrence-Free Survival of Living Donor Liver Transplantation Recipients with Hepatocellular Carcinoma

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Aims: This study was designed to analyze the impact of venous outflow congestion in the liver graft on hepatocellular carcinoma recurrence with liver transplantation

Methods: Hepatocellular carcinoma patients who underwent living donor liver transplantation in Samsung Medical Center between 2007 and 2018 were reviewed. Based on 2-week post-transplantation computed tomography, volume of the congested parenchyma was calculated. Patients were divided into five groups based on the congestion volume. Recurrence-free survival and overall survival was analyzed using multivariable Cox proportional hazard model including the degree of venous congestion.

Results: A total of 582 patients were included. There were 350 patients (60.1%) with no congestion, while congestion volume less than 100 cm^3, between 100 to 200 cm^3, between 200 to 300 cm^3, and ≥300 cm^3 were present in 58 (10.0%), 109 (18.7%), 40 (6.9%) and 25 (4.3%), respectively. Congestion volume (*P*=0.008) was a significant risk factor recurrence-free survival. Congestion volume of ≥300 cm^3 (HR=3.349, CI=1.703-6.587, *P*<0.001) showed significantly poorer recurrence-free survival compared to patients with no congestion.

Conclusions: Venous outflow congestion in the liver after living donor liver transplantation was related to poor recurrence-free survival of hepatocellular carcinoma.

PE-246

Application of Image-Guidance Using 2D Illustrations and 3D Modeling of Donor Anatomy During Living Donor Hepatectomy

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Aims: For living donor liver transplantation, preoperative imaging is required for the safety of donor and recipient. As we started our image-guidance program using 2D illustrations and 3D modeling since September 2018, we analyzed the changes in the clinical outcomes.

Methods: Living donors and recipients who underwent liver transplantation between September of 2017 to August 2019 were included. Cases with image-guidance were compared to cases without image-guidance regarding operational outcome especially bile duct opening in graft as well as surgical complications.

Results: Among 200 living donor transplantation, 90 transplantations were performed with image-guidance. The image-guidance group had higher rate of laparoscopy (80.9 vs. 97.8%, *P*<0.001) and shorter operation time (259.8±47.3 vs. 240.3±34.4 minutes, *P*=0.002) compared to the no image-guidance group. Although there was no difference in bile duct type (*P*=0.144), there was more grafts with single bile duct opening in the image-guidance group (52.7% vs. 80.0%, *P*=0.001). Consequently, achievement in bile duct openings was superior in the image guidance group. (*P*=0.022) There were no difference in bile leakage, graft failure, and death during the 1-month post-transplantation period.

Conclusions: As we initiated our image-guidance program for living donor liver transplantation, clinical outcomes, especially bile duct division were improved than before.

Drug and Toxic Injury

PE-247

Inhibition of Beryllium Induced Oxidative Stress, Altered Metabolic Pathways and Beryllium Burden by Co-Therapy of Moringa oleifera Lam. with Curcumin

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Aims: Beryllium is highly toxic to human, induces oxidative stress and leads to development of chronic beryllium disease (CBD), hepatomegaly and lung cancer. Therapeutic efficacy of Moringa oleifera root extract with curcumin was investigated against beryllium induced oxidative stress, altered carbohydrate and heme metabolism together with beryllium body burden in rats.

Methods: $Be(NO_3)_2$ at doses of 1.0 mg/kg, i.p. once a day, daily for 12 weeks were administered in female Wistar albino rats followed by the treatment of Moringa oleifera (150 mg/kg, p.o) with curcumin (5.0 mg/kg, p.o.), once a day, daily for 2 weeks. Markers of oxidative stress, blood sugar, hepatic glycogen, G6Pase, SDH, G6PDH, markers of liver function, markers of heme biosynthesis, beryllium body burden and histopathogical alterations were monitored.

Results: Beryllium induced oxidative stress by enhancing lipid peroxidation with decrease in cellular reduced glutathione, SOD and catalase activities. Beryllium altered the carbohydrate metabolism by decrease in blood sugar, glycogen, G-6-Pase, Succinate dehydrogenase (SDH) and increase in G6PDH activity.

Beryllium altered liver function by significantly increase in AST, ALT, LDH activities and by significantly decrease in albumin and SALP activity. Beryllium disturbed heme biosynthesis by decrease in ALAD activity with hemoglobin and increase in ALAS activity with total bilirubin. Beryllium significantly deposited in vital organs of rats and liver occupied maximum amount of administered beryllium. Beryllium also altered the histoarchitecture of liver. Post treatment of Moringa oleifera and curcumin alone was effective however combination therapy of Moringa oleifera with curcumin showed more pronounced therapeutic effect in minimizing toxic effect of beryllium as seen by reduction of oxidative stress, restoration of liver biochemical markers, maintaining hemoglobin and sugar level normal, reduction in beryllium body burden with almost normal histoarchitecture of liver.

Conclusions: Curcumin enhanced therapeutic efficacy of Moringa oleifera root extract against beryllium induced liver toxicity in rats.

Keywords: Beryllium poisoning, Liver dysfunction, Carbohydrate metabolism, Heme metabolism

PE-248

Hepatoprotective Evaluation of the Effects of The Hydroalcoholic Extract of Liv.52 Ds on Paracetamol Induced Liver Toxicity in Rats

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Aims: Oxidative stress induced by toxicants is known to cause various complications in the liver. Herbal drug such as Liv.52 is found to have hepatoprotective effect. However, the biochemical mechanism involved in the Liv.52 DS mediated protection against toxicity is not well elucidated using suitable *in vivo* models. Paracetamol causes oxidative stress and dysfunction of the liver. This study was undertaken to evaluate the effects of the hydroalcoholic extract of Liv.52 DS on some biochemical and histopathological parameters of liver tissue in against paracetamol induced hepatic damage in rats.

Methods: Wistar rats were orally administered with 2g/kg body weight Paracetamol. Vehicle (distilled water) and silymarin (50 mg/kg body weight) were used as the negative and positive control groups, respectively. Paracetamol -administered groups were treated with Liv 52 DS extract (100, 200, and 400 mg/kg). After 15 days of treatment, the blood specimens and liver samples were examined. Alteration in the levels of biochemical markers of hepatic damage like AST, ALT, ALP and lipid peroxides were tested, and phytochemical tests were also performed.

Results: In Paracetamol -treated group, the levels of serum urea, high density lipoprotein (HDL), and liver superoxide dismutase (SOD), catalase (CAT), and vitamin C significantly decreased (P<0.05) compared to control. Also, in this group, serum triglyceride (TG), total cholesterol (TC), very low density lipoprotein cholesterol (VLDL), protein carbonyl (PC), malondialdehyde, tumor necrosis factor-alpha (TNF-α), and TNF-α gene expression significantly increased (P<0.05) as compared to the control (vehicle-treated rats). Treatment with Liv. 52 DS extract in a significant increase (P<0.05) in CAT, SOD, vitamin C, HDL and a significant decrease (P<0.05) in the level of urea, MDA, PC, TG, TC, VLDL, TNF-α protein, and the gene expression of TNF-α compared with test without treatment group. Histopathological evidence demonstrated that treatment with Liv.52 DS extract could decrease liver lymphocyte infiltration.

Conclusions: The present study suggests that Liv. 52 DS extract possesses hepatoprotective activity. It could be an effective and promising preventive agent against Paracetamo-induced hepatotoxicity.

Keywords: Paracetamo-induced hepatotoxicity, Superoxide dismutase, Liv.52 DS, Hepatic damage

PE-249

Acute Hepatitis Complicated by DRESS Syndrome

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Background: Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe idiosyncratic reaction that is characterized by fever, rash, and internal organ involvement after exposure to drug. Herein report is a case of DRESS syndrome with acute hepatitis induced by treatment with carbamazepine on tinnitus.

Case: A 69-year-old man was hospitalized due to fever with whole body rash. He has been prescribed carbamazepine for tinnitus since 20 days ago. He complained of fever and itching sensation. Physical examination showed facial edema and whole body rash. On admission, BP was 120/70 mmHg, HR 84 beats/min, RR 20 breaths/min, and BT 38.5°C. Laboratory findings revealed WBC 10,800/mm3 (eosinophil 9.3%), Hb 15.2 g/dL, PLT 200,000/mm3. Eosinophil count was 411/ul. PT 13.21 sec, PT (INR) 1.21, AST 167 IU/L, ALT 349 IU/L, total bilirubin 1.36 mg/dL, albumin 3.3 g/dL, ALP 252 U/L, r-GTP 636 U/L, BUN 7 mg/dL, creatinine 0.98 mg/dL. HBsAg(-), anti-HCV(-), IgM HAV(-). HSV, EBV and CMV was all negative. Abdominal ultrasonography and CT showed mild splenomegaly. Intermittent high fever and facial edema persisted during 3 days of hospitalization and steroid treatment started. On the 11th day of hospitalization, he was discharged due to improved liver function and disappearance of rash.

Conclusions: Several drugs such as antiepileptics or antibiotics are well known to cause DRESS syndrome. DRESS syndrome can cause liver damage, even liver failure with poor prognosis. So, rapid withdrawl of suspected medications is important.

Keywords: DRESS syndrome; Acute hepatitis; Drug; Carbamazepine

PE-250

Bee Sting Induced Hepatotoxicity

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Background: Bee sting is known to cause hepatotoxicity, renal damage, hemolysis and myocardial infarction. Hepatotoxicity can appear immediately or weeks after exposure of bee sting. Herein report is a case of hepatotoxicity in a 79-year-old woman after bee sting.

Case: A 79-year-old woman accidentally touched the beehive and had multiple bee sting injury in various parts of her head, waist, and arms and then came to emergency room because of general weakness and urticaria. She denied drinking, smoking and taking any drugs or herbs. On emergency room, BP was 70/40 mmHg, HR 98 beats/min, RR 20 breaths/min, and BT 36.8°C. Under the suspicion of anaphylactic shock, epinephrine was administered immediately and blood pressure returned to normal. She was diagnosed with fatty liver 2 years ago. Her height was 156 cm, weight 52 kg, BMI 21.37. Laboratory findings revealed WBC 8,640/mm^3, Hb 14.9 g/dL, PLT 240,000/mm^3, PT 14.0 sec, PT (INR) 1.28, AST 645 IU/L, ALT 526 IU/L, total bilirubin 0.84 mg/dL, albumin 3.5 g/dL, sodium 141 mEq/L, potassium 3.1 mEq/L, chloride 103 mEq/L, BUN 14 mg/dL, creatinine 1.2 mg/dL, CK/LDH 172/988 U/L, amylase 40 U/L, Lipase 179 U/L. Viral markers (HBsAg, IgM HBV, IgM HAV, Anti HCV, HSV, EBV and CMV) were all negative. Abdominal ultrasonography showed moderate fatty liver and gallbladder distension with wall edema. Abdomen CT showed no defined focal mass lesion in the abdominal solid organs. Liver biopsy revealed fatty change (50~75%) with mild neutrophilic infiltration. On 12th admission day after conservative treatment, her liver function was improved and she was discharged.

Conclusions: The spectrum of bee sting induced totoxicity varies. Most of hepatotoxicity show a temporary increase in liver enzymes. The mechanism of hepatotoxicity is presumed to be a reversible pre-thrombotic condition and temporary autoimmune phenomena caused by bee sting, but additional evidence is needed.

Keywords: Bee sting, Acute hepatitis, Anaphylactic shock, Fatty liver

PE-251

Ginkgo Biloba Extracts Protects against Early Alcohol-Induced Liver Injury in the Male Rat

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Aims: Ginkgo biloba extracts (GBE), a phytoestrogen, has been widely used for treating coronary heart disease and neurological disease in clinical settings and demonstrated beneficial effects at biochemical and pharmacological levels. Oxidants have been shown to be involved in alcohol-induced liver injury. This study was designed to determine whether GBE, composed mostly of flavonol glycosides and terpene lactones, protects against early alcohol-induced liver injury in rats.

Methods: Total fifty eight male Wistar rats were fed high-fat liquid diets with or without ethanol (10-14 g/kg per day) and GBE extract (250 mg/kg per day) continuously for 4 weeks using an enteral feeding protocol.

Results: Mean body weight gains (approximately 4 g/day) were not significantly different between treatment groups. GBE extract did not affect average daily urine ethanol concentrations (approximately 200mg/dL). After 4 weeks, serum alanine amino transferase levels of the ethanol group were increased nearly fourfold (110+/-16 IU/L) compared to control values (35+/-3 IU/L); this effect of ethanol was blocked by GBE extract (60+/-6 IU/L). Additionally, enteral ethanol caused severe fat accumulation, mild inflammation, and necrosis in the liver; GBE extract significantly blunted these changes. Increases in liver TNF alpha protein levels caused by ethanol were completely blocked by GBE extract. Further, ethanol significantly increased the accumulation of protein adducts of 4-hydroxynonenal, a product of lipid peroxidation serving as an index of oxidative stress; again this was counteracted by the addition of GBE extract.

Conclusions: The result indicates that the GBE extract exhibit the antioxidant activity through correction of oxidative stress and validates the traditional use Ginkgo biloba in prevent early alcohol-induced liver injury.

Keywords: Alcohol induced liver injury, Ginkgo biloba extracts, Male rats, Antioxidant enzymes

PE-252

Protective Effects of White Tea (Camellia Sinensis) on Metabolic Functions and Oxidative Stress in Isoniazid-Induced Hepatotoxic Rat Model

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Aims: Oxidative stress and hyperlipidemia are associated risk factors for developing liver disease. White tea (WT) is very similar to green tea (GT) but it is exceptionally prepared only from the buds and young tea leaves of Camelia sinensis plant while GT is prepared from the matured tea leaves. Camellia sinensis is a well-known medicinal plant that has been used for its anti-cancer, neuroprotective, and hepatoprotective effects. This study aimed at investigating the hepatoprotective role of ethanolic extract of WT against isoniazid-induced hepatotoxicity in female albino rats.

Methods: Wistar rats (n=8 per group)were divided into four groups: saline-treated control, saline-treated control with WT extract (200 mg/kg), isoniazid treatment alone (100 mg/kg, intraperitoneal [i.p.]), and isoniazid-WT extract (200mg/kg) administered orally as cotreatment. Animals were treated for 28 days and euthanized 1 h after the last drug administration. Evaluated body weight, serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, g-glutamyl transferase, total protein, albumin, hepatic malondialdehyde content, superoxide dismutase, catalase, cytochrome P450 2E1 (CYP2E1)activity and glutathione (GSH).
Results: WT extract prevented isoniazid-induced hepatotoxicity, indicated by both diagnostic indicators of liver damage, liver functional profile, significantly inhibited CYP2E1 activity, markedly attenuated oxidative stress by improved enzymatic, non-enzymatic antioxidants levels and mitigate malondialdehyde, lipid hydroperoxide significantly.
Conclusions: These results suggest that WT extract exerts its hepatoprotective activity by inhibiting the production of free radicals and acts as a scavenger, reducing the free radical generation via inhibition of hepatic CYP2E1 activity, increasing the removal of free radicals through the induction of antioxidant enzymes and improving non-enzymatic thiol antioxidant GSH.
Keywords: Camelia sinensis plant, Isoniazid-induced hepatotoxicity, Hepatoprotective role, Female rats

PE-253

The Use of mTOR Inhibitors in Pediatric Liver Transplant Recipients: First Experience in a University Medical Center

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Aims: The role of mTOR inhibitors, such as EVL, has not been established for pediatric liver transplant recipients up to now, although data from adult solid organ graft transplantation are very promising. Major complications following pediatric liver transplantation in the long-term course include chronic graft rejection and CNI-derived nephrotoxicity.
Methods: The purpose of our study was to report first results using EVL as a rescue therapy in pediatric liver transplant recipients for the following indications: chronic graft dysfunction n=12, suspected CNI toxicity n=3, hepatoblastoma n=2, and recurrence of primary sclerosing cholangitis post-Ltx n=1.
Results: Four patients with chronic graft dysfunction developed completely normal liver function tests using EVL, six patients showed partial improvement, and two patients did not respond at all. One patient with CNI-induced nephropathy showed a slightly improved GFR. Both patients with hepatoblastoma did not develop any metastasis post-Ltx. First experience with EVL in pediatric liver transplant recipients shows promising results in patients with chronic graft failure when standard immunosuppression has failed.
Conclusions: The future role of EVL in immunosuppressive protocols for children post-Ltx has to be proven by controlled clinical trials.

PE-254

Solid Lipid Nanoparticle of Hesperidine Exerts Diethylnitrosamine Induced Hepatocellular Carcinoma via Alteration of PI3K/Akt Pathway

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Aims: Hepatocellular carcinoma (HCC) is the widely documented danger to the liver and 3rd most common reason for tumor death around the world. Identification of oncogene and its related possible pathway is crucial for understanding therapy resistance and effectual treatment. Researcher targeted the 5-bisphosphate 3-kinase/protein kinase B, phosphatidylinositol-4 and mitogen activated protein kinase's pathway to suppress the cell proliferation and expansion. We made attempt to fabrication the solid lipid nanoparticle (SLN) of hesperidine and examine against the diethylnitrosamine (DEN) induced HCC and explore possible mechanism of action.
Methods: Double emulsion solvent displacement model was used for the preparation of hesperidine-SLN. Intraperitoneal injection of DEN (200 mg/kg) was used for induction the HCC and various parameters were scrutinized. Morphological and histopathological component of hepatic tissue were estimated.
Results: Surface methodology suggests the 182.3 nm particle size and 0.230 polydispersity index for hesperidine-SLN. hesperidine-SLN significantly (P<0.001) reduced the hepatic nodules (84.5%) and hepatic nodules (93.4%). hesperidine-SLN significantly (P<0.001) modulated the hepatic parameter viz., AFP (83.4%), CEA (50.4%), ALT (58.5%), ALP (68.4%), AST (65.8%), GGT (63.4%); non-hepatic parameter viz., BUN (56.4%), total protein (64.5%), albumin (63.4%), direct bilirubin (67.4%), bilirubin (63.4%); antioxidant parameter LPO (71.3%), SOD (60.3%), CAT (64.9%), GPx (58.3%), GST (63.4%) respectively. hesperidine-SLN significantly (P<0.001) modulated the expression of Pik3r1(58.4%), Akt1(43.5%), Plk-3ca (54.9%), Erbb2 (53.6%) and Map3k1 (43.6%).
Conclusions: Collectively, we can conclude that hesperidine-SLN regulated the PI3K and Akt pathways, which involved in reduction of heatic cancer expansion and proliferation and its chemo-protective effect.

Cell Biology/Molecular Biology

PE-255

Attenuation of Intracellular Lipid Accumulation in Liver-Derived Cell Lines by Treatment of GRIM19-D1 Peptide

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Aims: Recently, our group identified the roles of genes associated with retinoid-IFN-induced mortality (GRIM)-19 in hepatitis C virus (HCV) infection. In this study we aimed to investigate the roles of GRIM19 in liver steatosis and develop the peptide drug using amino acid sequence of GRIM19 protein for non-alcoholic steatohepatitis (NASH).

Methods: For *in vitro* studies, Huh-7 and HepG2 cell lines were treated with palmitic or oleic acids. Peptides derived from various domains of GRIM19 protein were used to validate the anti-lipogenic effects of GRIM19 protein. *In vivo* experiments were performed with mice fed with high fat diet.

Results: First, we found that forced expression of GRIM-19 attenuated an increase in intracellular lipid droplets after oleic acid treatment or HCVcc infection. GRIM-19 overexpression abrogated fatty acid-induced upregulation of sterol regulatory element-binding transcription factor-1 (SREBP-1c) and its downstream genes such as fatty acid synthase (FAS), acetyl CoA carboxylase (ACC), and stearoyl CoA desaturase (SCD). Treatment with oleic acid or overexpression of SREBP-1c in GRIM-19-expressing cells restored the amount of intracellular lipid droplets. Mice fed with high fat diet showed reduced expression of GRIM19 in their fatty livers. We developed novel peptide drugs with each domain of the GRIM19 protein, and confirmed the anti-lipogenic activity of the specific domain of GRIM19 protein (GRIM19-D1). Sequence optimization enhanced the solubility and stability of GRIM19-D1.

Conclusions: Our data clearly demonstrate that GRIM19 and take critical roles for hepatic steatosis by regulating the expression of SREBP-1c and its target genes. GRIM19-D1, a novel peptide drug with minimal active domain of GRIM19 protein, effectively attenuated the accumulation of lipid droplets in liver-derived cell lines. This novel peptide drug can be applied to control hepatic steatosis in non-alcoholic steatohepatitis patients. This study was supported by the Research Supporting Program of The Research Foundation of the Department of Internal Medicine, The Catholic University of Korea.

Keywords: GRIM19, Peptide drug, NASH, Lipid droplet

PE-256

Effects of Macro-Encapsulated Mesenchymal Stem Cells Using Poly Lactic-Co-Glycolic Acid (PLGA) on Liver Disease: A Proof of Concept Stud

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Aims: Macro-encapsulation of human mesenchymal stem cells (MSCs) for treatment of liver diseases has not been studied. Here, we conducted a proof of concept study by macro-encapsulated MSCs using poly lactic-co-glycolic acid (PLGA) in liver disease models.

Methods: Acute liver injury was induced using thioacetamide (TAA) i.p. injection three times for a week. For chronic liver fibrosis model, TAA dose was gradually increased, starting from 100mg/kg to 400mg/kg over the duration of 16 weeks.

Results: In acute liver injury model, macro-encapsulated groups showed decreased liver inflammation and necrosis compared to control group. In chronic liver fibrosis model, compared to control group, hepatic fibrosis was reduced in macro-encapsulated group. Encapsulated MSCs implant in mice also showed increased periodic acid–Schiff staining and CYP2E1 expression. Moreover, in encapsulation group, MSCs migration and homing into liver, kidney and lungs was not observed. Encapsulated MSCs secreted more growth hormones under hypoxic condition including vascular endothelial growth factor, platelet-derived growth factor, angiopoietin-2 and, placental growth factor compared to monolayered MSCs. MSCs survival was assessed for 28 days. The results suggested that MSCs survived within macro-capsule for 28 days.

Conclusions: macro-encapsulated MSCs attenuated hepatic inflammation and fibrosis via upregulating hypoxia-induced growth hormone secretion in liver disease models.

Keywords: Macro-encapsulated mesenchymal stem cells, Poly lactic-co-glycolic acid

PE-257

Combination Therapy of Placenta-Derived Mesenchymal Stem Cells with WKYMVm in a Rat Model of Bile Duct Ligation

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Aims: Abnormal vascular formation is involved in liver cirrhosis as well as fibrosis. In previous report, we reported that pla-

centa-derived mesenchymal stem cells (PD-MSCs) have the anti-fibrotic effect in a rat model with chronic liver failure. Also, WKYMVm, which is composed of Trp-Lys-Tyr-Met-Val-D-Met, has been reported as the therapeutic factor by promoting migration and proliferation of angiogenic cells. However, the effects of WKYMVm in liver disease have not been elucidated. Therefore, our objectives were to evaluate the therapeutic effect for combination therapy of PD-MSCs with WKYMVm through transplantation of PD-MSCs and administration of WKYMVm in bile duct ligation (BDL) rat model.

Methods: PD-MSCs ($2x10^6$) were transplanted by intravenous injection and 2.5mg/kg of WKYMVm were administrated twice per week by intraperitoneal injection into the BDL rat model after 10 days from generation of BDL. The effects of combination therapy were evaluated by blood chemistry, histological analysis, qPCR, western blot, and ELISA.

Results: Collagen accumulation by Sirius Red staining in liver tissues of BDL was significantly decreased in PD-MSCs with WKYMVm combination group (Tx+WK) compared with non-transplantation (NTx) and PD-MSCs transplanted (Tx) group ($P<0.05$). Also, the Collagen Ⅰ and a-SMA were significantly decreased in Tx+WK group versus NTx and Tx group ($P<0.05$). However, the angiogenic factors were dramatically increased in Tx+WK group ($P<0.05$). Furthermore, combination of PD-MSCs with WKYMVm significantly promoted hepatic function through hepatocyte proliferation and albumin expression ($P<0.05$).

Conclusions: These findings suggest that combination therapy of PD-MSCs with WKYMVm could be efficient treatment in hepatic fibrosis, damaged vasculatures and injured hepatocytes. Therefore, the combination therapy of PD-MSCs with WKYMVm could be used new therapeutic strategy as a degenerative medicine.

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Keywords: Placenta-derived mesenchymal stem cells, WKYMVm, Liver cirrhosis, Therapy

PE-258

Enhanced PRL-1 in Placenta-derived Mesenchymal Stem Cells Promotes Liver Regeneration in Cirrhotic Rat Model via Regulating ER Stress-Dependent Calcium Homeostasis

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Aims: ER stress in liver is caused by the accumulation of cholesterol and perturbation of calcium in ER. In our previous report, placenta-derived mesenchymal stem cells (PD-MSCs) have the therapeutic potential of hepatic regeneration in cirrhosis rat model. However, whether phosphatase of regenerating liver 1 (PRL-1) is related ER stress remains unknown. Here, we demonstrate that PRL-1 genetically modified PD-MSCs (PD-MSCs^{PRL-1}) promote hepatic functions, regulating ER stress and calcium release in rat model with bile duct ligation (BDL).

Methods: Naïve and PD-MSCs^{PRL-1} ($2x10^6$) were intravenously transplanted into BDL rat model. WB-F344s (rat liver epithelial cell) exposed to thapsigargin (TG) were co-cultured with naïve and PD-MSCs^{PRL-1}. The therapeutic effects were analyzed by qPCR, western blotting, immunohistochemistry (IHC), and imaging using calcium biosensor.

Results: ER stress markers were increased in BDL model (NTx; non-transplantation), while PD-MSCs^{PRL-1} transplantation (Tx PD-MSCs^{PRL-1}) showed significantly decrease compared to naïve (Tx; Naïve PD-MSCs). PD-MSCs^{PRL-1} induced changes of voltage-dependent channels related gene expressions compared to naïve. In addition, PD-MSCs^{RPL-1} inhibited the expression of apoptosis related markers, while increased proliferation activity of hepatocyte using IHC with PCNA. *In vitro* TG treated WB-F344, ER stress induced by depletion of calcium in ER. PD-MSCs^{PRL-1} co-culture significantly decreased the expression of ER stress markers compared to naïve. Interestingly, PD-MSCs^{PRL-1} co-culture induced calcium influx by dynamic changes through ER and cytoplasm-specific calcium homeostasis compared to naïve ($P<0.05$). Also, decreased ER stress by PD-MSC^{PRL-1} enhanced hepatic regeneration.

Conclusions: PD-MSCs^{PRL-1} was involved in calcium homeostasis via decreased ER stress in cirrhotic rat model. Therefore, PD-MSCs^{PRL-1} could be new strategy in degenerative medicine including hepatic diseases.

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Keywords: Phosphatase of regenerating liver 1, Placenta-derived mesenchymal stem cells, ER stress, Calcium homeostasis

PE-259

Demethylzeylasteral (ZST93) Inhibits Pancreatic Cancer Stem Cells via Apoptotic and Autophagic Pathways

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Aims: Cancer stem cells (CSCs) indicate multipotent cells exhibiting self-renewal capacity, multilineage differentiation ability

and high carcinogenesis, and are closely related to tumor growth, metastasis, recurrence and chemoresistance. As tumorigenic drivers, CSCs should be effectively targeted to achieve long-lasting therapeutic responses. This study aimed to explore the mechanism of the novel Tripterygium wilfordii Hook F (TWHF) extract Demethylzeylasteral (ZST93) on inhibiting human pancreatic CSCs.

Methods: Serum-free floating culture system was used to isolate CSCs. CCK-8 assay was used to evaluate the chemosensitivity. Apoptosis was evaluated by flow cytometry. Autophagy level was evaluated by transmission electron microscopy and immunofluorescence. The activity levels of caspase-3, ERK1/2 and Akt/mTOR pathways were determined by Western blot.

Results: Tumorspheres had differentiation ability and stem cell-like properties. ZST93 could inhibit the number and diameter of tumorspheres. ZST93 could induce apoptotic cell death in pancreatic CSCs at high concentrations, but not at low concentrations. The apoptosis induced by ZST93 was associated with the significant up-regulation of active caspase-3 expression. ZST93 could induce autophagic cell death in pancreatic CSCs at low concentrations, but not at high concentrations. The autophagy induced by ZST93 was associated with the significant up-regulation of p-ERK1/2 and down-regulation of p-Akt and p-mTOR expression.

Conclusions: We revealed that ZST93 inhibits pancreatic CSCs through two different mechanisms, low concentrations of ZST93 could induce autophagic cell death by activating ERK1/2 pathway and inhibiting Akt/mTOR pathway, and high concentrations of ZST93 could induce caspase-3-dependent apoptotic cell death. ZST93 is a potential therapeutic agent for developing novel therapeutic strategies in human pancreatic cancer.

Liver, Infectious Disease

PE-260

Klebsiella Pneumoniae-Induced Liver Abscess Complicated with Septic Pulmonary Embolism in a Non-Diabetic Adult

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Aims: Liver abscess is caused by various strains of bacteria and is characterized by upper right abdominal pain and fever. Klebsiella pneumoniae was recently considered as the most common causative organism in Korea. The prevalence of *K. pneumoniae*-induced septic pulmonary embolism complicated with liver abscess is low, with a rate of 4.5%-6% among 86% of diabetic patients. The prognosis of patients with septic pulmonary embolism is poor. Thus, such condition must be considered, and early diagnosis and differentiation should be performed.

Methods: We report a case of multiple septic pulmonary embolism with a time difference in a non-diabetic patient who was on antibiotic treatment for *K. pneumoniae* liver abscess and who had percutaneous drainage for early-stage cholecystitis.

Results: A 72-year-old non-diabetic man was admitted to the intensive care unit because of liver abscess, cholecystitis, and septic shock. He underwent percutaneous catheter drainage and received intravenous antibiotics. Shock was improved, and the patient's fever subsided. Klebsiella pneumoniae was isolated in blood and bile cultures. However, he suddenly developed dyspnea and oxygen desaturation. Chest computed tomography scan revealed multifocal ground-glass opacities with consolidation with peripheral preponderance. Appropriate antibiotic therapy was provided for 2 weeks. The patient recovered fully, and cholecystectomy was then performed.

Conclusions: *K. pneumoniae* liver abscess is frequently associated with septic metastatic lesions, endogenous endophthalmitis, cerebral abscess, meningitis, and infectious spondylitis. Among these infections, septic pulmonary embolism is not common, and the diagnosis is often delayed. Septic pulmonary embolism can be identified based on the presence of a nodule in the parenchyma, including the pulmonary margins and various cavities and blood vessels supplying them, and heterogeneous, wedge-shaped lesions in the pleura. The disappearance of pulmonary nodules after proper antimicrobial therapy is an indication that the diagnosis of septic pulmonary embolism is correct. The mortality rate of septic pulmonary embolism associated with liver abscess is as high as 14%. Therefore, when patients with *K. pneumoniae* liver abscess complain of fever and respiratory symptoms, the possibility of septic pulmonary embolism should be considered. Thus, active evaluation, such as performing imaging and sputum tests, must be performed, and treatment should be provided.

Keywords: Klebsiella pneumonia, Liver abscess, Pneumonia

PE-261

The Effects of Asparagus Racemosu on Oxidative Stress, Constipation and Hepatic Function in Type 2 Diabetic Patient

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Aims: Diabetes mellitus is the most common endocrine disorder, causes many complications such as micro- and macro-vascular diseases. Asparagus racemosus is a widely found medicinal plant in tropical and subtropical parts of India. Our objective was to investigate effects of Asparagus racemosu root extract (ARRE) on constipation, liver dysfunctions and defence of red

blood cells in type 2 diabetic patients.

Methods: A total number of 100 subjects were selected with the age ranging from 45 to 60 years. Among them, 50 diagnosed type 2 diabetes individuals were included in the Group A and 50 apparently healthy individuals were selected as Group B for comparison. ARRE was prepared in hot water and orally administered to type 2 diabetic patients with constipation. This treatment was thrice a week in 1st month, twice in a week in corresponding 2nd and 3rd months and once in a week from 4th to 6th months. The defensive enzyme, glutathione peroxidase, superoxide dismutase, catalase and fasting blood sugar, hemoglobin A1c, apolipoprotein B, apolipoprotein A-I, and malondialdehyde were measured in the red blood cells. The liver function test was performed by measuring hepatic enzymes (Aspartate amino transferase, alanine amino transferase) and lipid profile levels.

Results: ARRE supplementation significantly reduced the levels of fasting blood sugar, serum hepatic enzymes, hemoglobin A1c, apolipoprotein B, apolipoprotein B/apolipoprotein A-I and malondialdehyde in ARRE group in comparison to baseline, as well as control group, while it increased the level of apolipoprotein A-I (P<0.05). The diabetic patients were found to be altered lipid profile with vulnerable to skin infection particularly in the pelvic regions, backside, legs, etc. which were reversed to normal after six months of ARRE treatments. The stools quality also changed to normal. The antioxidant enzymes decreased in red blood cells of diabetics by 20-30%, normalized after six months of treatment with ARRE extract. There was also normalize hepatic enzymes activity with ARRE treatment to diabetic patients.

Conclusions: ARRE treatment to diabetic patients not only normalize the defense of red blood cells but also corrects skin infection, liver disorder, neurological disorder and physiological disorder. The findings evidently suggest the hepatoprotective properties of ARRE in diabetic patients.

Keywords: Liver dysfunctions, Asparagus racemosu root extract, Lipid profile levels, Diabetic patients

PE-262

Hidden Risk of Liver Disease in Type 2 Diabetes Population

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Aims: This study aimed to find the association of liver biomarker with diabetes population. Also, this study focused to find out the risk factors associated with liver disease in Nepalese diabetes patient.

Methods: This study was carried out among 238 diabetes and 238 apparently healthy population who attended Modern diagnostic laboratory and Research center, Kathmandu, Nepal. HbA_1c and fasting plasma glucose was measure to assess the diabetes population and glycemic control. Aspartate to platelet ratio index (APRI), gamma-glutamyl transpeptidase to platelet ratio (GPR), fibrosis-4 index (FIB-4), and triglyceride and glucose index (TyG) were assess for prediction of hidden risk liver disease. Diabetic patient with higher than the cut-off value obtained from ROC curve analysis of different liver marker index were subjected to multivariate regression analysis to measure the independent risk factor for progression liver disease in different model.

Results: Patient with poor glycemic control had a significantly higher level of APRI (P=0.05), GPR (P=0.039), and TyG (P<0.001). Higher HbA_1c showed significantly positive correlation with APRI (r=0.154, P=0.017), GPR (r=0.203, P=0.002), FIB4 (r=0.132, P=0.042), and TyG (r=0.510, P<0.001) in diabetic population. The Area under ROC curve of GPR was 0.700 (0.654-0.747), APRI 0.839 (0.803-0.874), FIB-4 0.820 (0.783-0.857), and TyG 0.909 (0.882-0.874) with p-value <0.05. The cut-off value (sensitivity, specificity) of GPR was 0.227 (63.4%, 63%), APRI 0.241 (71.0%, 80.3%), FIB-4 1.65 (71.8%, 77.3%), and TyG 8.85 (79%, 93.3%) respectively. Triglyceride, AST, and GGT was independent risk factor followed same trend in different 4 model while HbA_1c and ALT showed independent risk factor in 3 models.

Conclusions: APRI, GPR, FIB4 and TyG can define the hidden risk liver disease in T2DM. The independent risk factors for progression of liver disease in those population are hypertriglyceridemia, higher AST, and higher GGT. Routinely screening for markers may prevent progression of liver disease in T2DM patients.

Keywords: Liver disease, Hypertriglyceridemia, Diabetes patient, Risk analysis

Table 1. Multivariate analysis for risk factor associated with hidden risk of liver disease

Variables	Model 1	Model 2	Model 3	Model 4
FPG	2.838[b] (1.261-6.389)	2.065[c] (0.874-4.876)	1.603[c] (0.643-4.453)	1.3[c] (0.404-4.176)
HbA_1c	2.384[a] (1.356-4.193)	2.006[b] (1.103-3.648)	2.202[b] (1.128-4.299)	1.915[c] (0.883-4.155)
TC	1.561[c] (0.827-2.949)	1.631[c] (0.843-3.156)	0.651[c] (0.257-1.650)	0.435[c] (0.168-1.015)
TG	6.055[a] (3.334-10.998)	5.746[a] (3.128-10.557)	6.937[a] (3.6-13.507)	5.529[a] (2.54-12.033)
HDL-C	0.769[c] (0.440-1.344)	0.726[c] (0.404-1.304)	0.49[b] (0.25-0.961)	0.409[b] (0.186-0.898)
LDL-C	1.565[c] (0.724-3.384)	1.733[c] (0.772-3.891)	2.102[c] (0.691-6.395)	2.289[c] (0.598-8.756)
AST	15.588[a] (7.532-32.262)	14.508[a] (6.938-30.339)	13.056[a] (5.842-29.178)	9.079[a] (3.568-23.1)
ALT	10.510[a] (4.603-23.998)	9.853[a] (4.289-22.637)	7.694[a] (3.177-18.632)	2.013[c] (0.639-6.346)
ALP	2.080[b] (1.080-4.006)	1.958[c] (0.997-3.848)	1.889[c] (0.915-3.899)	1.276[c] (0.54-3.016)
GGT	6.041[a] (3.116-11.713)	5.501[a] (2.812-10.761)	4.611[a] (2.215-9.598)	4.091[a] (1.736-9.642)

Model 1:-adjusted age, sex, and BMI; Model 2:- Model 1+ adjusted FPG, and HbA_1c; Model 3:- Model 2 + adjusted TG, TC, HDL-C, and LDL-C; Model 4:- Model 3 + adjusted AST, ALT, ALP, and GGT
FPG, Fasting plasma glucose; TC, Total Cholesterol; TG, Triglyceride; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; GGT, Gamma-glutamyl transpeptidase
[a] p value < 0.01; [b] p value ≤ 0.05; [c] p value > 0.05
all the values are represent as OR (95% of CI)

PE-263

Diagnosis of Liver Disease Based on Artificial Intelligence (AI) Systems Using the Decision Tree Model Algorithm Implementation

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Aims: The liver is one of the most important organs of the human body. The function of the liver is to detoxify poisons in the human body and control cholesterol and fat in the human body. If the liver is damaged, then health will be disrupted and even death can occur. So an effort is needed to detect liver disease early. This study will discuss the classification of liver disease using the Decision Tree C4.5 Algorithm using the Indonesian Liver Patient Dataset. This study will also prove the most influential variable of the 11 variables that determine the liver disease.

Methods: The research conducted includes processing the dataset using the help of the Rapidminer (computer program) data mining application. The dataset used in this study was taken from The Ministry of Health of the Republic of Indonesia Database. Indonesian Liver Patient Dataset contains 583 clinical data with 10 attributes with 416 positive liver output targets and 167 negatives. Based on 583 processed data, 433 data are used as training data and 150 data are used as testing data.

Results: This study shows that only two variables (Almine Alminotransferase and Age) among the 11 variables in the dataset are the most influential in determining the classification of liver disease. This study also showed an accuracy of 72.7% in determining the classification of liver disease using the Dataset of the Ministry of Health of the Republic of Indonesia.

Conclusions: Based on the results of this study, we can conclude that the detection or classification results can be said to be quite good based on an accuracy value of more than 70%.

Keywords: AI, Decision Tree Model, Diagnosis, Liver

PE-264

Prevalance and Factors Associated with SGOT, SGPT and Alkaline Phosphatase Among Suspected Liver Patients Attending Salyan District Hospital, Salyan, Nepal

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Aims: Serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-Pyruvate transaminase (SGPT) and alkaline phosphatase are reasonably sensitive indicators of liver damage or injury from different types of diseases or conditions. The study aimed to determine the level of SGOT, SGPT and alkaline phosphatase; and SGOT/SGPT ratio among suspected liver patients attending salyan District hospital of Nepal.

Methods: Blood samples were collected from suspected liver patients visiting Salyan hospital. The samples were collected from April, 2019 to October 2019. Enzyme kinetics method was used to process the serum samples. Descriptive statistics and chi-square test were computed at 5% level of significance

Results: Of total 116 suspected liver patients, 64.7% patients had high SGOT, 53.4% had high SGPT and 7.8% had high alkaline phosphatase. The prevalence of SGOT and SGPT and was higher among males (65.8% Vs 62.2%), (54.4% Vs 51.4%) respectively. Regarding alkaline phosphatase, there was no any higher level among female. Alcoholic behavior was statistically associated with high SGOT in the study (P<0.05); it was highest among alcoholic group. However, there was no statistical association of high SGOT with sex and ethnicity. Similarly, Alcholic behavior and ethnicity was statistically associated with high SGPT in the study (P<0.05). Likewise, Sex and ethnicity was statistically associated with high SGPT in the study (P<0.05); however, there was no statistical significance with alcoholic behavior.

Conclusions: The study shows high prevalence of SGOT, SGPT and alkaline phosphatase; among suspected liver patients attending Pyuthan hospital of Nepal. **Keywords:** SGOT, SGPT, ALP, Salyan, Nepal

Keywords: SGOT, SGPT, alkaline phosphatase, Nepal

PE-265

Early Percutaneous Catheter Drainage Reduces Hospital Stay but Not Mortality in Patients with Pyogenic Liver Abscess

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Aims: To investigate the factors associated with prolonged hospital stay and mortality among patients with pyogenic liver abscess (PLA) who underwent percutaneous drainage (PCD).

Methods: We retrospectively reviewed data from PLA patients

admitted from 2005 to 2018 at three tertiary hospitals in Jeonbuk province. We selected patients who underwent PCD during the admission period and early PCD was defined whether the procedure was done within 3 days of admission.
Results: Among 655 patients diagnosed with PLA, 366 patients who underwent PCD were enrolled for the study. The patients had a mean age of 65.5 ± 14.7 years, and mean maximal diameter of the hepatic abscess was 6.1 ± 2.6 cm and 71.9% of the lesion was single. Next, two groups were divided depending on the time period of PCD and 269 patients (73.5%) underwent PCD within 3 days of hospitalization. In baseline characteristics, early PCD group was significantly higher in the number of abscess as well as the maximal abscess diameter. However, hospitalization period was significantly lower in the early PCD group though in-hospital mortality was not different. We checked laboratory results at 1 week after the admission and CRP levels were significantly lower in the early PCD group. We further analyzed the factors related to the long-term hospitalization more than 14 days. In multivariate analysis, underlying diabetes, lower albumin levels, and PCD inserted after 3 days of admission were independent factors associated with prolonged hospital stay.
Conclusions: Early PCD facilitated improvement of inflammatory laboratory markers and shortened the hospital stay. Early PCD may be beneficial in patients with PLA.
Keywords: Liver abscess, Pyogenic, Drainage, Hospitalization, Hospital mortality

PE-266

Empyema Comlicated by Pyogenic Liver Abscess

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Background: Empyema complicated by transdiaphragmatic extension of pyogenic liver abscess is a very rare complication of liver abscess. Effective drainage with proper antibiotic use is essential for treatment. Reported herein is a rare case of empyema complicated by pyogenic liver abscess.
Case: A 58-year-old male was admitted due to fever with RUQ pain. He has been inactive HBV carrier state since 20 years ago. He was acute ill looking appearance. Initial vital signs were: BP 150/90 mmHg, HR 116 beats/min, RR 20 breaths/min, temperature 38.0°C. Laboratory studies revealed WBC 12,590/mm^3, hemoglobin 13.5 g/dL, platelet 128,000/mm^3, prothrombin time was 17.0 sec (INR of 1.55). CRP 25.6 mg/dl, AST/ALT 84/113 IU/L, total bilirubin 1.85 mg/dL, albumin 2.6 g/dL, r-GTP 53 U/L, ALP 102 U/L. Viral markers were HBsAg(+), anti-HBs(-), anti-HCV(-). Abdominal CT showed about 7x9cm sized septated cystic and low attenuation mass with mild rim enhancement in right heatic lobe posteror aspect. Percutanenous catheter drainage was performed and antibiotic treatment was started. On 6th day of hospitalization, he developed dyspnea. Follow up CT showed newly developed empyema of right lower lung. Chest tube drainage was performed. The cultured pus in liver abacess, empyema and blood samples were positive for *K. pneumoniae.* On the 20th day of hospitalization, liver function recovered completely to normal and follow up abdominal CT showed marked improved state of liver abscess and disappearance of empyema.
Conclusions: It is very rare for pyogenic liver abscesses to expand into the diaphragm and cause empyema. Effective drainage with appropriate antibiotics is essential for successful treatment.
Keywords: Pyogenic; Liver abscess; Empyema; *Klepsiella pneumoniae*

PE-267

Tacotsubo Cardiomyopathy Secondary to Pyogenic Liver Abscess

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Background: Takotsubo cardiomyopathy, also known as stress cardiomyopathy, is a type of non-ischemic cardiomyopathy in which myocardium suddenly weaken temporarily and is caused by emotional or physical stress such as sepsis, bleeding, asthma, or pheochromocytoma. Several infections have also been shown to precipitate Takotsubo cardiomyopathy. However, few cases have demonstrated the association with liver abscess. Reported herein is a rare case of Takotsubo cardiomyopathy precipitated by the liver abscess.
Case: A 73-year-old female was admitted due to fever. She has been without any illness. She was acute ill looking appearance. Initial vital signs were: BP 110/60 mmHg, HR 101 beats/min, RR 20 breaths/min, temperature 38.0°C. Laboratory studies revealed WBC 21,550/mm^3, hemoglobin 14.7 g/dL, platelet 101,000/mm^3, prothrombin time was 15.8 sec (INR of 1.44). AST/ALT 94/87 IU/L, total bilirubin 0.89 mg/dL, albumin 2.9 g/dL, r-GTP 66 U/L, ALP 139 U/L. Viral markers were HBsAg(-), anti-HBs(+), anti-HBc IgM(-), anti-HAV IgM(-), anti-HCV(-). Initial EKG showed sinus tachycardia. Abdominal CT showed about 5x6cm sized cystic mass like lesion with air bubbles in the liver S8. Percutanenous catheter drainage was performed and antibiotic treatment was started. On 2nd day after admission, she developed suddenly worsening of dyspnea followed by blood pressure drop. Follow up EKG revealed myocardial ischemic change of lateral wall. CK 602 U/L, CK-MB 105.4 ng/ml, LDH 613 U/L, Troponin-I 18.8 ng/ml. Transthorasic echocardiography showed diffuse myocardial hyokinesia (ejection fraction 26%). But, coronorary angiogram showed completely normal findings. The cultured pus and blood samples were positive for *K. pneumoniae.* On the 11th day of hospitalization, her cardiac function was restored and EKG showed normal sinus rhythm. Her liver function recovered completely to normal

and follow up abdominal CT showed marked decreased size of liver abscess on 38th day of hospitalization.

Conclusions: Tacotsubo cardiomyopathy caused by pyogenic liver abscess is rare. The presentation is vary from asymptomatic to chest pain, shortness of breath, nausea, vomiting, palpitations or fainting. It may also show an EKG change and troponin elevation similar to myocardial infarction. Although stress cardiomyopathy is a reversible condition, but it can be serious and fatal.

Keywords: Liver abscess, Sepsis, Takotsubo cardiomyopathy, *Klebsiella pneumoniae*

PE-268

Helicobacter Pylori Prevalence in Chronic Liver Disease Patients by Using 14CUrea Breath Test

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Aims: *Helicobacter pylori* are one of the major etiologies for stomach diseases in the Mongolian population. *H. pylori* infection prevalence is ranged 70% to 80% in adults, 60% in gastric cancer patients and around 70% in children. In Mongolia, the diagnosis of H.pylori infection is performed by using invasive (endoscopic biopsy for histopathology, culture, and rapid urease test) and noninvasive (stool antigen test, and serological tests) methods.

Methods: We enrolled in this cross-sectional study 168 chronic liver disease patients with at the Internal Medicine Department of Dornod Medical Center, 2018 to August 2019. The patient had drunk one urea C14 capsule with 30 to 50 mL water. After 15 minutes the patient blowing into the breath collecting cart until the cart's orange dot getting yellow. Then breath collecting cart inserted to the device and estimated the number of detecting Helicobacter. We use Microsoft Excel, SPSS (ver. 20.0) program for Statistical analysis.

Results: Total number of collected cases were 168, among of them 72 (42.85%) were male and 96 (57.14%) women, mean age was 36.42 years. 14C-UBT was positive in 151 patients (89.88%) and negative in 17 patients (10.11%). Active *H. pylori* infection were very high 55 patients (32.73%) among ≤29 aged people, 43 patients (25.59%) in 30 to 39 years, 21 patients (12.5%) in 40 to 49 years, 18 patients (10.71%) for 50 to 59 years and 14 patients (8.3%) for 60 years older people. 14C-UBT average results were 232.54, the highest result were 1,169 and the lower result was 5. During the evaluation of 14C-UBT results we could not find false negative results.

Conclusions: The prevalence of active infection of *H. pylori* was high in chronic liver disease patients, especially among 20 to 39 years old adults compared to other participants.

Keywords: *Helicobacter pylori*, 14C urea breathe test

PE-269

Changes in the Clinical Features of Acute Hepatitis A Between Two Peak Periods in Korea

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Aims: The number of the patients with acute hepatitis A is increasing due to improved hygienic environment and low seroprevalence of anti-HAV IgG in Korea. There were two peak periods of acute hepatitis A about 10 years ago and last year. This study aims to analyze the changes of the clinical features of acute hepatitis A patients between two peak periods in Korea.

Methods: Patients with acute hepatitis A who had been hospitalized at Dankook University Hospital from 1998 to 2019 were included. We reviewed patient's medical records especially, two peak periods (2008-2009 vs. 2019).

Results: From 1998 to 2019, total 798 patients had admitted with acute hepatitis A. The mean age of the patients was 33.0 ± 10.1 years, and male patients (61.4%) were more. The mean peak AST and ALT were 2407.1 ± 2892.2 IU/L and 2547.2 ± 1896.3 IU/L. Total 8 (1%) patients were not recovered. Among 8 patients, 6 patients took liver transplantation and 2 patients expired. There were two peak periods for 22 years. First peak period was 2008-2009 year (219 patients) and second peak period was 2019 year (106 patients). The mean age increased from 31.7 ± 8.8 to 40.1 ± 9.4 years The proportion of male patients decreased from 69.4% to 58.5%. The symptom duration days decreased from 7.6 ± 8.0 days to 6.0 ± 3.9 days and total admission days also decreased from 7.4 ±3.4 days to 5.9 ± 3.2 days. The peak INR increased from 1.3 ± 0.5 to 1.4 ± 0.6. The death or transplantation rate increased from 0.9% to 2.8%.

Conclusions: The mean age of patients with acute hepatitis A increased about 9 years over two peak periods. The death or transplantation rate increased very much although the admission days decreased.

Keywords: Acute Hepatitis A, Clinical Features, Peak Period

PE-270

Corelational Study of Liver Enzyme, Vitamin D and Probability of Liver Disease: A Cross Sectional Study

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Aims: To investigate the relationship between liver enzyme, vitamin D status, and occurrences liver disease.

Methods: We incorporated a total of 545 cases from hospital studies completed in 2018–2019. Serumenzymes such as as-

partate transaminase (AST)serum alanine transaminase (ALT), and gamma-glutamyl transferase (GGT) were measured as minimum basic assess and vitamin D status as measured by serum 25-hydroxyvitamin. Information on the patients (fetal and nonfetal liver disease) was collected from the patients' family and relatives by follow up method.

Results: Multivariable Cox regression analyses with age as underlying time axis and delayed entry showed a statistically significant inverse association between vitamin D status and incident liver disease with a hazard ratio = 0.78 (95% confidence interval 0.69–0.89) per 10 nmol/l higher vitamin D status at baseline (adjusted for season, gender, smoking, alcohol consumption, physical activity, dietary habits, education, body mass index, and ALT). The risk of having a high level of ALT, AST, or GGT tended to be higher for lower vitamin D levels, although not statistically significant.

Conclusions: In this study, the vitamin D status and incidence of liver disease are inversely proportional to each other. Further studies are required to know whether the patients are at risk of developing impaired liver disease due to vitamin D deficiency.

Keywords: Liver Disease, Vitamin D, Liver enzyme, Gamma glutamyl transferase

PE-271

Prevalence of HBV and HCV in Mongolia

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Aims: Mongolia is the highest prevalent of hepatitis B and C virus infections. Viral hepatitis is still decreasing when observing its movements, but the disease will remain highly prevalent until 2030. Using high-sensitivity test results of CLEIA we aimed to investigate the prevalence of hepatitis B and C virus, and compare levels of AST, ALT and M2BPGI in the Mongolian population in the age between 40-64.

Methods: In order to reflect the administrative and geographical features of Mongolia, the sampling was done at three levels: urban, province center, and rural. Immunological test was measured by chemiluminescence enzyme immunoassay (CLEIA). The statistical package for the social sciences (SPSS) version 25 was used for the statistical analyses.

Results: The survey covered 3196 people. 71.8 percent of the patients surveyed had a negative in hepatitis test. 10.1 percent had a positive HBsAg test. 17 percent had a positive anti-HCV test. 1.1 percent had both a positive both HBsAg and anti-HCV (<.0001). AST and ALT increased more frequently during co-infection. M2BPGI protein average level in the non-infected group was 1.00 C.O.I, in the HBsAg positive group 1.65 C.O.I, in the anti-HCV positive group 1.83 C.O.I, and in the co-infection group 1.87 C.O.I (<.0001).

Conclusions: 10.1 percent of 40-64year-olds in Mongolia were infected with hepatitis B virus, and 17 percent had Hepatitis C virus and 1.1 percent had hepatitis B and C virus co-infections. Serum M2BPGi is increasing in hepatitis C virus infection and in co-infection.

Keywords: HCC, Liver Fibrosis, HBV, HCV

PE-272

Comparative Study of Cirrhosis Stage in Patients with HBV Infection and HBV/HDV Co-Infection in Mongolia

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Aims: Comparative study of cirrhosis stage in patients with HBV infection and HBV/HDV co-infection

Methods: Our study continued from January 2015 to March 2017 and we measured liver fibrosis stage in patients with HBV infection and HBV/HDV co-infection using a Fibroscan (Fibroscan 502 Touch, Echosens, and Paris, France) who are controlled in Happy Veritas Clinic and Diagnostic Center. When we measured liver fibrosis stage in 5504 patients with HBV infection, 20% or 1115 of the patients is determined HDV co-infection. In our study in random sampling cases are selected 354 patients with HBV mono infection and 177 of all patients have HBV/HDV co-infection. We selected parameters from patient's medical histories in our study, such as serologic markers of HBV quantification of HBV and HDV in serum samples, blood test, liver function tests, and liver fibrosis stage.

Results: 354 patients 47.7% (169) was men. Range with an average age of 44±17 (range 18-75 years old) were included the study. According to the comparative study in laboratory tests, ALT level was HBV - 44 (36; 51.5) and HBV/HDV co-infection 61 (39.8; 97.5), AST level was HBV – 39.1(30; 83) and HBV/HDV co-infection – 50 (33.1; 77.8), Platelet count was HBV- 193±66 and HBV/HDV – 181±62.8. When we compared liver fibrosis stage were HBV- F0 67(37.9%), HBV/HDV-F0 57(32.2%), HBV-F1 22(12.4%), HBV/HDV-F1 17(9.6%), HBV-F2 39(22%), HBV/HDV- F2 39(22%), HBV-F3 29(16.4%), HBV/HDV-F3 41(23.2%), HBV- F4 20(11.3%) and HBV/HDV – F4 23(13%) . In table 1 shows the difference of liver fibrosis by age group.

Conclusions: 65.5% of all patients with HBV/HDV co-infection are from 30 to 50 years old. Liver fibrosis of patients with HBV/HDV co-infection is a higher 11.88kPa than patients with HBV mono-infection. Our study shows that, the hepatitis is more severe in patients with HBV/HDV co-infection and the platelet count is less than HBV infection only.

Keywords: HBV, Infection, Fibroscan, Patients

PE-273

Epidemiology of HCV and HBV Infections among Nurses in Mongolia

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Aims: M.Colombo, W.Lange studies showed that 30-40% of people become chronic after suffering from-Hepatitis B and C virus, about 50% chronic cases transformed into primary liver cancer. There are a few studies in our country were conducted on hepatitis among health care professionals, particular nursing personnel. The study was conducted to identify of hepatitis B and C virus among nurses and make recommendations to prevent and control of hepatitis B and C virus infections.

Methods: We carried out cross-sectional study among selected nurses to determine surface antigen of hepatitis B virus and antibodies to hepatitis C virus. For identification of these antibody and antigen and validation of results ELISA tests from CTK, Biotech company (USA) and simplifying diagnostics were used.

Results: There were 598 nurses from the First Central hospital, the Second Central hospital, the Third central hospital, Railway Central hospital, Hospital Ministry of Justice and Internal Affairs and National Center of Maternal and Child Health who participated in the study. From 5 hospitals 598 nurses surveyed and revealed the hepatitis B virus surface antigen positive 18.9%, hepatitis C virus antibodies in 23.1%, co-infection of hepatitis B and C were detected 1.2%. There is an urgent need to provide knowledge to medical personnel regarding standards during the procedures, concerning hepatitis infections monitoring and improve technology used during procedures.

Conclusions: The study identified that 43.2% of nurses surveyed on hepatitis B and C viruses were detected. It shows a high prevalence among the nurses in Mongolia.

Keywords: Nurse, Mongolia, HBV, HCV

PE-274

Acute Viral Hepatitis D in Mongolia

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Aims: To investigate prognosis and risk factors acute viral hepatitis D in Mongolia

Introduction: Hepatitis D virus (HDV) infection is considered to cause more severe hepatitis such as liver cirrhosis and HCC. Mongolia has the highest prevalence (> 15%) of HCV, (> 10%) HBV infection and HDV 75-100% of HBsAg carriers.

Methods: A total of 86 patients with acute viral hepatitis D were enrolled and their data collected 2016-2017.

Results: The mean age of patients was 29.7+-7.17. 52 (60.4%) of them were males and 34 (39.6%) were females. Risk factors were unprotected sexual contact 41 (47.67%), dental care 11 (12.8%), tattooing 8 (9.3%), admit hospital 42 (48.83%), history of surgery 13 (15.1%), acupuncture 12(13.9%), share with nail clipper 74(86%) and family contacts with viral hepatitis B 23(26.7%). Anti-HDV IgM and anti-HD total Ab tests were both positive in 34/86 samples, anti HDV IgM was the only positive delta marker in 65/86 samples and anti-HD total Ab was the only marker in 61/86 samples. During follow-up, three of 5 (4.9%) patients with co D infection showed HBsAg loss and 58 patients with super D infection (100%) showed persistent hepatitis B and D viremia.

Conclusions: Risk factors for hepatitis D virus infection were unprotected sexual contact, admitted hospital, share with nail clipper and family contacts with viral hepatitis B. During follow-up, three of 5 (60%) patients with co D infection showed HBsAg loss and 58 patients with super D infection (100%) showed persistent hepatitis B and D viremia.

Keywords: HDV, anti-HDV, anti-HDV IgM, Mongolia

PE-275

Functional Abnormalities of the Liver in Diabetic Patients with and without Viral Hepatitis C in Mongolia

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Aims: We aimed to compare liver function of diabetes mellitus patients with and without viral hepatitis C using the non-alcoholic fatty liver disease fibrosis score, aspartate transaminase to platelet ratio index, Fibrosis-4 Index, Mac-2-binding protein biomarker and ultrasonic liver stiffness measurements.

Introduction: Diabetic patients with viral hepatitis have a high risk of liver cirrhosis. M2BPGi biomarker helps to determine the stage of liver fibrosis in those with fatty liver disease and viral hepatitis in Mongolia.

Methods: The study was conducted based on convenience sampling of 123 patients from the General hospital outpatient clinic. Slightly more than half of the study participants were male (53%, n=64). Thirty-three of the diabetics with hepatitis (mean age 52.31±9.8 years) and 90 diabetics without hepatitis (mean age 53.26±8.58) agreed to participate. Anthropometric measurements, non-alcoholic fatty liver disease fibrosis score,

aspartate transaminase to platelet ratio index, Fibrosis-4 Index, Mac-2-binding protein biomarker, and ultrasonic transient elastography measurements were compared using independent t-tests for continuous variables and Wilcoxon rank sum tests for ordinal variables.

Results: The median values of the Fibrosis-4 Index for those with hepatitis C and without were 1.3 vs 0.9(*P*<.05), Mac-2-binding proteinbiomarker2.0 vs 1.3 (*P*<.0001), ultrasonic liver stiffness measurements 10.3 vs 6.9 (*P*<.0001),aspartate transaminase to platelet ratio 0.6 vs 0.3 (*P*<.001), and Non-alcoholic fatty liver disease fibrosis scores were -0.2 vs -0.9(*P*<.004), respectively.

Conclusions: Diabetic patients with hepatitis had statistically significantly higher Mac-2-binding protein biomarker, NAFLD Fibrosis Scores than patients without hepatitis. However, other fibrosis test results were similar in diabetic patients with hepatitis and without hepatitis C.

Keywords: Liver Fibrosis, Chronic Hepatitis, Non-alcoholic Fatty Liver Disease, Diabetes

PE-276

Liver Stiffness Decrease Post Ledipasvir/Sofosbuvir Combination Treatment in Mongolian Patients with Chronic Hepatitis C

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Aims: The prevalence of liver cancer in Mongolia is 7 times higher than that of world average, generally caused by HBV and HCV. The most prevalent cause of HCC in Mongolia, HCV, accompanied with liver stiffness and cirrhosis, is an emerging public health issue. Mongolia is one of the first countries that registered Ledipasvir/Sofosbuvir (LDV/SOF) regimen from developing countries.

Methods: We followed and evaluated treatment outcome of patients with HCV infection using combination of 90 mg ledispavir/400 mg sofosbuvir (manufactured by Gilead Science) in 298 treatment naï¨ve patients. All patients were treated with LDV/SOF for 12 weeks and, their treatment was evaluated by quantitative HCV-RNA assays prior and W (week) 4 and W12 of treatment. Sustained virological response (SVR) after 12 weeks treatment was assessed. Virus genotype analysis using cDNA microarray, liver enzymes, CBC and drug related adverse events were assessed in every patient.

Results: Out of 298 patients underwent treatment, 138 patients were examined for pre-treatment liver stiffness using Fibroscan. When patients were examined by Fibroscan test, 25% (n=35) of assessed patients were F0 stage; 13.57% (n=19) were F1 stage; 10% (n=14) were F2 stage; 20.71% (n=29) were F3 stage; and 30.72% (n=43) were F4 stage. Patients (n=35) with fibrosis stage F0 were omitted from post-treatment control examinations. The one hundred three patients were selected for further post-treatment fibrosis staging. The twenty three patients were successfully contacted and complied posttreatment Fibroscan scanning. 23/23 (100%) patients achieved SVR12. W, were all genotype 1b. Median ALT level significantly dropped during treatment from 121.19 ± 98.3 IU/L to 33.2 ± 14.7 IU/L and slightly increased by the end of treatment 41.4 ± 18.8 IU/L. The ninety one percent of the patients had improved in liver stiffness while remaining patients were observed increased stiffness.

Conclusions: After treatment, 30.43% (n=7) of patients moved to the F0 stage from liver stiffness. There are many studies that assess liver fibrosis after cure of HCV, but varying numbers were observed. We assess liver stiffness after treatment of HCV in Mongolian population for the first time. Though study population was small, we had 91% of patients improved in liver stiffness.

Keywords: HCV, Liver stiffness, Treatment, Fibrosis

PE-277

Role of Fibroscan and APRI Score in Detection of Liver Fibrosis in Patients with Hepatitis B

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Aims: The assessment of liver fibrosis is essential for predicting the prognosis and outcome of all forms of chronic liver disease. A liver biopsy is the gold standard for the assessment of liver fibrosis, but it has its limitations which include life-threatening complications. Alternative methods of non-invasive laboratory and radiological testing for the assessment of liver fibrosis in hepatitis have evolved during the past decade and these methods may be able to overcome the limitations of liver biopsy. This study was conducted in order to asses liver fibrosis using Fibroscan and to compare these results to the AST. Platelet ratio index (APRI scores) on HBV patients.

Methods: A cross-sectional study was conducted on HBV patients who underwent Fibroscan examinations between March 15, 2015 and February 30, 2017 in Happy Veritas Clinic and Diagnostic Center. Demographic data was collected including sex, age, and nationality, serum alanine aminotransferase levels (ALT 6-24 U/l), serum aspartate aminotransferase levels (13-33U/L) and platelet counts (180-320-10^9) wre also determined. The stages of fibrosis (F0 0-7.2; F1 7.2-8.2; F2 8.2-11; F3 11-18.3 and F4 >18.3) were in kPa. The result of APRI was compared with the Fibroscan fibrosis scores.

Results: The results of 228 patients were analyzed including 126(55%) males with a mean age of 42 years (SD: 9.9, range : 22-67). The males were significantly younger than the females (47 years (SD: 10.5 (range 18-72) (*P*<0,001). The mean stiff-

ness score was 11:29(SD: 8.7)kPa and most patients exhibited no fibrosis (37%) and mid-moderate level (38%) of fibrosis. Thirty patients (13%) had advanced fibrosis. The mean platelet and serum ALT levels were 1.11 (SD: 1.42; range 0.12-3.7). There was a significant positive correlation between the Fibroscan results and the APRI scores (P<0,001). Similarly, there was a significant positive correlation between age and fibrosis score and a significant negative correlation between platelet count and stiffness score.

Conclusions: This study has shown that the combination of Fibroscan and APRI methods providers a valuable approach for assessing liver fibrosis in patients with hepatitis. This can eliminate the need for liver biopsy in patients without clear indication.

Keywords: Fibroscan, Fibrosis, APRI, HBV

PE-278

Adverse Events of HCV Treatment Using Ledipasvir/Sofosbuvir Combination

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Aims: The incidence of liver cancer in Mongolia generally caused by HBV and HCV. It is 7 times higher that that world's average in recent studies. 27% of the population has been diagnose and it is very one of four people has the virus and most prevalent cause of HCC and causing number one public health issue. Mongolia is one of the first countries that registered LED/SOF regimen from developing countries.

Methods: We followed and evaluated treatment outcomes of the patients with HCV infection using Harvoni (manufactured by Gilead Science). We started our prospective analysis on August until December 2016. For 3 months on 1230 patients. All patients were treated with SOF/LDV for 12 weeks and their treatment was evaluated by quantitative HCV RNA assays prior and week 4 and week 12 of treatment. Sustained Virological Response (SVR) after 12 weeks of treatment was assessed. Virus genotype analysis using cDNA microarray liver enzymes. CBC and drug related adverse events were assessed in every patient.

Results: Total of 40 adverse events were observed in 527/1230 patients (43%). Single adverse events were observed in 358/527(68%), whereas 2 events were observed in 116/527(22%) and 3 or more events were observed 52/537(10%) on patients respectively. Age wise35 or lower aged patients were 43/153 (28%), age of 36 to 55, 295/655(45%) and age of 56 of more, 190/422(45%) were adverse events were observed. Our result by gender wise, out of 406/781(52%) on female patients, on male patients 121/449(27%) were observed adverse events.

Conclusions: Treatment of HCV in Mongolia using all-oral dual DAA was divided in 3 phases due to shortness of drugs and logistics arrangements. We have achieved 95.5% SVR 12 week for 3 months treatment with SOF/LDV this time. Despite the identical adverse events were found in other Asian and other regions in the world during treatment, unrecorded adverse events were observed such as the facial paralysis, paraproctitis, AFP and facial skin darkening in Mongolia.

Keywords: Adverse events, Treatment, Ledipasvir

PE-279

Management of Primary Hepatic Tuberculosis: A Single Center Experience

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Aims: Primary hepatic tuberculosis is a rare benign disease, without typical manifestation and specific test, which usually contribute to the misdiagnosis of the disease. Therefore, we reviewed eleven cases of primary hepatic tuberculosis in our medical center, in order to find the common features, which might be conductive to improve the diagnostic accuracy of the disease.

Methods: Eleven cases of hepatic tuberculosis confirmed by histopathological examination from 2012 to 2017, were collected in our hospital. Clinical features and outcomes were retrospectively analyzed.

Results: All the patients were in good condition at admission, including seven male and four female, aging from 18 to 66 years (average 42.7 years). They disclaimed history of pulmonary and any extra-pulmonary tuberculosis. Tumor markers including AFP, CA19-9 and CEA were within the normal range. All the patients, with liver function classified as Child Pugh A, showed no signs of infection. The lesions were presented as hypo-echoic, cystic or solid-cystic in ultrasonography, low density with periphery enhancement on CT scan, and mixed signals on MRI. Two patients were initially diagnosed as liver cancer, two as liver benign tumor, three as hilar tumor, two as liver abscess, and one as others. Five cases underwent partial hepatectomy, two received laparotomy and drainage of the abscess, two experienced laparotomy and liver biopsy, and two with percutaneous needle biopsy. All recovered well after the operation, subsequently received regular treatment of anti-tuberculosis, and completely cured for hepatic tuberculosis.

Conclusions: Surgical intervention is an effective way to clarify the diagnosis of asymptomatic primary hepatic tuberculosis.

Surgery,Technical Issues

PE-280

The Impact of the Advanced Multidisciplinary Team Working on Stage IV Colorectal Cancer

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Aims: The management of stage IV colorectal cancer is optimized by bringing together all relevant specialties in colorectal metastatic (CRLM) disease management in a centralized high volume liver cancer surgery centre. The major objective is to increase respectability so as to achieve long- term potential survival (> 5 years). New chemotherapy regimes including biologicals are bringing more patients to resection. Including respectable extrahepatic disease, respectability is the complete removal of liver metastasis while leaving at least 30% of functional remnant liver

Methods: A British Association of Surgical Oncology (BASO) Ronald Raven traveling fellow '2 week' observational study on the role of the advanced MDT in the management of stage IV colorectal cancer at the Aintree hepatobiliary centre, Liverpool UK.

Results: There are 3 categories of patients with resectable disease: 1) 10-20% of patients with liver- limited disease are resectable with curative intent at time of detection (I.e. easily resectable), 2) 10% are amenable to surgical intervention- resection with ablation or two stage hepatectomy with concomitant resectable extrahepatic disease (I.e. borderline resectable), 3) 30-40% of patients with initially liver- limited irresectable disease made resectable by chemo/ biological therapy. Thus, 50- 70% of CRLM are potentially resectable.

Conclusions: The major end point of the advanced multidisciplinary approach to stage IV colorectal cancer management is respectability due to an impact on patient survival of 40% > 5 years and 30% in 10 years. CRLM can no longer be viewed as one disease as the molecular pathology (Kras/BRAF) be mutated molecular profiles has implications in personalised therapy.

PE-281

Short Term Result of Anterior Approach with Liver Hanging Maneuver for Anatomical Resection: A Single Center Experience

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Aims: Anatomical liver resection is the treatment of choice for hepatocellular carcinoma (HCC). Anterior approach with liver hanging technique is useful to prevent the dissemmination of tumor cells to systemic circulation. Thus, we aim to evaluate the short term results of anterior approach with liver hanging maneuver for anatomical resection.

Methods: A retrospective review of all patients with HCC who underwent anatomical resection from July 1 to December 20, 2019. The procedures were performed by 4 liver surgeons.

Results: Among 9 patients, there were 5 men and 4 women. The mean age was 53.3 ±11.5 years. The right hepatectomy was performed in 5 patients, the right anterior sectionectomy in 2 patients, and ventral segment preserving right hepatectomy in 2 patients with small left lobe. Anterior approach with liver hanging maneuver was performed in all patients. The mean tumor size is 8.9 cm. Two patients had macrovascular invasion (right hepatic vein and right posterior portal vein). The mean operative time was 231.1 ± 37.2 minutes with a mean estimated blood loss of 303.3 ± 450.6 ml. Complications included 1 bilake (Clavien-Dindo grade II) and 1 acute portal vein thrombosis (grade IVa) were reported. The mean length of hospital staybil was 12.2 ± 8.4 days. There was no reported 30 days mortality.

Conclusions: The anterior approach with liver hanging technique can be apply for various kind of anatomical resection. This procedure is technically safe and feasible.

PE-282

The Problem of Diagnosis and Treatment of Liver Echinococcosis in the Region of Uzbekistan

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Aims: In Uzbekistan, one of the five endemic foci of the disease, the number of operations performed annually for echinococcosis has increased from 1.5 thousand in the 2000s to 4.5 thousand in 2015. The frequency of complicated forms of liver echinococcosis reaches 84.6%, and relapses, according to different authors, are observed in 22-54% of the operated patients.

Methods: The main criteria for evaluating the effectiveness of surgical treatment of EP are a low level of early postoperative complications, elimination of the residual cavity, and a decrease in the number of relapses of the disease.

Results: The main criteria for evaluating the effectiveness of surgical treatment of EP are a low level of early postoperative complications, elimination of the residual cavity, and a decrease in the number of relapses of the disease. An uncomplicated course of the disease was observed in our clinic over the past year, 66.7%, 33.3% had a complicated course in the form of the presence of cystobiliary.

Conclusions: Complications of the disease are of interest. Despite the fact that the frequency of the complicated course of the disease in primary and complicated echinococcosis did not differ, with residual echinococcosis, one of the complications associated with the death of the parasite was significantly

more frequent - calcification of the fibrous membrane (P<0.05). A combination of different complications more often occurred with primary echinococcosis (P<0.05). Complications associated with the large size of the cysts (breakthrough of the echinococcal cysts into the

Biliary and Pancreatic Disease

PE-283

A Fluctuating Dermatoglyphic Trait Asymmery as a Risk Marker in Chronic Pancreatic Diabetic Patients in Caribbean Region. A Case-Control Study

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Aims: Dermatoglyphic patterns are the epidermal ridges seen on the surface of palm, sole & digits. These ridges play a significant role in assessing various diseases in mankind. Pancreatic Diabetes in today's world is a challenge and is very important to know about the early diagnosis and undertake the preventive measures. It can be very important & significant to ascertain the person at higher risk for becoming diabetic beforehand. The aim of current study is to compare and evaluate the dermatoglyphics patterns in Pancreatic Diabetes Patients of Guyana.

Methods: The research includes the Pancreatic diabetes patients visiting to the Internal Medicine outpatient department at Georgetown Public Hospital Corporation, Guyana. The subjects ranging 30-70 years of age group will be chosen from both genders for the study. The ethical clearance and informed consent will be obtained. Various parameters of dermatoglyphics patterns has been studied and compared with the normal healthy adults of Guyana.

Results: This study shows significant results such as increased whorls, increased TFRC and AFRC in diabetic male whereas decreased in diabetic female. The mean values of a-b ridge count were lower in male and higher in the female. The mean values of atd and adt angles were also higher in the cases.

Conclusions: Various dermatoglyphic researches across the globe are supporting, that finger print patterns may be altered in several clinical disorders. Hence, present study may reveal the similar changes in various standardized parameters of dermatoglyphic patterns in the palm and digits of the hand in Chronic Pancreatic Diabetic Patients of Guyana.

Keywords: Dermatoglyphics, Pancreatitis, Diabetes mellitus, Guyana

PE-284

Management of Chronic Pancreatitis- Step Up?

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Aims: Endoscopic treatment is used in several units prior to surgical treatment for pain in chronic pancreatitis. There is limited information on patients who undergo surgical 'salvage' after endoscopic failure. We conducted a comparative study between patients who had undergone surgery after prior non-surgical intervention and upfront surgery.

Methods: Patients who underwent surgical drainage in our institution over the last 6 years were reviewed, in two groups- Group A (n=29) - surgery with prior non-surgical interventions (ESWL and/or endoscopy); Group B (n=79) - upfront surgery. Pain scores and QOL scores were measured prospectively.

Results: The two groups were comparable for baseline characteristics except that group A patients had more strictures/stones in body and tail region (P<0.05). Short term morbidity was more in Group A vs Group B (65% vs 26%, P<0.01) - wound infection (45% vs 10%, P<0.01; Gastroparesis (10% vs nil, P<0.01). On long term followup complete pain relief was worse in Group A patients (37% vs 68%, P=0.05). Quality of life scores (WHOQOL- BREF) in social domain was significantly better in Group B. Improvement in exocrine and endocrine insufficiency was similar in both groups.

Table. Long term outcome

	Group A (n=24)	Group B (n=54)	*p*- value
Follow up duration[a]	58± 22 (19-92) *	66 ± 20 (17-92) *	0.170
IFC pain score at last follow-up	3.7 ± 2.4	2.67 ± 2.1	0.104
Complete pain relief, n (%)	9 (37)	37 (68)	0.053
WHOQOL BREF			
Environmental[a]	61±12	65±10	0.115
Physical[a]	52 ± 7	52± 10	0.937
Psychological[a]	55±10	56 ±10	0.731
Social[a]	59±16	69±14	0.012
Endocrine function, n			
Insufficiency persisted	3	11	
Insufficiency developed	2	4	0.218
Insufficiency resolved/improved	3/8	5/16	
Exocrine function, n			
Insufficiency persisted	1	8	
Insufficiency developed	2	9	
Insufficiency resolved/improved	2/8	4/16	0.217
Body weight, n			
Stable	6	13	
Gained	17	39	0.310
Lost	1	2	

[a]Value expressed in median ± 2 SD.
*Range

Conclusions: Patients with chronic pancreatitis who undergo 'salvage' surgery after non-surgical interventions are at increased risk of postoperative morbidity, lower quality of life and poor pain control as compared to those who undergo upfront surgery. Patients with pancreatic body/tail strictures/stones have poor outcomes with non-surgical interventions and may be considered for upfront surgery.

Keywords: Chronic Pancreatitis, Surgical, Endoscopic

PE-285

Frey's Plus versus Frey's Procedure for Chronic Pancreatitis: Analysis of Postoperative Outcomes and Quality of Life

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Aims: Additional surgical procedures are often required in patients with chronic pancreatitis (CP) related complications. The present study aims to analyze the type of additional procedures required in patients who underwent Frey's procedure (Frey's plus) and to compare with the short-term outcomes and quality of life of patients who underwent only Frey's procedure.

Methods: Retrospective analysis of a prospectively maintained database of patients who underwent surgery for CP between January 2012 and February 2018 and completed at least one year of follow-up. Patients who underwent non-Frey's surgical procedures were excluded. Clinical parameters, postoperative pain relief (using Izbicki pain score) and functioning scale score (EORTC QLQ C30) of patients who underwent Frey's plus procedure and only Frey's procedure were compared.

Results: Of the 146 patients who underwent surgery for CP during the study period, 100 patients (Frey's procedure - 68 Frey's plus procedure – 32) were included in this study. Roux-en-Y hepaticojejunostomy was the commonly performed additional procedure (n=10). The demographic and clinical parameters were comparable, except for more patients with jaundice (21.9%Vs.2.9%, P=0.002) and prolonged operative time (374.7mins Vs. 326.3 mins, p<0.001) in Frey's plus group. However, there was no significant difference in mean intraoperative blood loss, postoperative morbidity or duration of hospital stay. At median (range) follow up of 34 (12-86) months, there was no significant difference in the pain control and quality of life between two groups.

Conclusions: Frey's plus procedure for chronic pancreatitis can be safely performed wherever indicated without adversely affecting the postoperative outcome or quality of life.

Keywords: Freys, Freys plus, Chronic pancreatitis

PE-286

General Surgery

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Aims: Although hepatobiliary scintigraphy has been widely used in patients with biliary pain, the histopathological factors of gallbladder that affect the findings of hepatobiliary scintigraphy is not fully known. The aim of the present study is to investigate the relationship between hepatobiliary scintigraphy findings and histopathological results in patients with recurrent biliary colic.

Methods: A total of 107 patients who underwent hepatobiliary scintigraphy for recurrent biliary colic and subsequent cholecystectomy were retrospectively enrolled. According to the hepatobiliary scintigraphy findings, patients were categorized into three groups; patients with non-visualization of gallbladder activity (non-visualized GB group), gallbladder ejection fraction (GBEF) of <35% (low GBEF group), and GBEF of ≥ 35% (normal GBEF group). Differences of histopathologic factors between three patient groups were evaluated and multivariate logistic regression analyses were performed to identify histopathological predictors for non-visualization of gallbladder activity and low GBEF.

Results: Of all patients, 31 patients were classified as non-visualized GB group, 33 were low GBEF group, and 43 were normal GBEF group. Non-visualized group showed higher rates of patients with severe neutrophil, lymphoplasma cell, and eosinophil infiltrations and empyema and showed more increased cystic duct wall thickness than other groups (P<0.05). Low GBEF group showed higher muscle-to-total wall thickness ratio and muscle-to-fibrosis thickness ratio than those with normal GBEF group (P<0.05). On multivariate logistic regression analysis, Severe degrees of lymphoplasma cell infiltration (P=0.027) and eosinophil infiltration (P<0.001) were independent predictors for non-visualization gallbladder activity, and muscle-to-fibrosis thickness ratio (P=0.030) was an independent predictor for low GBEF.

Conclusions: In patients with recurrent biliary colic, non-visualization of gallbladder activity on hepatobiliary scintigraphy was related with the degree of inflammation in the gallbladder, while GBEF was related with muscular hypertrophy of the gallbladder.

Keywords: Hepatobiliary scintigraphy, Bilary, Pathology

PE-287

Chronic Cholecystitis

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Aims: Although hepatobiliary scintigraphy has been widely used in patients with biliary pain, the histopathological factors of gallbladder that affect the findings of hepatobiliary scintigraphy is not fully known. The aim of the present study is to investigate the relationship between hepatobiliary scintigraphy findings and histopathological results in patients with recurrent biliary colic.
Methods: A total of 107 patients who underwent hepatobiliary scintigraphy for recurrent biliary colic and subsequent cholecystectomy were retrospectively enrolled. According to the hepatobiliary scintigraphy findings, patients were categorized into three groups; patients with non-visualization of gallbladder activity (non-visualized GB group), gallbladder ejection fraction (GBEF) of <35% (low GBEF group), and GBEF of = 35% (normal GBEF group). Differences of histopathologic factors between three patient groups were evaluated and multivariate logistic regression analyses were performed to identify histopathological predictors for non-visualization of gallbladder activity and low GBEF.
Results: Of all patients, 31 patients were classified as non-visualized GB group, 33 were low GBEF group, and 43 were normal GBEF group. Non-visualized group showed higher rates of patients with severe neutrophil, lymphoplasma cell, and eosinophil infiltrations and empyema and showed more increased cystic duct wall thickness than other groups (P<0.05). Low GBEF group showed higher muscle-to-total wall thickness ratio and muscle-to-fibrosis thickness ratio than those with normal GBEF group (P<0.05). On multivariate logistic regression analysis, Severe degrees of lymphoplasma cell infiltration (P=0.027) and eosinophil infiltration (P<0.001) were independent predictors for non-visualization gallbladder activity, and muscle-to-fibrosis thickness ratio (P=0.030) was an independent predictor for low GBEF.
Conclusions: In patients with recurrent biliary colic, non-visualization of gallbladder activity on hepatobiliary scintigraphy was related with the degree of inflammation in the gallbladder, while GBEF was related with muscular hypertrophy of the gallbladder.
Keywords: Biliary colic, Hepatoscintigraphy, Chronic cholecystitis, Pathology

PE-288

First Single-Port Laparoscopic Pancreatectomy in Regional Clinical Hospital Shymkent

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Aims: Pancreatic surgery is an extremely challenging field, and the management of pancreatic diseases continues to evolve. In the past decade, minimal access surgery is moving towards minimizing the surgical trauma by reducing numbers and size of the port. In the last few years, a novel technique with a single-incision laparoscopic approach has been described for several laparoscopic procedures. We present a single-port laparoscopic spleen-preserving distal pancreatectomy. To our knowledge, this is the first single-port pancreatic resection in Regional Clinical Hospital Shymkent.
Methods: A 35-year-old woman with neuroendocrine tumor underwent spleen-preserving distal pancreatectomy via single-port approach. A single-incision advanced access platform with gelatin cap, self-retaining sleeve and wound protector was used.
Results: Operative time was 182 minutes. Blood loss was minimal, and the patient did not receive a transfusion. The recovery was uneventful, and the patient was discharged on postoperative day 4.
Conclusions: Single-port laparoscopic spleen-preserving distal pancreatectomy is feasible and can be safely performed in specialized centers by skilled laparoscopic surgeons.
Keywords: Distal pancreatectomy, Single-port laparoscopic, A single-incision, Spleen-preserving

PE-289

Laparoscopic Management of a Cystic Duct Cyst

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Aims: Choledochal cysts are rare cystic dilatations of the biliary tree. These cysts are usually referred for surgical resection because of their association with developing malignancy. We describe one rare case of a cyst of the cystic duct that we successfully treated via laparoscopic resection.
Methods: A 43-year-old male was found to have a biliary abnormality on a routine follow-up computed tomography (CT) scan for an unrelated medical condition. Further magnetic resonance cholangiopancreatography (MRCP) imaging identified a cystic dilation consistent with a Type II choledochal cyst.
Results: Laparoscopic resection was performed using a total of 5 trocars, at which time a cyst of the cystic duct was found instead of the expected Type II choledochal cyst. Intraoperative cholangiography was used as a surgical adjunct to confirm the anatomy, and resection of the cyst was completed without complications.
Conclusions: Our case adds to the body of reports showing that cysts of the cystic duct, while extremely rare, do occur and need to be recognized. Given the preoperative similarity between cystic duct cysts and other choledochal cysts, proposal for a new "Type VI" category for choledochal cysts may be considered so that clinicians can be prepared for this variation. Once recognized, cysts of the cystic duct can be safely and effectively removed by laparoscopic excision, as we have demonstrated.
Keywords: Cysts, Laparoscopic resection, A biliary abnormality, Magnetic resonance cholangiopancreatography

PE-290

Laparoscopic Drainage of Pancreatic Pseudocysts

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Aims: This paper describes our tailored and methodological approach to laparoscopic drainage of pancreatic pseudocysts (PPs) based on an anatomical classification.
Methods: We adopted the laparoscopic approach in "all comers" who had PPs requiring surgical drainage. The recipient organ for drainage (e.g., cystgastrostomy, cystjejunostomy, or cystduodenostomy) and method of access (e.g., transgastric, endogastric, exogastric or lesser sac, and infracolic) were decided based on preoperative computed tomography (CT) and intraoperative findings. The results shown represent median (range).
Results: Between 2001 and 2016, 30 laparoscopic drainage procedures for PPs were performed in 28 consecutive patients. The surgical approach included transgastric (n=17) or endogastric (n=3) cystgastrostomy for large retrogastric PPs (n=20), exogastric cystgastrostomy for small perigastric PPs (n=4), cystduodenostomy (n=1) under ultrasound guidance, cystjejunostomy for infracolic PPs (n=4), and one external drainage. The operative time was 118 (25-300) min. There was one conversion to laparotomy (3.3%), low morbidity (3.3%), and no mortality. The postoperative hospital stay was 2 (1-7) days. At a follow-up of 15 (1-48) months, PPs recurred in two patients (7.1%) and were drained by laparoscopic cystgastrostomy.
Conclusions: CT findings and laparoscopic exploration demonstrate the anatomical characteristics of PPs and enable successful planning and execution of their laparoscopic drainage.
Keywords: Laparoscopic drainage, Pancreatic pseudocysts, Cystgastrostomy, Cystjejunostomy, or Cystduodenostomy, Transgastric, Endogastric, Exogastric

PE-291

Pyogenic Liver Abscess Following Pancreaticoduodenectomy

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Aims: Pancreaticoduodenectomy (PD) remains a challenging operation with a 40% postoperative complication rate. Pyogenic liver abscess (PLA) is an uncommon complication following PD. This study was done to examine the incidence, risk factors, treatment, and long-term outcome of PLA after PD
Methods: We retrospectively reviewed 1,189 patients undergoing PD (N=839) or distal pancreatectomy (N=350) at a single institution over a 24-year period (January 1, 1993-January 1, 2017). No PLA occurred following DP. Twenty-two patients (2.6%) developed PLA following PD. These 22-patients were matched (1:3) for age, gender, year of operation, and indication for surgery with 66-patients without PLA following PD.
Results: PLA occurred in 2.6% (22/839) of patients following PD, with 13 patients (59.1%) having a solitary abscess and 9 (40.9%) multiple abscesses. Treatment involved antibiotics and percutaneous drainage (N=15, 68.2%) or antibiotics alone (N=7,31.8%) with a mean hospital stay of 12-days. No patient required surgical drainage, two abscesses recurred, and all subsequently resolved. Three patients (14%) died related to PLA. Postoperatively, patients with biliary fistula (13.6 vs. 0%, p=0.014) or who required reoperation (18.2 vs. 1.5%, p=0.013) had a significantly higher rate of PLA than matched controls. Long-term follow-up showed equivalent 1-year (79 vs.74%), 2-year (50 vs. 57%), and 3-year (38 vs. 33%) survival rates and hepatic function between patients with PLA and matched controls
Conclusions: Postoperative biliary fistula and need for reoperation are risk factors for PLA following PD. Antibiotics and selective percutaneous drainage was effective in 86% of patients with no adverse effects on long-term hepatic function or survival.
Keywords: Pyogenic liver abscess, Pancreaticoduodenectomy, Drainage, Biliary fistula

PE-292

IgG4-Related Autoimmune Pancreatitis Presented in Pre-Existing Retroperitoneal Fibrosis

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Background: Autoimmune pancreatitis is a rare systemic autoimmune disease that is difficult to diagnose. The features are diffuse enlarged and fibrous pancreas with lymphocyte infiltration, occasionally accompanied by retroperitoneal fibrosis. Reported herein is a case of IgG4-related autoimmune pancreatitis developed in pre-existing idiopathic retroperitoneal fibrosis.
Case: A 76-year-old man was hospitalized due to epigastric pain with jaundice. On admission, BP was 150/90 mmHg, HR 60 beats/min, RR 20 breaths/min, and BT 36.5℃. He was diagnosed with retroperitoneal fibrosis and bilateral hydronephrosis 3 years ago. He did not take any health food or herbal medicine. Laboratory findings revealed WBC 6,980/mm^3, Hb 11.3 g/dL, PLT 252,000/mm^3, PT 10.7 sec, PT (INR) 0.98, AST 299 IU/L, ALT 316 IU/L, total bilirubin 5.34 mg/dL, r-GTP 714 U/L, albumin 3.3 g/dL, BUN 19 mg/dL, creatinine 1.4 mg/dL. HBsAg(-), anti-HCV(-). AFP 2.4 ng/ml, CA 19-9 5.47 U/mL. Abdomen CT showed mild progression of retroperitoneal soft tissue infiltration, bilateral hydronephrosis and diffuse swelling of pancreas. Abdominal MRI revealed diffuse swelling of pancreas with subtle hypointense rim. On the 13th day of hospitalization, jaundice worsened (total bilirubin 13.4 mg/dL). An autoimmune pancreatitis was suspected and an IgG4 test was performed. The level of IgG4 increased to 15,900. Abdominal pain and

jaundice improved after starting steroid treatment. Pancreatic size was significantly reduced on follow-up CT 5 months after administration of steroid and the IgG4 level was also reduced to 2,300. The patient is undergoing follow-up from an outpatient basis.

Conclusions: IgG4-related autoimmune pancreatitis is difficult to diagnose, but it is important to suspect and actively detect when accompanied by abdominal pain and jaundice of unknown cause. IgG4-related autoimmune pancreatitis can be metachronously associated with retroperitoneal fibrosis.

Keywords: Autoimmune; Pancreatitis; Retroperitoneal fibrosis; Jaundice

PE-293

The Benefit of Lekodepleted PRC Transfusion for Biliary Patient after Kasai Procedure

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Aims: Patients with choledochal tract problems often needed surgery. The common procedure for this problem is Kasai portoenterostomy. However, some problems arising after surgery. Many patients encounter the bleeding problem that needed packed red cell (PRC) transfusion. This transfusion, which may increase the risk of transfusion reaction mediated by inflammatory cytokine. Accumulation of interleukin-8, one of the inflammatory cytokines produced by leukocyte contain in PRC, has been known to contribute to increasing transfusion reaction risk. Lekodepletion is an effort to decrease leukocyte number in PRC, give expectation to decrease IL-8 accumulation in PRC.

Methods: The study is a quasi-experimental study. Subjects were biliary patients after Kasai Procedure who need PRC transfusion in Dr. Sardjito General Hospital Yogyakarta. The interleukin-8 level is measured using the ELISA sandwich method. Delta IL-8 is obtained from the subtraction of IL-8 level one hour after transfusion with before transfusion. Statistical analysis was performed using the difference test to know significant differences of delta IL-8 mean value between lekodepleted and non-lekodepleted PRC.

Results: Total study subjects were 77 persons, most were women 52 (67,5%). There was no significant differences between group received lekodepleted with non-lekodepleted PRC transfusion based on age (P=0.484), gender (P=0.410). There was a statistically significant median difference in delta interleukin 8 between groups. Increased level of IL-8 value for group received lekodepleted PRC transfusion is less than group received non-lekodepleted PRC transfusion.

Conclusions: Lekodepletion PRC have potential benefit for biliary patients after Kasai procedure.

PE-294

Does Increasing Experience Improve Outcomes of Surgical 'Step-Up Approach' in Acute Necrotizing Pancreatitis? Lessons Learnt from a Tertiary Referral Center

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Aims: Step-up approach is becoming a standard of care for management of acute necrotizing pancreatitis. We aimed to investigate the learning curve effect and increasing experience on management and outcomes of surgical step-up approach at our high-volume tertiary referral center.

Methods: In a retrospective analysis of database of patients with acute necrotizing pancreatitis referred to our unit, we divided patients into three distinct time periods: Group-1 (2008-2012), Group-2 (2013-2016) and Group-3 (2017-2019). Outcomes between different time periods were compared.

Results: Total of 335 patients were included, with 92 patients in Group-1, 117 in Group-2 and 126 in Group-3. Patients treated on surgical side in later time period had higher incidence of multiorgan failure (26.1% vs. 49.6% vs. 45.2%, P<0.001), APACHE II scores at presentation (8 vs. 10 vs. 9, P=0.006) and at first intervention (9 vs. 11 vs. 10, P=0.037), as well higher mCTSI score (8 vs. 10 vs. 10, P<0.001). Over time, median percutaneous drain size (10Fr vs. 12Fr vs. 14 Fr, P<0.001) as well as sepsis reversal after drainage (40.2% vs. 59% vs. 49.2%, P=0.026) increased, whereas median number of drains (P=0.001) and interventions (4 vs. 3 vs. 3, P=0.005) decreased significantly. Necrosectomy requirement, length of stay and mortality remained similar over time despite more severe cases referred to surgical side.

Conclusions: With increasing experience of step-up approach, sicker patients with higher severity of pancreatitis could be managed successfully with fewer drains and procedures leading to significantly higher sepsis reversal with drainage, with no increase in surgery requirement or mortality.

PE-295

Clinicopathological Differences in T2 Gallbladder Cancer According to Tumor Location

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Aims: We aimed to identify clinicopathological differences and factors affecting survival outcomes of stage T2a and T2b gallbladder cancer (GBC) and validate the oncological benefits of regional lymphadenectomy and hepatic resection in these patients.
Methods: This single-center study enrolled patients who were diagnosed with pathologically confirmed T2 GBC and underwent curative resection between January 1995 and December 2017. Eighty-two patients with T2a and 50 with T2b GBCs were identified, and clinical information was retrospectively collected from medical records and analyzed
Results: Three- and 5-year overall survival rates were 96.8% and 96.8% and 80.7% and 80.7% in T2a and T2b groups, respectively (*P*=0.007). Three- and 5-year survival rates among all T2 GBC patients without and with lymph node metastasis were 97.2% and 94.4% and 81.3% and 81.3%, respectively (*P*=0.029). There was no difference in survival rates between the two groups according to whether hepatic resection was performed (*P*=0.320). However, in the T2b group, those who underwent hepatic resection demonstrated a better survival rate than those who did not (*P*=0.029). Multivariate analysis revealed that lymph node metastasis, vascular invasion, tumor location, and adjuvant chemotherapy were significant independent prognostic factors.
Conclusions: Hepatic resection was not always necessary in patients with peritoneal-side GBC. Considering the clinicopathological features and recurrence patterns of hepatic-side GBC, a systematic treatment plan, including radical resection and adjuvant chemotherapy, should be established.

PE-296

Does Preoperative Serum Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR) and Lymphocyte to Monocyte Ratio (LMR) Predict Prognosis in Resectable Pancreatic Adenocarcinomas? - Results of a Retrospective Study

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Aims: Pretherapy serum neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and lymphocyte to monocyte ratio have been shown to predict prognosis in patients with pancreatic ductal adenocarcinoma (PDAC). The aim of this study was to evaluate whether NLR, PLR and LMR help in predicting survival outcomes in patients with PDAC treated with curative intent surgery and chemotherapy at our center.
Methods: A retrospective analysis was done of all operated cases of PDAC who underwent curative resection between 2011 to 2018. The pretherapy NLR, PLR and LMR were calculated and analyzed with respect to pathological and survival outcomes
Results: 134 operated patients of PDAC were included in the analysis. 94 patients were operated upfront and 40 following neoadjuvant chemotherapy. The median overall survival and disease free survival was 24 months and 17 months respectively. The 1 and 2-year survival was 77.2% and 48% respectively. The Overall survival for NLR values of less than 2, 2.7 and 5 was 27, 25 and 25 months and for NLR more than 2, 2.7 and 5 was 22, 18 and 17 months respectively and was statistically insignificant . Similarly, the PLR and LMR were not significant for a cut off of 150 and 2.8 respectively. On univariate analysis only stage of disease was found to have significant correlation with survival
Conclusions: The NLR, PLR and LMR do not correlate with survival in patients with pancreatic ductal adenocarcinomas in this study.

PE-297

Bile Duct Injuries (BDI) Following Laparoscopic Cholecystectomy Management in Cipto Mangunkusumo Hospital as Tertiary Hospital in Indonesia

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Aims: Laparoscopic cholecystectomy technique has changed the way surgeons treat cholelithiasis. The Global incidence of BDI has remained constant around 0.5%. BDI often encountered during laparoscopy cholecystectomy. Early diagnosis and appropriate management played an important role in managing BDI injuries.
Methods: We aim to retrospectively review the management of BDI cases after laparoscopic cholecystectomy in CMH between 2015-2019.
Results: We found 16 cases in this study with 10 females and 6 males. All subjects were a referral from primary or secondary health-care hospital The median age was 47 (25-58). Seven cases sustained BDI from laparoscopic procedure four were classified as Strassberg E3, one as Strasberg type A, one as Strasberg D, and 9 cases were BDI from the open procedure. All cases from laparoscopy procedure experience biloma. Hepaticojejunostomy Roux-en-Y was performed in all cases. One relaparotomy was performed due to bile anastomosis leakage.
Conclusions: Proper demonstration of the anatomy may help to reduce BDI injuries. Early diagnosis and appropriate management played an important role in managing BDI injuries.

PE-298

Redo Surgery in Recurrent Biliary Cystadenocarcinoma at Common Bile Duct: A Case Report and Literature Review

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Aims: Biliary cystadenocarcinoma is a very rare cystic tumor and constitutes less than 5% of intrahepatic cysts of biliary origin1[4]). Unilocular or multilocular cystic disease of the liver, presenting commonly in middle-aged women with the mean age of 50 (range 38 – 64) years. Differential diagnosis varies from simple liver cysts to cystic liver metastases. The etiology of this lesion is unclear, but congenital and acquired theories have been proposed[5]. We report a case of biliary cystadenocarcinoma in a 63-year-old man with a review of the literature.
Methods: Therefore we report a case of recurrent biliary cystadenocarcinoma in a 65-year-old woman treated by re-surgery after four years since the first operation left hepatectomy followed by six courses of chemotherapy. The surgery, the post-operative course was uneventful and the patient discharged from hospital at day 10 without complication. There is no recurrence noted for 1 year of follow-up.
Results: We performed a resection of CBD and hepaticojejunostomy. The surgery, the post-operative course was uneventful. The surgical specimen shows yellow-brownish multilocular cystic lesions with mucinous fluid contents of 6x3cm. Histology shows a cystic neoplasm forming papillary projections, covered by an atypical mucin-producing glandular epithelium. The tumor was determined as well-differentiated biliary cystadenocarcinoma
Conclusions: In conclusion, we report here a rare case of recurrent biliary cystadenocarcinoma in extra hepatic biliary tract a 65-year-old woman who was treated with redo surgery of common bile duct. Since the naturally low malignant cystadenocarcinomas are less invasive on surrounding vessels and tissues during redo surgery.

PE-299

Postoperative Choledochoscopic Removal of Intrahepatic Stones via Subcutaneous Hepaticojejunal Access Loop for Complicated Recurrent Pyogenic Cholangitis (RPC)

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Aims: Complicated recurrent pyogenic cholangitis (RPC) is a lifelong, progressive disease. A high rate of residual stones, recurrent stones and repeated symptoms after the initial surgery are the major concern. Reoperation can be a formidable challenge and definitely hazardous, and the patient morbidity is high because of dense adhesion, the risk of bleeding and nearby organ injury.
Methods: Roux-en-Y hepaticojejunostomy with subcutaneous access loop was done in all patients with complicated RPC admitted to Surgical Ward (3), Yangon General Hospital in 20 months duration. During one year follow up period, the patients having residual or recurrent stones with symptoms were chosen for stone removal using choledochoscope via access loop. Outcome was determined by successful utilization of the access loop, clearance of the stones and relief of the symptoms after the procedure.
Results: There were 77 patients who underwent Roux-en-Y hepaticojejunostomy with subcutaneous access loop. The overall incidences of residual stone, stone recurrence and symptom recurrence were 27.2%, 13.6% and 31.8%. Total ten sessions of choledochoscopic stone removal were done in eight patients. Successful utilization of the access loop was accomplished in 85.7%. There were 75% successful stone clearance. Symptom relief after endoscopic intervention was 88.9%. There was no complication after the procedure. The mean hospital stay after procedure was 2.6 days.
Conclusions: Subcutaneous hepaticojejunal access loop is effective in treating residual and recurrent calculi occurred in complicated RPC. High success rates, short hospitalization periods, and no complications make it a well-accepted method for management of complicated RPC.

PE-300

Pancreaticojejunostomy, Hepaticojejunostomy and Double Roux-En-Y Digestive Tract Reconstruction for Benign Biliary Obstruction and Chronic Pancreatitis

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Aims: Biliary obstruction due to chronic pancreatitis is not uncommon. Moreover, the patients with chronic pancreatitis sometimes have biliary stones diseases. The pain due to chronic pancreatitis need to be addressed while treating biliary obstruction. Biliary and pancreatic stenting in these conditions require repeated changing of the stents with multiple admissions, and the long-term success rate is low.
Methods: This is a retrospective analysis of five cases of chronic pancreatitis with benign biliary obstruction. Pancreaticojejunostomy, hepaticojejunostomy and double Roux-en-Y digestive tract reconstruction were performed in all patients. Four patients had pancreatic duct dilatation with stones, and cystic dilatation of the duct with distal CBD compression in pancreatic head region found in one patient. Longitudinal pancreaticojejunostomy performed in four patients, and distal pancreatectomy and end-to-side pancreaticojejunostomy done in one patient. Biliary stricture due to chronic pancreatitis was found in three patients, and multiple stones in both intra and extrahepatic ducts found in one patient whom additional subcutaneous access loop was created for future removal of stones.
Results: The recovery of all patients was uneventful and no complication such as leakage and digestive tract obstruction occurred in the postoperative period. All patients did not complaint of pain during follow-up visits. One patient needed read-

mission to medical ward for pancreatic endocrine insufficiency.
Conclusions: Surgery is the best option for chronic pancreatitis with biliary obstruction. For the good-risk patients and for the patients with failed endoscopic procedures, double Roux-en-Y digestive tract reconstruction is effective alternative surgical treatment modality where Frey procedure is not appropriate.

PE-301

Low Muscle Mass Does not Contribute to Increased Post-Operative Morbidity Following Pancreaticoduodenectomy in High Volume Centres

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Aims: Studies suggest that loss of muscle mass possibly contributes to increased post-operative morbidity following pancreaticoduodenectomy(PD).The extent and exact effect of low muscle mass has however not been clearly elucidated. We are sharing, possibly the first study from India, assessing the impact of radiologically demonstrable muscle loss in patients undergoing PD for pancreatic and periampullary tumours.
Methods: A prospective study was conducted from May 2016 to November 2019 in patients undergoing PD for pancreatic and periampullary tumours in the Department of G.I. Surgery, Medanta - The Medicity, Gurugram, Haryana, India, which is a high volume centre, performing ~ 77 PDs (range 72 – 83) per year. Pre-operative abdomen computerised scan was used to calculate psoas muscle area. Low muscle mass was defined as values less than 10th percentile of a normal cohort (data collected from prospective organ donors). Post-operative data was collected for each patient.
Results: Out of 271 patients undergoing PD, pre-operative radiological images were available for 192 patients on PACS (Picture archiving and communication system), of which, 40.8% were found to have low muscle mass. The incidence of delayed gastric emptying (52.1% vs 41.9%, p - 0.270) and clinically relevant post op pancreatic fistula (20.8% vs 17.6%, p value – 0.652) was not statistically different between the two groups. The length of stay, readmission rate and mortality were unaffected by loss of muscle mass.
Conclusions: Though low muscle mass has traditionally been shown to predict outcomes following PD, it's contribution, however, may be mitigated by the surgery being performed at high volume

PE-302

Molecular Validation of the 8th Edition AJCC Cancer Staging System in Patients with Resected Pancreatic Cancer

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Aims: Even though the 8th edition AJCC cancer staging system for pancreatic cancer has validated with major clinicopathologic factors in multiple clinical cohorts, there is still an unmet need for integrative consideration using multi-omics data to stratify the patients with pancreatic cancer elaborately.
Methods: We performed a comprehensive analysis and profiling using genomic, transcriptomic, and proteomic data from TCGA-PAAD and other translational cohorts (4 cohorts, n=340). Molecular features and major subtypes were analyzed mutually with clinical and pathologic factors, especially the 8th AJCC staging system.
Results: Aggressive molecular subtypes, basal-like and squamous subtype, were significantly associated with a higher nodal stage, but tumor size didn't show a clear association with molecular features. The activated stroma of pancreatic cancer microenvironment was significantly correlated with poor differentiation and large tumor size. The mutational pattern of KRAS and several transcriptomic pathways such as eptihelial-mesenchymal transition and DNA repair were differently presented in each clinical stage from the 8th AJCC TNM staging system. The optimal algorithm was identified to show significantly higher performance for the prediction for cancer relapse and cancer-specific survival in discovery and validation cohorts. The in silico prediction for molecular target agents and immunotherapy were performed for final clusters from optimal stratification system revealed from the integrative analysis.
Conclusions: Our comprehensive multi-omics analysis reveals clear needs for the combination of clinical staging and molecular profiling and provides crucial evidence for precision strategy in patients with resectable pancreatic cancer.

PE-303

Review of Series of 9 Cases of Hepatolithiasis Managed at Community-Based Hospital of Nepal

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Aims: Hepatolithiasis is a rare disease with high rate of treatment failure and recurrence. This study aims to review the management and outcome of hepatolithiasis from an endemic region.
Methods: Retrospective review of prospectively maintained database of patients with hepatolithiasis managed surgically (2015-2019) was performed. Diagnosis was based on the clinical findings and radiological investigation (CT/MRI). Demographic data, clinical presentation, extent of disease and operative procedure were evaluated. The outcome measures included immediate

stone clearance, postoperative complications.
Results: Hepatolithiasis was seen in nine (0.34%) out of 2,600 patients being evaluated for gallstone disease. Three patients were young, while the remaining six were in the middle-age group. Seven (78%) were females. The presenting symptoms were abdominal pain (78%) and jaundice (22%). Hepatolithiasis was located in the left, right and bilateral ductal systems in 5, 1 and 3 patients respectively. Concomitant cholelithiasis and choledocholithiasis was seen in 6 (66.6%) patients each. Liver resection for unilateral disease was done in 3 (33.3%) patients: left hepatectomy- (n=2) and left lateral segmentectomy (n=1). High bile duct exploration and bilio-enteric drainage was done in 5 patients. One patient required hepatolithotomy and T-tube drainage due to cholangitis. Complete stone clearance was achieved in 78% of patients. Complications included minor surgical site infection and cholangitis in two patients. Histopathology revealed recurrent pyogenic cholangitis. At median follow-up of 28 months, 78% are symptom-free.
Conclusions: Hepatectomy is an effective treatment when disease is confined to the left lobe. Combined surgical procedure is an acceptable option for bilateral or right-sided hepatolithiasis.

PE-304

Primary Signet Ring Cell Carcinoma of the Pancreas in the Elderly with Indistinct Imaging Characteristics: A Case Report

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Aims: Signet ring cell carcinoma occur in <1% of pancreatic cancers with few reported cases worldwide. Commonly, it arises in the stomach (96%) and some are reported to occur in the colon, breast and Gallbladder. Early diagnosis is of importance due to its poor prognosis. Further studies are needed to understand this type of malignancy.
Methods: A 69/F, with 4 wks epigastric discomfort w/ jaundice & weight loss, came for 2nd opinion. No cause of obstruction on previous Ct scan. On MRCP, biliary tree dilatation & a vague mass at pancreatic head was seen. Normal tumor markers, no evidence of metastasis. Underwent Whipples procedure. Histopathology: SIGNET RING CELL ADENOCARCINOMA, R0 resection. Chemotherapy was planned, but patient opted alternative treatment. 5 months later, recurrence documented by CT scan.
Results: Etiology of SRCC is still unknown, most researchers consider a genetic mutation in the pancreatic parenchyma secondary inflammation. EUS-FNA only provides cytologic sample with inadequate cellularity that is needed for proper identification. Reliability of tumor markers such as Ca 19-9 and CEA can still be in question since clinicopathologic behavior of SRCC especially in pancreas.
Conclusions: High index of suspicion should prompt the search of cause for biliary obstructive diseases especially in the elderly where malignancy is common. Risk factors should always be considered in profiling a patient. Utilization of a high yield imaging is vital in decision making process whether to proceed with surgical treatment that has a high morbidity percentage. Further studies are needed to understand the clinicopathologic character of this rare subtype.

PE-305

Analysis of the Cases with Carcinoma Gallbladder (CA GB) in a Tertiary Level Hospital of Nepal

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Aims: Gallbladder cancer (GC) is a relatively rare disease in some parts of world but is common in countries like Chile, Japan India and Nepal. Nepal stands as one of the five countries with the highest mortality.
Methods: A retrospective analysis of the consecutive operated and non-operated admitted cases of GC in TUTH from 2018 to 2019 was done. Patient demographics, disease characteristics, diagnostic modalities and various curative and palliative treatment variables were analyzed.
Results: Of the 59 patients, there were 33 females (56%) who outnumbered the 26 males(44%) with a male to female ratio of 0.7:1. The median age at diagnosis was 56 years with younger group (<60 years) comprising 62.7% of the disease. Among all, the most common presenting symptom was abdominal pain followed by jaundice. Onset of first symptoms was within mean duration of 40 days (SD 37.45 days). USG and CT availability (100%) lead to preoperative diagnosis in majority. Curative resection (extended cholecystectomy) was done in 16 (27%). The most common anatomic location of mass was fundic followed by neck. Pathological examinations revealed most cases of adenocarcinoma. Of the advanced metastatic Ca GB in 30% of cases, the most common site of metastasis was liver. Mean survival after diagnosis in advanced cases was 4.5 months.
Conclusions: CA GB is more common in Nepal, more among females and younger patients often presenting with pain abdomen and jaundice. Most are advanced at the time of diagnosis Radical surgery can be offered to few patients where the outcome seems reasonably good.

PE-306

Algorithmic Approach for Safe Optimization and Surgical Planning in Hilar Blocks- Single Center Experience

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Aims: To study the outcomes of our algorithmic-approach for safe optimisation and surgical planning in patients with Hilar-Block.
Methods: Retrospective-analysis of prospectively-maintained database of patients undergoing surgery for hilar-block from Jan2013-May2019 was done.Our approach includes Imaging, Biliary-decompression, Future-liver-remnant-Volume(FLR)augmentation based on CT-Volumetry and FLR-function assessment.
Results: 45cases of hilar-blocks underwent resections.32were Hilar-cholangiocarcinoma,5-Intrahepatic-cholangiocarcinoma,6-Ca-Gall-Bladder with hilar-block,2-IgG4-sclerosing-cholangitis-presenting as malignant-masquerade. The mean age was57±12years and 30(67%) were males. On MRCP, hilar-blocks types 2,3a,3b,4 were 3,15,17,10 respectively. Pre-operative biliary-decompression of FLR were done in 21cases[19 PTBD(Percutaneous-Transhepatic-biliary-drainage)/2 EBD(Endoscopic-biliary-drainage)]. Additional PTBD were done in 2 cases for inadequate fall in SB, and 3 for cholangitis. The mean SB(Serum-Total-Bilirubin) at presentation was 9.57±5.58mg/dl. The rate of fall of S.bilirubin was faster in patients <50yrs of age and type-3 hilar-blocks than in type-4 hilar-blocks. PVE was performed in 14cases and FLR hypertrophy of 11.3± 3.03%was achieved.The quality of FLR was assessed with LAI(n=39),fibroscan(n=17), ICGR15(n=12), HVPG (n=35), and selective-remnant-biopsy(n=14,if HVPG>10 mm Hg,ICGR15>15%, or in-suspected steatosis or fibrosis).After optimization,surgical procedures done were Right-Hepatectomy(7), Right-TriSectorectomy(7), Extended-Right-Hepatectomy(9), Left-Hepatectomy(6),Extended-Left-Hepatectomy(5), Left-Trisectorectomy(8) and Bile-duct-excision-alone(3).Eleven patients required concomitant vascular-resections and reconstructions(-8portal-vein-resections, 2 hepatic-arterial-resection,1both) to obtain R0. R0 and R1 resections were achieved in 42(93%) and 3 patients. Clavien-Dindo-Grade3/4 complications were 22.2%(n=10). 8(18%)patients had Post-Hepatectomy-Liver-Failure.Overall operative-mortality was 5/45(11.1%).
Conclusions: Our algorithmic approach for safe optimization by preoperative-biliary-drainage, FLR-augmentation and FLR-functional-assessment have led to a high rate of R0 major liver resection and good outcomes in patients with hilar-blocks.Augmentation of FLR can also increase resectability in borderline resectable cases.

PE-307

A Study on the Efficacy of Single Layer Full Thickness Duct to Mucosa Pancreatojejunostomy Following Pancreatoduodenectomy

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Aims: Pancreatoduodenectomy is the procedure of choice for treating periampullary and pancreatic head malignancy. Mortality is less than 5%. Unfortunately, the morbidity still hovers around 40%. The Achiles heal of pancreatoduodenectomy is the pancreatoenteric anastamosis, the failure of which leads to significant morbidity. Literature is flooded with a plethora of techniques of reconstruction, and the results are variable. In the present study, we have analyzed a technique in which a single layer full thickness duct to mucosa pancreatojejunostomy was used.
Methods: The prospective observational pilot study was performed for a period of 21 months. During the study period, those patients who underwent a pancreaticoduodenectomy (for various conditions) and intra-operatively in whom the duct could be identified were included for the study. In those patients in whom the pancreatic duct could not be identified intraoperatively were excluded.
Results: A total of 25 (Male: Female, 1.25:1) patients were included in the study. 56% of them had an ampullary carcinoma, 36% had pancreatic head cancer and 8% patients had duodenal cancer. 20% patients developed a pancreatoenteric leak, out of which 80% patients had a grade A leak and 20% patient had a grade B leak, with no grade C leak.
Conclusions: This observational pilot study concludes that single layer full thickness interrupted duct to the mucosa, pancreatic-jejunostomy is efficient and is comparable to the other methods of reconstruction described in the literature pertaining to pancreatic specific complications.This technique is least traumatic to the pancreas and has an equal efficacy to the other conventional techniques.

PE-308

Pancreaticodudenectomy after Management of Liver Metastatis for Cancer Pancreas

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Aims: Best treatment option for pancreatic cancer is surgery depending upon the stage of the cancer. Some times we have to downstage the tumor before resection. Extra pancreatic spread must be ruled out. In our case, we came across adenocarcinoma pancreas which was metastasized to the liver but later on after down staging no metastasis was found in the liver and tumor resection of pancreas was done.It was very much new for us as we have hardly seen any case where carcinoma head of pancreas with liver metastasis was downstage and then operated.
Methods: A 50 years old male patient was initially diagnosed with cancer head of pancreas. It was already involved the liver at the time of diagnosis. Three nodules in the liver had char-

acteristic features of metastasis. Oncologist downstaged the tumor and later on he became free from the tumor both in the liver and pancreas. After 6 months he developed features of obstructed jaundice. MRCP confirmed the presence of tumor head of pancreas. There was no liver metastasis. ERCP stenting was done. Biopsy confirmed the pancreas tumor. Surgery was done and specimen was found with tumor free margin.

Results: Patient was discharged with out any complication. He is in the regular follow up for last 6 months.

Conclusions: Adenocarcinoma pancreas is very much aggressive tumor and most of the time it is found to be beyond the resection. This is the one case but need more cases to make a final decision.

PE-309

Endoscopic Papillary Balloon Dilatation for Common Bile Duct Stones Removal During Acute Phase of Cholangitis at Yan Chai Hospital

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Aims: An alternative technique in endoscopic sphincteroplasty is using a large CRE wireguided balloon dilatation as an adjunct to endoscopic sphincterotomy in removing common bile duct (CBD) stone. However, there are few evidence demonstrating the outcomes and complication using CRE balloon dilatation sphincteroplasty during acute phase of cholangitis. This study aims to reveal the outcome of the technique from a single hospital experience.

Methods: A retrospective descriptive study was conducted at the Endoscopy Center of Yan Chai Hospital over a period of 2 years from January 2018 to December 2019. A total of 45 cases was identified where patients, presented with acute cholangitis, had endoscopic papillary balloon dilatation with CRE wireguided balloon during the index admission. Acute cholangitis was defined according to "Tokyo Classication - Cholangitis" (guidelines). Cases with concomitant malignancy and obstruction causes other than common bile duct stones were excluded. The stone clearance rates as defined with occlusive cholangiogram and post ERCP complications were analyzed.

Results: There were 14 (31%) male and 31 (69%) females. Age of the study population ranged from 36-95 years. Stone clearance proven by occlusive cholangiogram in first session was achieved 29/45 (64%) cases. For complication, 6 (13%) cases developed mild papillary bleeding and 3/42 (7%) cases mild pancreatitis. No septic shock was documented.

Conclusions: Endoscopic sphincteroplasty using CRE Wireguided balloon dilatation as an adjunct to endoscopic sphincterotomy is a safe and effective technique for CBD stone removal during acute cholangitis. This procedure can potentially avoid further attempt of ERCP for residual CBD stones.

PE-310

Appropriation of Protocol for Laparoscopic Pancreaticoduodenectomy in Treatment of Periampullary Cancer

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Aims: Laparoscopic pancreaticoduodenectomy (LPD) is considered as a safe and effective procedure in well - selected patients and appropriate surgical technique. Our aim is to evaluate suitability of using protocol for LPD in treatment of periampullary cancer at a single team.

Methods: case series

Results: Indication for LPD included 37 cases with resectable tumors which were classified basing on NCCN. All witness evaluation risk of complications with PREPARE score, ASA and evaluation risk of postoperative pancreatic fistula (POPF) with FRS classification. There were 2 open conversions because of vein resections, accounting for 5.4%. Standard lymphadenectomy was performed in all of 37 cases. In term of PREPARE score, major complications (Clavien – Dindo >= III) were 17.8%, 0% and 0% (5/28, 0/5 and 0/2 cases) in low risk, intermediate risk and high risk group, respectively. All of cases had ASA I or II. POPF happened 11.1% (1/9), 4.1% (1/24) and 50% (1/2) in low risk, intermediate risk and high risk group, respectively. Frozen section was needed for R0 margin. Retrieved lymph nodes was 8 – 18 with 12 lymph nodes in average.

Conclusions: Indication for LPD with resectable tumors is acceptable. ASA I or II is a safe measure to select patient for LPD. FRS classification shows appropriation to evaluate risk of POPF.

PE-311

Clinical Benefit of Frozen Section of Proximal Bile Duct Margin in Perihilar Cholangiocarcinoma

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Aims: R0 resection is the best chance of prolonging the survival of cholangiocarcinoma patients. Frozen section analysis of duct margin often be used to determine bile duct in an attempt to achieve R0 resection, but the clinical benefit remains controversial.

Methods: All 132 patients underwent hepatectomy for perihilar cholangiocarcinoma between January 2006, and December 2019 were analyzed into prospective and retrospective group. Resection status, the accuracy of the frozen section, surgical variables, prognostic factors, survival, and recurrence were evaluated.
Results: R0 status in frozen section group was higher than non-frozen section group but not significant (48.72 vs 35.48 percent) (*P*=0.175). Median survival in both groups were 24 and 17 months that tend to be better in frozen section group although there were no statistically significant difference (*P*=0.25). And one-year survival rates were 65.38 and 67.57 percent. In all populations, the median survival of R0 resection patients was better than R1 resection patients (32 vs 13 months) (*P*=0.001). However, median survival of secondary R0 and R1 resection was not different (*P*=0.43). The median follow up time in frozen section and non frozen section group were 19.12 and 77.67 months.
Conclusions: The clinical benefit of the frozen section of the proximal bile duct margin is still inconclusive. Intraoperative frozen section analysis tends to increase the number of R0 resection and prolong survival, although they were not significant. The frozen section should be done if possible for increasing R0 resection rate that has better survival.

PE-312

How much to Push the Boundaries to Achieve R0 Resection : An Interesting Case Report

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Aims: Tumors of the body and tail of the pancreas are often more aggressive that the tumors of the head and have often undergone metastatic spread to other organs at the time diagnosis. Pancreatic cancer arising in background of Chronic pancreatitis accounts for only 0.1–5% of all cases (Tropical pancreatitis : 8.3%.Hereditary pancreatitis : 40 -55%) Surgery is only indicated in those patients in whom there is no evidence of metastatic spread. Surgery is often not possible in cancers of the body and tail of the pancreas if the tumor invades celiac artery.
Methods: 56 year old female with chief complaints of pain in left upper quadrant of abdomen since 2 months radiating to back and occasional vomiting on and off was evaluated. CECT abdomen revealed a mass arising from distal pancreas infiltrating the stomach, splenic hilum, left kidney, splenic flexure and the jejunal loop (LPJ loop) and entire pancreas atrophic and completely replaced by fat.
Results: This patient underwent En Bloc resection of tumor with : 1.Distal Pancreatectomy with jejunal loop (LPJ) resection 2.Splenectomy 3.Left nephrectomy 4.Total gastrectomy 5.Segmental Colectomy with reconstruction by Esophagojejunostomy, Jejunojejunostomy and Colocolic anastomosis.
Conclusions: The infrequent occurrence of tumor in the distal gland and advanced tumor stage at the time of diagnosis have both combined to produce therapeutic nihilism/dilemma in the minds of many surgeons. Multi-organ resection (En bloc resection with distal pancreatectomy, gastrectomy, splenectomy) should be attempted with the intent of achieving R0 status inspite of the complexity of surgery.

PE-313

Preoperative Volume Rendering Can Pervent Intraoperative Surprises and Post Operative Catastrophe for Pancreaticodudenectomy

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Aims: Pancreatic adenocarcinoma is one the leading cause of cancer related deaths all over the world. Pancreaticoduodenectomy is a complex surgical procedure used to resect tumours of the head of the pancreas, distal common bile duct, and duodenum. There is considerable anatomic variability in the arterial supply to this region and preoperative knowledge of the variants is important. Aim : The purpose of this study was to determine the benefit of preoperative Volume Rendering in predicting the arterial variants that cross the anticipated surgical resection plane in pancreaticoduodenectomy.
Methods: Retrospective analysis of prospectively maintained database of 137 patients who underwent pancreaticoduodenectomy with preoperative CT abdomen with 64-MDCT over a period of 3 years. 3D Volume Rendering, Maximum Intensity Projection and Multiplanar Reconstruction were used for evaluation to determine anatomical variation.
Results: Out of 137 patients, 27 patients (20%) had replaced Right Hepatic artery, 14 patients (10%) had Accessory Right Hepatic artery, 1 patient (0.73%) with rare variants where common hepatic artery and superior mesenteric artery were arising from the common trunk, 1 patient (0.73%) Common Hepatic artery arising from Superior Mesenteric artery and 1 patient (0.73%) with accessory right and left hepatic artery..
Conclusions: Preoperative three dimensionally constructed MDCT images have been found to prevent the intraoperative surprises and post operative catastrophic complications faced by the surgeons due to aberrant vascular anatomy in pancreaticodudenectomy. The study highlights the incidence of arterial variations encountered in patients of pancreatic malignancy who underwent pancreaticoduodenenctomy.

PE-314

Major Hepatectomy for Gall Bladder Cancer with Jaundice – A Formidable Procedure?

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Aims: Jaundice in gall bladder cancer (GBC) is a sign of advanced disease, inoperability and poor prognosis. Resection with curative intent requires extended right hepatectomy (ERH) after preoperative biliary drainage (PBD) and portal vein embolization (PVE). We report our results of surgical resections in GBC with jaundice.

Methods: Retrospective analysis of a prospective database in a tertiary center in India (October 2009 - August 2019).

Results: 196 (21%) of 914 patients with GBC had jaundice; 7/196 died in hospital (3 PTBD bleed, 3 cholangitis and 1 aspiration). 74/196 had metastasis and 122/196 had locally advanced disease. 167/196 had biliary drainage (endoscopic 82, PTBD 85; definitive palliative 127, PBD 40). Major complications of biliary drainage were bleed 4, bile leak 2, stent block 3, pancreatitis 1 and perforation 1. 48/122 were operated but only 17/48 underwent resection (extended cholecystectomy + Common bile duct excision 12, ERH 2, central hepatectomy 1, Hepatopancreatoduodenectomy 2) after PBD (no PVE). 33/122 were considered for ERH after PBD and PVE. Out of 33, 8 developed metastasis, 8 developed locally advanced unresectable disease between PBD and PVE and 8 didn't want to undergo any further management. 9/33 underwent PVE after PBD but none underwent resection - 2 disease progressed, 2 inadequate hypertrophy, 1 procedure abandoned due to cardiac event and 4 metastasis (3 at laparotomy, 1 at laparoscopy). 16/33 were operated but none was resected.

Conclusions: The plan of ERH after PBD and PVE in patients with GBC and jaundice could not be executed for various reasons.

Others

PE-315

Effectiveness of Transcutaneous Bilirubin Measurement in Managing Neonatal Jaundice

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Aims: Neonatal jaundice is a common cause of concern in immediate newborn period for parents. Obtaining blood bilirubin samples is a painful procedure; it predisposes the baby to infections and requires skilled health personnel. Moreover, laboratory tests are costly and time consuming, leading to unnecessary delays in commencing phototherapy and discharge from hospital. Transcutaneous bilirubinometer has been in use since 2017 as screening tool in postnatal wards.

Methods: Ninety newborns with jaundice were referred to the postnatal ward of Dornod Medical center from 2017 august to 2019 December. For patients, we used breastfeeding, intravenous fluid and phototherapy. Before and after the treatment, transcutaneous bilirubinometer were cheked.

Results: From the 210 participants of the age (day) 1-35 (mean 17), male were 123 (58.9%), female were 87 (41.1%), body mass were 1.1-4.9 kg (mean 3.7). Phototheraphy and nursing care had significantly decreased bilirubin level from 129.0-469.0 (mean 295.1) mmol/l to 97-298 (mean 173.4) mmol/l (T test, $P \leq 0.05$).

Conclusions: In conclusion, specially of transcutaneous bilirubin measurement is safe and effective in neonatal jaundice.

Keywords: Transcutaneous Bilirubin Measurement, Neonatal jaundice

PE-316

Remained Unsatisfied Hepatitis A Immunity among Young Individuals in South Korea

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Aims: The incidence of hepatitis A virus (HAV) infection has recently increased in susceptible populations in South Korea. However, no data is available on the immunity to HAV in South Korea from 2015. We aimed to evaluate the HAV immunity level by age or gender over time from 2016 to 2019 by evaluating anti-HAV IgG antibody-positive rates

Methods: The data of 7,245 subjects who underwent HAV IgG antibody testing at Inha university hospital in South Korea from January 2016 to October 2019 were analyzed. Age-adjusted prevalences of anti-HAV IgG-positivity were assessed for each year, and the immunity to HAV was analyzed for the following age categories; <10, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years.

Results: Age-adjusted overall anti-HAV IgG antibody-positive rates tended to increase as follows; 71.1% in 2016, 74.6% in 2017, 73.2 in 2018, and 77.1% in 2019. Anti-HAV IgG antibody-positive rates by age group were lowest for individuals in their 30s (42.3%), followed by 20s (49.9%), 10s (56.6%), and

40s (73.4%). Positive rates increased significantly with time for those in their 10s and 20s, respectively (all p-values <0.05), but decreased significantly for those in their 40s (*P*=0.001). However, positive rates remained constant throughout the study period for those in their 30s (*P*=0.677).

Conclusions: The current HAV vaccination program appears to be working in 10 to 29 years olds although their immunity to HAV is still unsatisfactory. More efforts must be done to increase HAV immunity among 30 to 49 year olds.

Keywords: Hepatitis A virus, Immunoglobulin G, Positive rate, Immunity

PE-317

Association of Coffee and Caffeine Consumption with Fatty Liver Disease, Non-Alcoholic Steatohepatitis, and Degree of Hepatic Fibrosis

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Aims: Coffee caffeine consumption (CC) is associated with reduced hepatic fibrosis in patients with chronic liver diseases, such as hepatitis C. The association of CC with nonalcoholic fatty liver disease (NAFLD) has not been established. The aim of this study was to correlate CC with the prevalence and severity of NAFLD

Methods: Patients involved in a previously published NAFLD prevalence study, as well as additional NASH patients identified in the Hepatology Center of Almaty, were queried about their caffeine intake. A validated questionnaire for CC was utilized to assess for a relationship between caffeine and four groups: ultrasound negative (controls), bland steatosis/not-NASH, NASH stage 0-1, and NASH stage 2-4. A total of 306 patients responded to the CC questionnaire. Average milligrams of total caffeine/coffee CC per day in controls, bland steatosis/not-NASH, NASH stage 0-1, and NASH stage 2-4 were 307/228, 229/160, 351/255, and 252/152, respectively. When comparing patients with bland steatosis/not-NASH to those with NASH stage 0-1, there was a significant difference in CC between the two groups (*P*=0.005). Additionally, when comparing patients with NASH stage 0-1 to those with NASH stage 2-4, there was a significant difference in coffee CC (*P*=0.016).

Results: Spearman's rank correlation analysis further supported a negative relationship between coffee CC and hepatic fibrosis (r = -0.215; *P*=0.035).

Conclusions: Coffee CC is associated with a significant reduction in risk of fibrosis among NASH patients

Keywords: Fatty liver disease, Nonalcoholic steatohepatitis, Hepatic fibrosis, Caffeine

PE-318

Essential Amino Acid Supplementation Decreases Liver Damage Induced by Chronic Ethanol Consumption in Rats

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Aims: The liver sustains the greatest damage from ethanol (EtOH) abuse. EtOH and its metabolites impair hepatocyte metabolism, causing intracellular accumulation of proteins and lipids and increasing radical oxygen species production. These processes are toxic to the mitochondrial respiratory chain and to mitochondrial DNA. It has recently shown that supplementating the diet of rodents with an essential amino acid-enriched mixture (EAAem) significantly increases mitochondrial mass and number in cardiac and skeletal muscles and improves mitochondrial function in aged animals

Methods: Thus, in this study we sought to test whether EAAem supplementation could reduce EtOH-induced liver damage. Groups of adult male Wistar rats were fed a standard diet and water ad libitum (the control group), drinking water with 20 percent EtOH (the EtOH group), or drinking water with 20 percent EtOH and EAAem supplementation (1.5 g/kg/day) (the EtOH+EAAem group) for 2 months. The blood EtOH concentration was measured, and markers for fat (Oil-Red-O), mitochondria (Grp75, Cyt-c-ox), endoplasmic reticulum (Grp78), and inflammation (Heme Oxigenase 1, iNOS, and peroxisomes) were analyzed in the liver of animals in the various experimental groups

Results: EAAem supplementation in EtOH-drinking rats ameliorated EtOH-induced changes in liver structure by limiting steatosis, recruiting more mitochondria and peroxisomes mainly to perivenous hepatocytes, stimulating or restoring antioxidant markers, limiting the expression of inflammatory processes, and reducing ER stress

Conclusions: Taken together, these results suggest that EAAem supplementation may represent a promising strategy to prevent and treat EtOH-induced liver damage

Keywords: Essential amino acid, Ethanol, Radical oxygen, Antioxidant markers

PE-319

Portal Vein Thrombosis after Hepatectomy

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Aims: This study evaluated the incidence, risk factors, and clinical outcomes of PVT after hepatectomy.

Methods: The preoperative and postoperative clinical characteristics of patients who underwent hepatectomy were retrospectively analyzed. A total of 208 patients were reviewed. The incidence of PVT after hepatectomy was 9.1% (n=19), includ-

ing main portal vein (MPV) thrombosis (n=7) and peripheral portal vein (PPV) thrombosis (n=12). Patients with MPV thrombosis had a significantly higher incidence of right hepatectomy (P<0.001), larger resection volume (P=0.003), and longer operation time (P=0.021) than patients without PVT (n=189)

Results: Multivariate analysis identified right hepatectomy as a significant independent risk factor for MPV thrombosis (odds ratio 108.9; P<0.001). Patients with PPV thrombosis had a significantly longer duration of Pringle maneuver than patients without PVT (P=0.002). Among patients who underwent right hepatectomy, those with PVT (n=6) had a significantly lower early liver regeneration rate than those without PVT (n=13; P=0.040), and those with PVT had deterioration of liver function on postoperative day 7. In all patients with MPV thrombosis who received anticoagulation therapy, PVT subsequently resolved.

Conclusions: Postoperative PVT after hepatectomy is not rare. It is closely related to delayed recovery of liver function and delayed liver regeneration.

Keywords: Portal vein, Hepatectomy, Thrombosis, Peripheral portal vein

PE-320

Chronic Renal Dysfunction Following Liver Transplantation

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Aims: With most of the immunosuppressive protocols consisting of calcineurin inhibitors (CI), nephrotoxicity has become a major long-term complication often compromising outcome.

Methods: In a single-center retrospective study, we reviewed 173 liver transplantations to identify variables indicative for the occurrence of chronic renal dysfunction (CRD) (defined as > or = 1 episode of serum creatinine increase > or = 1.8 mg/dL > or = 2 wk). Chronic renal dysfunction was found in 20 (11.7%) of all transplants [12 (7%) early (after 3-12 months), 8 (4.7%) late-onset (> 12 months)]. Compared to 5-/10-yr survival rates in non-CRD transplants (84/74%) survival was significantly decreased in early (66/46%), but unchanged in late-onset CRD (98/86%). Rates of alcoholic cirrhosis and prior renal dysfunction were significantly increased in patients with CRD. In a multivariate logistic regression analysis, only cyclosporine A (CyA) as immunosuppression remained an independent risk factor. No correlations to age, gender, rejection/retransplantation or diabetes were found. Surprisingly, renal function (creatinine) showed no difference between patients on CI monotherapy (FK/CyA) compared to those who had mycophenolate mofetil (MMF) added.

Results: In liver transplantation, early onset CRD significantly compromises survival. CyA-based immunosuppression appears to have a stronger impact than FK.

Conclusions: The fact that patients with long-term severe chronic renal dysfunction failed to improve under MMF rescue therapy emphasizes the importance of new diagnostic strategies to earlier identify at-risk patients.

Keywords: Chronic renal dysfunction, Liver transplantation, Cirrhosis, Retransplantation

PE-321

Vitamin D Deficiency in Chronic Liver Disease patients

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Aims: One of the most nutritional deficiency in the world is the deficiency of 25-hydroxyvitamin D [25(OH)D]. Study assessed that there are more than 1 billion people living in the world that has serum 25(OH)D<20 ng/ml deficiency. Vitamin D deficiency is widespread in individuals irrespective of their age, gender, race and geography. Deficiency of 25(OH)D not only causes children's arthritis but to a range of common chronic diseases in adulthood such as diabetes, cancer, infectious diseases, cardiovascular disease, and autoimmune disease, this continuous to be a major public health problem in the world.

Methods: Study participants were 102 chronic liver disease over the age of 18 from the citizens of "Choibalsan" city, "Dornod" province, who were referred to the outpatient of Dornod Medical center, Dornod, Mongolia. Overnight fasting blood samples were collected. All patients had tests for blood 25(OH)D were measured by ELISA and 28 patients who took 6 questionnaire tests.

Results: Of all patients, 66 were men (68.1%) and 34 were women (31.9%). The mean age was 46 (between 18 and 89 years). There were 55 patients with cirrhosis (54%), and were 47 patients with chronic hepatitis B and C in the study group. 94 (92%) participants had 25(OH)D<20 ng/ml deficiency. Age and season had no correlation on the 25(OH)D level. From the results of the questionnaire test we can see that 5 have efficient 25(OH)D, 17 had the possibility of deficiency of 25(OH)D, and 6 had to reapply for the tests but these participants had 25(OH)D<10 ng/ml and this has no relevance on the level 25(OH)D (Pearson r=0.07, P=0.5).

Conclusions: In conclusion, our pilot results show that patients as in 92% have 25(OH)D deficiency.

Keywords: Chronic Liver Disease, Nutritional deficiency, Vitamin D

PE-322

Oral Administration of Hydrolysed Casein Based Supplements on Chronic Liver Disease Patients

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Aims: Medical conditions that may lead to malnutrition include: gastrointestinal disease, chronic kidney disease, cardiovascular disease, after surgery and infections such as cancer. Malnutrition - hypoalbuminemia can present edema, appetite loss, muscle weakness, ascites, plural effusion and several other complications. Regardless of its cause, hypoalbuminemia has strong predictive value on mortality and morbidity.

Methods: Thirty adult patients with liver cirrhosis Child Pugh classification B and C were referred to the outpatient of Dornod Medical center, Dornod, Mongolia. Appeton Wellness Recovery is a breakthrough nutritional formulation that is specially formulated with hydrolyzed casein and calcium 198 mg, potassium 270 mg etc. For patients, we dissolved Appeton Wellness Recovery (55g) into 210 ml of warm water to prepare a 250 ml drink during the period of 30 days. Before and after the treatment, overnight fasting blood samples were collected. All patients had tests for blood chemistries ALT (0-45 u/l), AST (0-35 u/l), total protein (66.0-83.0 g/l), albumin (35.0-50.0 g/l), potassium (3-3.5 mg/dl), calcium (8.5-10.2 mg/dl), and abdominal ultrasound.

Results: Oral supplement had significantly increased total level of protein from 70,34±6.8 to 75.25±6.2 ($P<7.1*10^{-16}$), albumin from 33.38± 4.61 to 38.37±4.62 ($P<4.6*10^{-11}$), potassium from 3.5±1.0 to 4.7±0.7 ($P<1.631*10^{-08}$), calcium from 8±1.1 to 9.2±1.6 (0.007). Assessments of biochemical parameters of oral supplement before and after the examination are shown in table 1. Eight patients had ascites, and after oral supplement, in two cases ascites were removed, in four cases ascites fluid were decreased, and in two cases they were not increased.

Table 1.

	Before	After	*P* value (t test)
Total protein (g/l)	Mean 70,34±6.8	Mean 75.25±6.2	$7.1*10^{-16}$
	Min 56	Min 60.3	
	Max 80.9	Max 85.4	
Albumin (g/l)	Mean 33.38±4.61	Mean 38.37±4.62	$4.6*10^{-11}$
	Min 25.8	Min 29	
	Max 39.3	Max 46.4	
Calcium (mg/dl)	Mean 8±1.1	Mean 9.2±1.6	0.007
	Min 5.3	Min 7.8	
	Max 10.8	Max 10.9	
Potassuim (mg/dl)	Mean 3.5±1.0	Mean 4.7±0.7	$1.631*10^{-08}$
	Min 1.2	Min 3.4	
	Max 5.5	Max 6.0	

Conclusions: In conclusion, specially formulated with hydrolyzed casein supplement is safe and effective in improving serum protein, albumin, potassium, calcium in patients with liver cirrhosis.

Keywords: Malnutrition, Hydrolysed Casein Based Supplements

PE-323

The Effect of Selenium on the Immunity of Patients after Partial Liver Resection – A Pilot Study

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Aims: The liver is enriched in several innate and adaptive immune cells. The immunity of liver is very important. The selenium is known as the trace element that is associated with inflammatory, immune cell function and immune-related disease and cancer. We investigate the effect of selenium on the immunity of patients after liver resection.

Methods: We collected prospectively the count of T cell and B cell at preoperative (POD) day before and POD one month after liver resection. Thirty-one patients were enrolled from Oct. 2018 to Aug. 2019. We categorized the patients into two group based on taking selenium or not. We investigated the immune cell count and the difference of immune cell counts was compared between the day before surgery and the month after surgery.

Results: Eight patients (Group 1) did not take selenium and 23 patients (group 2) took. The frequency and count of preoperative T and B cell and POD T cell were similar between both groups. However, the frequency and count of B cell were higher in group 2 [136 (61.6-339.5), 9.3 (4-22.6)] than in group 1 [74 (6-264), 6.4 (0.6-12.3)]. Another inflammatory marker, neutrophil to lymphocyte ratio was rapidly decreased in group 2 (preop 2.31, POD 5days 8.38, POD 1month 2.28) than group 1 (2.40,9.89,10.11).

Conclusions: B cell and the change of inflammatory marker was reported as a good predictive marker for liver regeneration and survival after liver resection. Although we need large-scale and long-term results, the selenium may increase survival by inducing improvement of immune system.

PE-324

Critical Appraisal for Prevalence of Malnutrition in Chronic Liver Disease

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Aims: The prevalence of malnutrition in patients with chronic liver diseases varies widely. This big difference is related to various diagnostic tools, mixed etiologies, and different disease severity in different studies. This study aimed to critically appraise

the prevalence of malnutrition according to various diagnostic tools and proportion of severity used in previous studies

Methods: A literature review was conducted for a total of 16 studies published between 1980 and 2020 regarding malnutrition in patients with chronic liver disease. Most of the analyzed studies were conducted before 2010, and only a few studies were conducted after 2010.

Results: The prevalence of malnutrition was 36.4% (10–80.3%) in all patients with liver disease, 39.9% (13.3–80.3%) in compensated disease, and 44.1% (26.7–93.6%) in decompensated cirrhosis. It was 38.2% and 23.7% in alcoholism-related and hepatitis C virus (HCV)-related diseases, respectively. Malnutrition also largely depended on the judgement tool. Malnutrition prevalence according to the diagnostic tool was approximately 30–85% for SGA, 30.8–78.5% for the anthropometric approach, and 21–80.3% for the clinical judgment. It became similar over time. Malnutrition prevalence in studies published prior to 2000 ranged between 13.3% and 85% (mean, 37.6%), whereas that in studies published after 2000 ranged between 13.3% and 78.5% (mean, 35.2%).

Conclusions: Malnutrition prevalence largely depends on the diagnostic tool and proportion of disease severity in the target population

Keywords: Malnutrition, Chronic liver disease

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ISALPDC-01

Interaction between CD40L and CD40 Mediates Hepatic Exosomal Delivery to Kupffer Cells in Alcoholic Liver Disease

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Aims: Cluster of differentiation 40 (CD40) is a costimulatory molecule on antigen presenting cells including macrophages. An interesting study reported that extracellular vesicles (EVs) containing CD40L promote macrophage activation through CD40, thereby accelerating alcoholic liver diseases (ALD) in mice and patients. However, other effects of CD40L-expressing EV on Kupffer cells (KCs) have not been investigated clearly. Here, we explored CD40-mediated delivery of hepatic exosomes and its effects on KCs in acute alcoholic liver injury.

Methods: To induce acute liver injury, binge ethanol drinking (4 g/kg, 40% ethanol) was performed by oral gavage into wild-type (WT) and CD40 knockout (KO) mice. Interleukin-17A (IL-17A) positive cells were analyzed by flow cytometry. Isolated hepatocytes, KCs and DiI-stained exosomes, neutralizing antibody and dynasore were used for in vitro experiments.

Results: Although the number of exosomes and mRNA expression of CD40L in hepatocytes were significantly increased by ethanol exposure, protein levels of CD40L in ethanol-induced exosomes were similar with controls, reflecting proportional increase of CD40L to the numbers of exosomes. However, freshly isolated KCs from ethanol-fed WT mice exhibited increased expression of CD40 (protein receptor of CD40L). In vitro, ethanol-induced exosomes increased CD40 expression in KCs by a TLR3-dependent manner. Moreover, DiI-stained exosomes were successfully delivered to WT KCs, but not in CD40-deficient KCs. In addition, treatments with neutralizing antibody of CD40 and dynamin inhibitor (dynasore) decreased internalization of hepatic exosomes into KCs, thereby reducing IL-1β production in KCs. Furthermore, binge ethanol drinking increased IL-17A production of γδ T cells in WT mice but not in CD40 KO mice.

Conclusions: Alcohol-induced hepatic exosomes could be delivered to KCs through a CD40L/CD40-dependent endocytic uptake and they stimulate IL-1β expression in KCs, subsequently leading to IL-17A production in γδ T cells in ALD. Thus, CD40L/CD40 axis could be a potential target to reduce IL-17A production in ALD.

Keywords: CD40, Kupffer cells, Extracellular vesicles, Alcoholic liver disease

ISALPDC-02

The Effect of Intestinal Flora Modification on Alcoholic Liver Injury in Obese KK-A^{y} Mice

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Aims: Alcoholic hepatitis occurs with background of chronic drinking for many years and a history of recent excessive alcohol consumption, carrying a poor short-term prognosis. Recently, the overlap of metabolic syndrome and alcoholic liver disease is increasing in industrialized countries; however, the treatment of alcoholic hepatitis has not been established. Here we investigated the effect of intestinal flora modification using rifaximin (RFX), non-absorbed antibiotic, on liver injury following ethanol (EtOH)-feeding plus binge in obese KK-A^{y} mice.

Methods: Female 8-week-old KK-A^{y} mice were fed a liquid diet containing 5% EtOH or a pair-fed control diet for 10 days. Some mice were given RFX (0.1 g/L) during the feeding period. At day 11, mice were sacrificed. Some mice received a single gavage of EtOH (4g/kg BW) or isocaloric dextrin maltose as controls, and then be sacrificed 6 h later. Some mice were euthanized without EtOH binge for collecting of small intestinal contents. The net amount of intestinal microbiota was quantified using aerobic and anaerobic conventional culturing techniques, and qualitatively evaluation analyzed by 16S rRNA sequencing.

Results: Livers from EtOH group showed severe steatohepatitis; which were ameliorated by RFX. The treatment with RFX significantly prevented increase of oxidative stress and inflammatory cytokines in mice given EtOH-feeding plus binge. Portal endotoxin was increased after EtOH-feeding plus binge, and RFX significantly prevented the increase. Overexpression of hepatic mRNA levels for cell differentiation (CD)-14 and toll-like receptor (TLR)-2 and -4 following EtOH-feeding plus binge was also significantly prevented by RFX. The net amount of small intestinal bacteria was significantly increased after chronic EtOH feeding as compared to controls; RFX had no effect on the net amount of viable bacterial cells increased by chronic EtOH feeding. In the profile of small intestinal microbiota in the order level, EtOH-feeding dramatically increased the relative abundance of the Erysipelotrichales. RFX drastically reversed the Erysipelotrichales and enriched the Bacteroidales.

Conclusions: EtOH-induced intestinal microbial changes are one of the key events in the pathogenesis of alcoholic liver disease. Intestinal flora modification has a potential to prevent alcoholic liver injury comorbid with obese.

Keywords: PAMPs, Microbiota, Alcoholic hepatitis, Rifaximin, Oxidative stress

ISALPDC-03

CYP2E1 Regulation of Ethanol-Induced Intestinal miRNAs in Liver Injury

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Aims: While binge alcohol-induced gut leakage has been studied extensively in the context of reactive oxygen species (ROS)-mediated signaling, it was recently revealed that post-transcriptional regulation plays an essential role as well. Ethanol-inducible cytochrome P450-2E1 (CYP2E1) is a key enzyme in ethanol metabolism, and promotes alcohol-induced hepatic steatosis and inflammatory liver disease at least in part by mediating changes in intestinal permeability. For instance, gut leakage and elevated intestinal permeability to endotoxins have been shown to be regulated by enhancing CYP2E1 mRNA and CYP2E1 protein levels. Although it is understood that ethanol promotes CYP2E1 induction and activation, the mechanisms by which CYP2E1 expression is regulated in the context of intestinal damage remain poorly defined. Specific miRNAs, including miR-132, miR-212, miR-378, and miR-552, have been shown to repress the expression of CYP2E1, supporting our hypothesis that these miRNAs contribute to ethanol-induced intestinal injury.

Methods: We utilized in vitro cell model and in vivo mouse model to study intestinal and hepatic cell death and growth after modulation of specific miRNA levels directly or indirectly by depletion or overexpression of microRNA-binding proteins.

Results: We made two key observations that CYP2E1 expression is regulated post-transcriptionally through miRNA-mediated degradation: 1) the RNA-binding protein AUF1 binds mature miRNAs, including CYP2E1-targeting miRNAs, and this binding modulates the degradation of corresponding target mRNAs; 2) the Serine/Threonine kinase MST1 mediates oxidative stress-induced phosphorylation of RNA-binding proteins such as AUF1. This finding suggests that ROS-mediated signaling modulates AUF1/miRNA interaction through MST1-mediated phosphorylation.

Conclusions: Thus, our study demonstrated the critical functions of AUF1 phosphorylation by MST1 in the decay of miRNAs targeting CYP2E1, the stabilization of CYP2E1 mRNA in the presence of ethanol, and subsequent injury of intestine and liver.

Keywords: MiRNAs, RNA-binding protein, CYP2E1, MRNA decay

ISALPDC-04

Chronic Alcohol Consumption Alters the Phenotype of F4/80+CD11b+ Bone Marrow Cells by Neuro-Metabolic Signaling Pathway

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Aims: Alcohol-medicated metabolic and immunologic stress is generated not only in the liver, but also adipose tissue, gut and bone marrow (BM). However, the metabolic and immunologic effects of alcohol on BM have not been investigated. Here, we investigated that novel neuro-metabolic signaling pathway changed the phenotype of BM-derived macrophages and its detrimental contribution to alcoholic liver disease.

Methods: C57BL/6J wild type (WT), and natural killer (NK) cell-specific metabotropic glutamate receptor 5 (mGluR5) knock-out (mGluR5△NK) mice were fed with liquid ethanol or isocaloric diet for 8 weeks. The phenotypic changes of immune cells in BM, blood and liver were assessed by flow cytometry. In vitro, BM stromal cells (BMSCs), NK cells and macrophages were treated with ethanol, glutamate or interferon (IFN)-γ. In addition, western blotting, immunostaining, and qRT-PCR analysis were performed.

Results: In immunostaining, alcohol dehydrogenase (ADH) 1 was detected around sinusoids of BM in EtOH-fed mice. Additionally, we found that the mRNA expression of Adh1 and Aldh2 was highest in leptin receptor-positive (LepR+) BMSC by analyzing the public data. In vitro, PCR analysis exhibited increased expression of cystine/glutamate transporter xCT in EtOH-treated BMSC, thereby leading to glutamate secretion into BM. Interestingly, IFN-γ production was increased in BM NK cells of EtOH-fed WT mice. Moreover, chronic alcohol consumption decreased the expression of CX3CR1 but increased the expression of inflammatory mediators in F4/80+CD11b+ BM cells in an IFN-γ-dependent way, leading to egression of pro-inflammatory F4/80+CD11b+ cells from BM and migration to the liver to exacerbate alcoholic liver injury. However, all these findings were not observed in mGluR5△NK mice.

Conclusions: In BM, glutamate excretion by alcohol metabolism in BMSC stimulated mGluR5-expressing NK cells to produce IFN-γ, polarizing F4/80+CD11b+ BM cells into pro-inflammatory cells and aggravating alcoholic liver injury. Thus, mGluR5 in NK cells might be a potential target for alcoholic liver disease.

Keywords: Alcohol, Bone marrow, Bone marrow stromal cell, NK cell, Macrophage, Glutamate||IFN-γ

ISALPDC-05

Catecholamine Signaling Pathway Protects Alcoholic Fatty Liver by Inducing Growth Differentiation Factor 15

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Aims: Growth differentiation factor 15 (GDF15), a novel neu-

rometabolic regulator, is highly expressed in various liver diseases. However, the underlying mechanism and its role on alcoholic steatosis have not been fully understood. Here, we suggest that chronic alcohol consumption increases GDF15 expression in hepatic β2-adrenergic receptor (ADRB2)- and cytochrome P450 2E1 (CYP2E1)-dependent manners to protect the liver from the development of alcoholic hepatic steatosis.

Methods: C57BL/6J wild type (WT), hepatocyte-specific GDF15 knockout (GDF15ΔHEP) and ADRB1/2 double KO (DKO) mice were fed with isocaloric (Pair) or 4.5 % of ethanol containing diet (EtOH) for 8 weeks. Isolated mouse and human hepatocytes were treated with different doses of ethanol or β-agonist. qRT-PCR, western blot and immunostaining were performed, and RNA-sequencing data of mouse samples were analyzed.

Results: In isolated mouse hepatocytes, ethanol treatment increased GDF15 expression in dose- and CYP2E1-mediated oxidative stress-dependent manners. In vivo, chronic ethanol consumption enhanced the expression of CYP2E1 and GDF15 that was co-localized around central veins. RNA-sequencing and western blot analysis revealed that hepatic Adrb2 expression and protein kinase A (PKA) activation were increased in EtOH-fed mice compared to Pair-fed mice. Interestingly, β-agonist treatment dose-dependently induced GDF15 expression in isolated mouse hepatocytes. In vivo, GDF15ΔHEP or ADRB1/2 DKO mice showed increased liver damage and fat accumulation compared to those of WT mice after chronic ethanol consumption. Consistently, in isolated human hepatocytes, ethanol treatment induced GDF15 expression in a CYP2E1-dependent manner, and increased expression of CYP2E1 and GDF15 and PKA signaling were found in patients with alcoholic liver disease.

Conclusions: Our findings suggest that ADRB2/CYP2E1/GDF15 axis plays important roles to protect against hepatic fat accumulation and damage by chronic alcohol consumption. Therefore, the regulation of neurometabolic pathway between ADRB2 and GDF15 could be a potential therapeutic target of alcoholic hepatic steatosis.

Keywords: Alcoholic fatty liver, Catecholamine, β2-adrenergic receptor, Cytochrome P450 2E1, Growth Differentiation Factor 15

ISALPDC-06

The Evolution of Living Donor Liver Transplantation for Alcoholic Liver Cirrhosis in a High Volume Center: The Eastern Perspective

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Aims: Alcoholic liver disease (ALD) has been a growing indication for living donor liver transplantation (LDLT) in Asia but certain medical, ethical and psycho-social issues question its appropriateness. Reports on long-term outcomes of LDLT for ALD are also scarce and so our aim was to report our center's experience for the past 15 years and how LDLT has evolved to be the treatment of choice for end-stage liver disease secondary to ALD in a high volume center.

Methods: A total of 1,384 consecutive LDLT was performed from January 2003 to August 2016 at Kaohsiung Chang Gung Memorial Hospital, and 87 patients had a pre-operative diagnosis of alcoholic liver disease (ALD) with or without hepatocellular carcinoma (HCC). This group was systematically matched with non-ALD (NALD) patients in a ratio of 1:2 using equiprobability method. Overall patient survival was compared using Kaplan-Meier analysis, and incidences of post-transplant De novo malignancy and alcohol relapse were described.

Results: Patient demographics were comparable, as well as preoperative and intra-operative data. Of the 87 patients in the ALD group, 26 (30%) had concomitant HCC. Median follow-up for this study was 50 months. Overall patient survival at 1, 3 and 5 years for ALD were 98%, 97% and 92% respectively, while the NALD group had similar survival rates (*P*=0.282). The rate for De novo malignancy was 6% while that for recidivism was 7% despite only 76% of the patients meeting the 6 months abstinence rule.

Conclusions: Results from our center show that LDLT for ALD has comparable short and longterm outcomes when compared to NALD, and the close relationship between donor and recipient seems to positively affect alcohol relapse rate and patient compliance to medication.

Keywords: Liver Transplant, Alcoholic Liver Disease, Outcomes after LDLT

ISALPDC-07

Incidence Trends in Liver Cancer by Histological Subtype in the Philippines, 2003-2012: A Population-Based Study

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Aims: Liver cancer (LC) is currently the sixth most common type of cancer with an increasing incidence in the Philippines. The study aimed to analyze time trends in LC incidence over the 10-year period. Herein, we provide model-based estimates of limited time LC cases by histological subtype from year 2003-2012.

Methods: Data for calculating LC incidence rates in 2003-2012 were obtained from the population-based Department of Health- Rizal Cancer Registry. Joinpoint regression was used to analyze trends and estimate annual percentage change (APC) with 95% confidence intervals (CI) on LC incidence by histological subtypes, time- period, sex, and calculated incidence counts, rates per 100,000 person-years.

Results: LC incidence shows increasing average annual rates in the past 10 years, observed rates overall (10.94), men (15.53)

and women (6.39). Among LC histological subtype in carcinoma, hepatocellular contribute highest rates, in men (15.19) and women (5.23), followed by unspecified carcinoma, in men (1.73) and women (0.78). Incidence trend declines in both sexes, and increases thereafter, in men in 2007 (APC: 16.82, 95% CI: -5.70; 44.80) and women in 2008 (APC: 19.95, 95% CI: -21.7; 83.7). The highest increase in average annual percentage change (AAPC) among LC histological subtype were observe to hepatoblastoma, in men (AAPC: 4.91, 95% CI: -8.90; 20.80) and women (AAPC: 16.33, 95% CI: -0.60; 34.50). Along with cholangiocarcinoma shows an increasing AAPC, in men (AAPC: 3.68, 95% CI: -7.90; 16.70) and women (AAPC: 0.15, 95% CI: -14.1; 16.7).

Conclusions: The study revealed from 2003-2012, LC incidence trends by histological subtype were consistently increased. Among LC histological subtypes, an increase in incidence was observed in hepatocellular carcinoma for the past 10-year period. Targeted screening and treatment in hepatitis B virus (HBV) and hepatitis C virus (HCV), treatment of diabetes, and primary prevention of obesity, will be the possible solutions in reducing the increasing LC incidence.

Keywords: Incidence trend, Liver Cancer, Histologic subtypes, Population-based study

ISALPDC-08

Percutaneous Transhepatic Cholangiogaphy in the Diagnosis of the Common Bile Duct Diseases Complicated by Mechanical Jaundice

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Aims: The aim of the study is evaluation of the efficacy of percutaneous transhepatic cholangiography (PTCG) in the diagnosis of the common bile duct diseases complicated by mechanical jaundice.

Methods: In the period 2011-2017, 88 patients with the common bile duct diseases were hospitalized: "endoscopically complex forms" of choledocholithiasis - 6 (6,8%), strictures of the common bile duct - 2 (2,3%), strictures of biliodigestive anastomosis - 7 (8%) and cholangiocarcinomas - 73 (82.9%) of different localization according to the Bismuth-Corlette classification. PTCG were performed on the angiograph "Integris Allura 12" ("Philips", The Netherlands).

Results: PTCG was performed in 82 (93.1%) patients. Re PTCG made 20 (22.7%) patients. The diameters of segmental and lobular hepatic ducts ranged from 4 to 12 mm and from 6 to 14 mm, respectively (on average 7.8 mm and 9.6 mm, respectively), and the common bile duct - from 8 to 21 mm (average 13.8 mm). Contrasting with only one part of the liver was noted in 11 (13.4%) patients. The nature and level of obstruction set in 80 (97.5%). The proximal biliary block was detected in 59 (71.9%) patients, distal in 23 (28%). Partial passage of contrast agent in the duodenum was observed in 59 (71.9%) patients, complete occlusion - 23 (28%). Partial passage of contrast medium through the stricture zone was detected in 8 (9.75%) patients. Full biliary block detected in 15 (18.3%) patients, partial - in 67 (81.7%). The sensitivity, specificity and accuracy of PTCG for the common bile duct diseases were calculated: for choledocholithiasis - 80%, 98.5%, 86.5%; for strictures of the common bile duct - 66,6%, 95,7%, 84,1%; for strictures of biliodigestive anastomosis - 71,4%, 95,7%, 87,8%; for cholangiocarcinomas - 98.5%, 92.8%, 97.5% respectively. The wrong diagnosis was made in 2 (2.5%) patients. False-positive conclusions made in 8 (9.8%) and false-negative in 5 (6.1%).

Conclusions: PTCG in diseases of the common bile duct complicated by mechanical jaundice in 97.5% of cases makes it possible to contrast all parts of the bile ducts, as well as to assess the level and completeness of the biliary block.

Keywords: Common bile duct diseases, Mechanical jaundice, Percutaneius transhepatic cholangiography

ISALPDC-09

Safety and Reasonability of Liver Resection for Intrahepatic Cholangiocarcinoma in Elderly Patients

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Aims: The incidence of intrahepatic cholangiocarcinoma (ICC) in elderly patients is increasing worldwide. Little is known regarding postoperative outcomes in elderly patients undergoing liver resection for ICC.

Methods: 84 patients undergoing liver resection for ICC between 2004 and 2018 were identified. Perioperative characteristics, postoperative morbidity, mortality and survival were compared between elderly (>60 years, group 1, n=31) and non-elderly (<60 years, group 2, n=53) patients.

Results: Gender (*P*=0,34) and body mass index distribution (*P*=0,61), duration of stay (*P*=0,071) were comparable between groups. Surgical characteristics and pathologic data we present in table 1. Incidence of surgical site infections (19,3% vs 18,8%, *P*=0,95), posthepatectomy liver failure (18,6% vs 22,6%, *P*=0,47), reoperation (9,6% vs 9,4%, *P*=0,97) and clinically relevant complications (29,1% vs 32,1%, *P*=0,77) were comparable between the different age groups. 3-year OS (29.1% vs 32,5%, *P*=0,06) and DFS (16,5% vs 18.4%, *P*=0,004) were comparable between the elderly and non-elderly patients.

Table 1.

Operative procedure, n (%)		60 + 31	60 – 53	*P*-value
Type of hepatectomy				
Hemihepatectomy				
Right-sided		4	4	0,41
Left-sided		1	3	0,61
Extented hemihepatectomy				
Right-sided		3	14	0,06
Left-sided		6	15	0,36
Trisectenectomy (with total caudate lobectomy)				
Right-sided		9	13	0,65
Left-sided		4	1	0,04
Bisegmentectomy		4	3	0,24
Combined vascular resection, n (%)		7 (22,5%)	21 (39,6%)	0,1
Combined BD exploration, n (%)		10 (32,2%)	14 (26,4%)	0,56
Combined resection of nearby located organs, n		4	6	0,82
Operative time, min, mean +- SD		369,8 ± 150,5	375,2 ± 132,1	0,04
Blood loss, mL, mean +- SD		950,3 ± 670,3	963,2 ± 586,7	0,23
Perioperative red blood cells transfusion, mL, mean +- SD		375,9 ± 403,6	476,7 ± 459,2	0,003
Perioperative frozen plasma transfusion, mL, mean +- SD		532,3 ± 228,8	504,5 ± 383,8	0,64
TNM staging (8ht edition of AJCC staging system), n				
T	1a	1	2	0,89
	1b	2	2	0,57
	2	15	23	0,65
	3	5	9	0,97
	4	8	17	0,54
N	0	22	33	
	1	9	20	
M	0	31	51	
	1	0	2	
Stage	Ia	1	2	0,89
	Ib	1	1	0,69
	II	11	14	0,38
	IIIa	5	6	0,52
	IIIb	13	28	0,33
	IV	0	2	
G grade	1	3	3	0,49
	2	25	49	0,1
	3	3	1	0,1
Growth type, n (%)	Mass-forming	24 (77,4%)	47 (88,6%)	0,17
	Periductal	4 (12,9%)	0	
	Intraductal	3 (9,7%)	6 (11,4%)	0,8
Intrahepatic vascular invasion, n (%)		23 (74,1%)	43 (81,1%)	0,45
Multiple tumors, n (%)		10 (32,2%)	17 (32%)	0,98
Tumor >5 cm in diameter		28 (90,3%)	48 (90,5%)	0,97

Conclusions: Liver resection for ICC in elderly patients can obtain acceptable perioperative morbidity rates with a chance of long-term survival.

Keywords: Intrahepatic cholangiocarcinoma, Elderly patients, Liver resection

ISALPDC-10

Methanol Extract of Moringa Oleifera Rejuvenate Pancreatic β-Cells in Experimental Type 2 Diabetic Model Rats

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Aims: Diabetes mellitus is an endocrine disease of multiple aetiologies in insulin secretion. A deficiency in insulin results in hyperglycemia with metabolic disturbances of biomolecules. Moringa oleifera is endemic in the tropics with a variety of ethnomedicinal importance. The leaf of this plant has been reported to possess antioxidant and medicinal properties that may be helpful in the treatment and management of diabetes and its associated complications. This study evaluated the antidiabetic potentials of flavonoid-rich aqueous fraction of methanolic extract of Moringa oleifera (MOE) on the pancreatic β-cells of streptozotocin (STZ) and high-fat diet induced type 2 diabetes mellitus (T2DM) in rats.

Methods: Diabetes was induced intraperitoneally in rats by a single dose of streptozotocin (55 mg/kg) and treated with MOE (50, 100, 200 mg/kg b.wt) for six weeks. The rats were randomly divided into normal (NC), T2DM, metformin (Met), low, middle (Mid), and high (Hig) does of MOE groups. After six weeks of continuous administration of MOE, the serum indices and tissue protein expression were determined, and the pathological changes in liver and pancreas tissues were observed. Animals were sacrificed; the splenic portion of their pancreas and serum were evaluated for histopathological and biochemical parameters respectively.

Results: The results showed that compared with the type 2 diabetes mellitus group, the fasting blood glucose (FBG), total cholesterol (TC), and triglyceride (TG) levels in the serum of rats in the dose dependent MOE treatment groups were significantly ($P<0.05$). decreased, while superoxide dismutase (SOD) and glutathione peroxidase (GSH-PX) levels were noticeably increased. The expression of Fas ligand (FasL), cytochrome C (Cyt-c), and caspase-3 in pancreatic tissue was obviously decreased, and the pathological damage to the liver, kidney, and pancreas was improved. These indicate that MOE can reduce oxidative stress in rats with diabetes mellitus by improving blood lipid metabolism and enhancing their antioxidant capacity, thereby regulating the mitochondrial apoptotic pathway to inhibitβ-cell apoptosis and improve β-cell function. The morphology of the pancreas of MOE-treated diabetic rats revealed remarkable improvements in the islet of Langerhans. Stereological studies also revealed that MOE-treatment remarkably improved volume of the pancreatic islets and the numerical density of β-cell (number of β-cells per unit area of islet) depleted by STZ diabetes.

Conclusions: The study concluded that possible antidiabetic

mechanism of MOE in STZ diabetes is through induction of β-cell regeneration and its strong antioxidant potential.

Keywords : Methanolic extract of Moringa oleifera, Pancreatic β-cells, Diabetes mellitus (T2DM) rats

ISALPDC-11

Hepatoprotective Effect of Hispidulin for the Treatment of Non-Alcoholic Fatty Liver Disease (NAFLD): Involvement of Nuclear Factor-κB and Cytochrome P450 Through Molecular Mechanism

Dinesh Kumar Patel, Kanika Patel

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Aims: Herbal drugs were mainly used for the cure and treatments of disorders until the synthetic drugs have been developed in the world. Hispidulin is a naturally occurring flavone class chemical present in Chinese herb *Saussurea involucrate*, Artemisia and Salvia species. Inflammations play an important role in nonalcoholic fatty liver disease (NAFLD) progression.

Methods: In orders to know the importance of hispidulin against liver disorders, here in the present investigation we have analyzed all the pharmacological data of scientific research and presented in the concise form. Liver system is full of enzymes responsible for the metabolism of various molecules in the body, so effect of hispidulin on various liver enzymes have been evaluated in the present investigation through different databases analysis. Further *In-silico* molecular study data has been also analyzed for hispidulin against Cytochromes P450 enzyme and nuclear factor-κB to predict their molecular mechanism against nonalcoholic fatty liver disorders. Further binding energy and type of interaction of hispidulin against Cytochromes P450 and nuclear factor-κB were also analyzed through data analysis of various scientific research in the present investigation to predict their molecular mechanism.

Results: From the analysis of the scientific data of different research, we found that hispidulin interacted liver mitochondria and inhibited enzymatic activities, however hispidulin also counteract reduced glutathione depletion induced by bromobenzene in starved mice. Scientific investigation revealed the importance of hispidulin against nonalcoholic fatty liver disease through different data analysis as hispidulin interact liver enzymes and regulated them significantly. Molecular study data analysis revealed the interaction of hispidulin and Cytochromes P450 enzyme and nuclear factor-κB as it showed negative binding energy and interaction with the respective ligand molecule. From the present investigation it was found that hispidulin have hepatoprotective effects in the nonalcoholic fatty liver disease.

Conclusions: Present work summarized pharmacological importance of hispidulin against nonalcoholic fatty liver disease and this work will be beneficial to the researcher for the development of novel molecule against hepatic disorders.

Keywords: Hepatoprotective activity, Hispidulin, NAFLD, Nuclear factor-κB, Cytochrome P450

ISALPDC-12

Hepatoprotective Activity of Rutin Against Liver Damage Through Interaction with Cytochromes P450 and Antioxidant Enzymes: *In-vivo* and *In-vitro* Experimental Data Analysis and Molecular Modelling

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Aims: Plant based drugs have numerous phytochemicals mainly belongs to the phenolic flavonoid and carotenoids class chemicals. These phytochemicals play important role in the plant's defence mechanism and used for the treatment of numerous human disorders in the modern system of medicine. Plants and their derived products contain important class of phytochemicals which are still considered as one of the important sources of materials for the development of noble molecule with better therapeutic goal. Cytochromes P450 enzymes are capable of catalyzing the oxidative biotransformation of numerous drugs in the human body. Rutin is a low molecular weight polyphenolic compound mainly found to be present in various citrus class drugs. Rutin have important physiological functions both in the human body and plants.

Methods: To know the beneficial effect of rutin in liver system, various scientific databases have been searched and analyzed in the present investigation to know the therapeutic potential of Rutin in the biological system. Pharmacological importance of rutin in Hepatic system have been searched and analyzed. Molecular simulation database of rutin against cytochrome P-450, superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA) have been searched to know the importance of rutin in liver antioxidant systems. Binding energy and type of molecular interactions have been also analyzed in the present investigation through databases analysis to uncoil the molecular mechanism of rutin against hepatic disorders.

Results: Scientific research databases analysis revealed the importance of rutin in the hepatic system as higher intake of rutin for 20 days in rat tissues showed improve liver antioxidant level and reduced systemic inflammation and oxidative stress. However, rutin significantly reduced transaminases and phosphatases enzymes in liver and restores oxidative damage. Molecular simulation study database analysis signified the importance of cytochrome P-450 in liver disorders. Further investigation also revealed the importance of the SOD, CAT and MDA in the treatment of hepatic disorders.

Conclusions: Present investigation revealed the importance of rutin as hepatoprotective agent and signified their role in the oxidative stress and could be used for the development of

newer medicine to treat liver disorders.

Keywords: Hepatoprotective, Rutin, Liver damage, Cytochromes P450, Antioxidant, Enzymes

ISALPDC-13

Molecular Studies of Hyperin as Valuable Dietary Flvonoid on the Metabolic Interactions of with TNF-a, ALT and AST Enzymes and Hepatoprotective Activity

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Aims: Plant and their derived product including various forms of marketed Herbal products have been used in the various system of medicine for the treatment of human disorders. Various pure chemical based drugs have been used in the medicine since very early age and large numbers of phytochemicals have been derived from the natural sources. Flavonoids are important and widely distributed plant chemicals having benzo-pyrone nucleus. Flavonoidal class chemical was used in the medicine, food supplement and neutraceuticals being used for the treatment and cure. Hyperin is a flavonoidal class plant chemical found to be present in the *Hypericum perforatum* and *Drosera rotundifolia*.

Methods: Present study aim is to collect and analyzed all the available scientific information of hyperin for the treatment of various forms of hepatic disorders. Pharmacological activities of hyperin were investigated in order to discover new molecule for the treatment of hepatic complication and disorders. Present study includes detailed data analysis of pharmacological activity and importance of molecular simulation study for their molecular mechanistic study. All the data's were analyzed statistically to get significant results. *In-silico* database analysis was performed in the present investigation to predict the pharmacological activity of hyperin through molecular mechanism. Interaction of hyperin with liver enzymes was also investigated through database analysis in the present investigation in order to know their biological potential against hepatic complication. Molecular modeling studies of the hyperin on tumor necrosis factor alpha (TNFa), alanine aminotransferase (ALT) and aspartate transaminase (AST) were also analyzed through various scientific work analysis to know the importance of hyperin in hepatic system.

Results: Analysis of the selected scientific research data's of hyperin in the present investigation revealed the importance of hyperin in the biological system as it have DPPH free radical scavenging activity and inhibitory potential on LDL oxidation. Hyperin have been known for their antioxidant, antiinflamatory, cardioprotective and Hepatoprotective activities which further support the present study analysis. Data analysis revealed the protective effects of hyperin against nitrofurantoin-induced cytotoxicity and amiodarone-induced cytotoxicity in Hep G2 cells and cultured rat hepatocytes. *In-silico* molecular study data analysis revealed the importance of hyperin on TNF-a, ALT and AST enzymes.

Conclusions: Present research work is beneficial to understand the importance of hyperin in the medicine and helpful to explore the potential health benefits of hyperin as a safe natural compound for hepatic disorders and complication in the future.

Keywords: Hyperin, Flavonoid, TNF-a, ALT, AST, Hepatoprotective

ISALPDC-14

Therapeutic Importance of Senegin through Interaction on Nuclear Factor Kappa B, SOD and Catalase for their Hepatoprotective Potential: *In-vitro* and In-Silico Study

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Aims: Plants derived natural products are well known for their contributions to human health. Inflammation and oxidative stress are key parameters for the development of liver disorders and molecule having good antioxidant potential could be used for the treatment of liver damage. Oxidative stress, inflammation and apoptosis cause scar formation in the liver cells, however inflammatory mediators such as IL-1, ICAM-1 and TNFa also play important role in hepatic failure. Antioxidant enzyme such as Catalase, SOD, and GSH-Px are used as indexes to evaluate the level of oxidative stress. Acute infection damages the liver cells and killed healthy tissue and formed scar tissue which is called fibrosis.

Methods: Different electronic database have been searched to collect needed information of senegin for their medicinal importance in acute liver inflammation and infection and all the information have been analyzed through statistically. Pharmacological activity of senegin has been also validated through different experimental work. Molecular study has been investigated in the present work through interaction of senegin with ligand to know their mode of action. Molecular docking and dynamic experiments were performed with senegin against nuclear factor kappa B (NF-κB), superoxide dismutase (SOD) and Catalase to know how senegin fit on active site.

Results: Data analysis revealed the importance of senegin for the treatment of various form of inflammatory disorders including hepatic disorders. Senegin have been found to have neuroprotective and anti-inflammatory activity which are used for the treatment of Hepatic disorders. Scientific databases analysis has also proved their importance as immunomodulatory, hypoglycemic and anticancer potential in the medicine. Database analysis also demonstrates that senegin could prevent liver damage and therefore play important role in the Hepatic inflammation. *In-silico* studies showed that senegin exhibited a higher docking score against NF-κB, SOD and Catalase which

signified their therapeutic potential and role in the various form of hepatic inflammation and complication.

Conclusions: Senegin prevent liver damage through its antioxidants and anti-inflammatory potential. However protective effect of senegin in Hepatic cells could be due to interaction of NF-κB, SOD and Catalase.

Keywords : Senegin, Hepatoprotective, Molecular study, Nuclear factor kappa B, SOD, Catalase

ISALPDC-15

The Evaluation of Pancreatic Enzyme Replacement Therapy for Chronic Pancreatitis Patients

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Aims: Non-invasive tests are not widely used in clinical practice for a reliable determination of the pancreas exocrine function. The aim of the study was to evaluate the effects of pancreatic enzyme replacement therapy (PERT) on the pancreas exocrine function of patients with chronic pancreatitis with the help of a fecal elastase 1 test.

Methods: Observational cross-sectional study. 109 patients with chronic pancreatitis were treated using enzyme replacement therapy. Before and after the treatment all patients had gone through laboratory tests and imaging diagnosis.

Results: There were 62 men and 47 women in our sample. The mean age was 49.76 ± 1.21 years (22 to 81). We determined the fecal elastase (200 mcg/g) for 70 patients (mean 151,33 ± 14.24 mcg/g). Among 39 patients, an exocrine pancreatic insufficiency was found severe (n = 24), and moderate (n = 15). After the PERT we observed a decrease in abdominal pain among the patients (P=0.0063) and decrease in urine amylase levels: 274.29 ± 46.72 ME/l and 167.25 ± 14.09 ME/l; P=0.0128 and blood amylase levels: 74.38 ± 9.66 ME/l and 64.12 ±7.87 ME/l (n=89, P=0.043). Average fecal elastase levels in case of consuming capsules was reliably less compared to the initial levels: 279.46 ± 27.41 mcg/g and 254.87 ± 26.74 mcg/g (n=52, P=0.0152); and reliably less than elastase levels during the intake of pancreatin tablets: 289.38 ± 38.44 and 303.75 ± 36.88 mcg/g (n=24, P=0.0127). Fecal elastase activity during tablet pancreatin didn't differ much from the initial levels: 276.14 ± 29.41 and 266.29 ± 29.74 mcg/g (n=35, P=0.4190).

Conclusions: Determination of fecal elastase-1 is highly sensitive to the diagnosis of severe and moderate exocrine pancreatic insufficiency and the results of this test are not affected by ongoing PERT.

Keywords : Pancreatic Enzyme Replacement, Chronic Pancreatitis

ISALPDC-16

Classification of Pancreatic Cancer Stadium Using Recurrent Neural Network (RNN) Model Algorithm

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Aims: One way to detect the presence of pancreatic cancer is by examining it using Computed tomography (CT) scan. After a pancreatic cancer is detected, classification is done to determine the stage of cancer. In this study, we used the RNN model for the classification of Pancreatic cancer stadium. This study aimed to explain the procedure and the accuracy of the Elman tissue RNN modeling in pancreatic cancer stadium classification from the CT scan.

Methods: The process carried out is to convert the image of red green blue (rgb) to a grayscale image on the CT scan data. After that the image was extracted with Gray Level Co-occurrence Matrix which was designed using Graphical User Interface with Matlab. There are 14 features, namely energy, contrast, correlation, Sum of Square, Inverse Different Moment, sum average, sum variance, sum entropy, entropy, differential variance, differential entropy, maximum probability, homogeneity, and dissimilarity. The feature is used as input, which is then divided into training data and testing data. After that, Elman network RNN modeling was carried out with data normalization, best model design, and data denormalization. The best model design was done by finding the number of hidden neurons and eliminating network inputs using the backpropagation algorithm.

Results: The results of the best model training data and testing data were measured using sensitivity, specificity, and accuracy. So that from 74 training data obtained 92% accuracy rate, 96% sensitivity level as a reliable indicator when the results show pancreatic cancer, and 79% level of specificity as a good indicator when the results show normal pancreatic. While in 18 data testing showed 94% accuracy, 100% level of sensitivity, and 80% level of specificity.

Conclusions: The conclusion in this study can be said that good classification results are obtained.

Keywords: Classification, Pancreatic Cancer, Stadium, RNN Model

ISALPDC-17

The Prevalence of Non-Alcoholic Fatty Pancreas by Abdominal Ultrasonography

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Aims: Pancreatic steatosis or fatty pancreas refers to the fat

accumulation in the pancreas, which can lead to inflammation and fibrosis, β-cell dysfunction, fibrosis, and, possibly, pancreatic cancer. The aim of this study was to investigate the prevalence and risk factors of fatty pancreas in patients referred to an ultrasonography center of Dornod Medical center.

Methods: A cross-sectional study. During 12 months, 627 patients who were referred to our abdominal ultrasonography center for various reasons were evaluated for fatty pancreas. Fatty pancreas was defined as hyperechoic pancreas echotexture compared with spleen echotexture. All patients had gone through laboratory tests and abdominal ultrasonography.

Results: The prevalence of fatty pancreas was 45.8%. The fatty pancreas patients had higher levels of aspartate aminotransferase, alanine aminotransferase, serum uric acid, fasting blood glucose, total cholesterol, triglycerides and low-density lipoprotein, and lower levels of high-density lipoprotein than did the non-fatty pancreas patients (all $p < 0.05$).

Conclusions: Fatty pancreas is a common disorder. The prevalence of fatty pancreas in the examined population is approximately 45.8%. Increased age, central obesity and fatty liver disease are independent risk factors for fatty pancreas.

Keywords : Fatty Pancreas, Ultrasonography

ISALPDC-18

Medical Physiology

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Background: Nonalcoholic fatty liver disease (NAFLD) is a condition in which excessive fat accumulates in the liver of a patient who drinks little or no alcohol. The development of NAFLD is associated with obesity, insulin resistance, and hyperlipidemia and is characterized by the accumulation of fatty acids, especially excess triglycerides, in hepatocytes. The increasing prevalence of obesity, metabolic syndrome, and NAFLD has been connected to excess caloric intake, such as the excessive consumption of refined food with high fructose levels. Recent research suggests diets specifically high in fructose have been shown to contribute to a metabolic disturbance in animal models. NAFLD is a component of the metabolic syndrome. High fructose consumption has been implicated in the progression and severity of NAFLD by promoting de novo lipogenesis and increasing insulin resistance, oxidative stress, inflammation, and fibrosis. However the mechanism responsible is still unknown.

Aim: The aim of the present study is to assess relationship between high fructose diet and risk, progression of NAFLED.

Methods: Thirty six female albino mice of 21 years old were divided into six groups. Group A: normal control diet for 30 days (control 30), Group B: High fructose diet for 30 days (HFD 30 days), Group C: Palm jaggery diet for 30 days (PJD 30), Group D: normal control diet for 90 days (Control 90), Group E: High fructose diet for 90 days (HFD 90), Group F: Palm jaggery diet for 90 days (PJD 90). The mice are fed control diet, refined high sugar diet, Palm jaggery 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.

Results: HFD 90 mice shows liver parenchyma with partially effaced architecture. Many hepatocytes show apoptotic changes and cytoplasmic vaculations around central vein. The concentration of collagen fibres were increased apparently. Fat droplets were observed with degenerative changes of hepatocyes in some regions of liver. PJD 90 mice shows apoptotic changes in some part of liver also shows less number of fat droplets was observed. Most of the perivenular and periportal hepatocytes appear normal. Control groups (control 30, 90) show normal liver parenchyma with intact architecture. No significant changes were observed in HFD30 & PJD30 liver architecture. Serum insulin level was increased significantly in PJD 30, HFD 30 & HFD 90. Increased TBARS level in HFD 90 with other findings shows features of dyslipidemia ($P<0.01$).

Conclusion: 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 non alcoholic fatty liver disease (NAFLD). Our study suggests that intake of palm jaggery will be a good alternative to fructose to maintain the normal liver morphology.

Keywords: NAFLD, HFD, PJD

ISALPDC-19

Biliary Cancer Treatment

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Aims: Cholangiocarcinoma (CCA) is rare malignant disease in gastrointestinal system and accounted as aggressive disease with poor survival. Recently, many trials have attempted to improve survival by new promising intraductal radiofrequency ablation (RFA) therapy. The aim of this study is to prove the survival benefit of endoscopic RFA for unresectable extrahepatic CCA with malignant biliary obstruction (MBO).

Methods: Systematic search was performed from MEDLINE, EMBASE, Cochrane's Library and ClinicalTrials since 1970 and eligible studies (CCT) reporting relative risk (RR), hazard risk (HR) or odd ratio (OR) regarding survival rate and stent patency period between RFA with stent and stent only group among extrahepatic CCA with MBO cases were selected. Pooled HRs among studies and their 95% CIs (confidence intervals) were estimated using the random-effects model. Risk of bias and quality of the study were assessed.

Results: Total 7 studies, 2 randomized and 5 non-randomized trials, with total 368 patients were included for meta-analy-

sis. Pooled overall survival analysis showed favored in patient treated by RFA with sent (HR, 0.44, 95% CI, 0.31-0.61, I square=45%, *P*=0.09), however, we failed to prove the longer duration of stent patency in same groups (HR, 0.79, 95% CI,49-1.28, I square=48%, *P*=0.20).

Conclusion: According to recently published studies, RFA therapy with stent insertion might have survival benefit compared to stent only among the patient with CCA with MBO.

Keywords: Cholangiocarcinoma, Malignant biliary obstruction, Radiofrequency ablation, Meta-analysis, Stent Patency, Survival rates, Intra-luminal

ISALPDC-20

Biological Importance of Glycitin in the Medicine for the Treatment of Hepatic Disorders and Complication through Different Molecular Mechanism

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Aims: Flavonoids are most important class of plant chemicals found to be present in the various medicinal plants and their derived product. Flavonoidal compounds have more than 4000 different phenylbenzopyrones mainly found to be present in the edible plants. Flavonoidal compounds have different pharmacological activities including anti-nflammatory and anti-oxidative properties. Glycitin is a type of flavonoidal class plant derived chemical having antibacterial, antiviral and estrogenic potential. Acute lung injury is a type of pulmonary disorders caused by various types of inflammatory response and some of the plant derived medicines have been used for the treatment of such type of disorders.

Methods: Plant based food material have different types of phytochemicals which showed numerous biological activities such as anti-inflammatory, antioxidant and hypocholesterolemic potential. To know the biological potential of glycitin in various form of liver disorders, in the present investigation different scientific databases have been searched and analyzed in order to know their therapeutic potential in the medicine. Various scientific data's of pharmacological activities of glycitin have been analyzed in the present investigation through both *In-vivo* and *In-vitro* methods. Further molecular study database have been also searched and analyzed to support the hepatoprotective activity of glycitin. All the data analysis has been performed through statistically in order to get better results.

Results: From the analysis of the various scientific databases it was found that, glycitin is present in the soy food products also called 4'-hydroxy-6-methoxyisoflavone-7-D-glucoside. Various scientific studies have proven their pharmacological potential against alcoholism, cardiovascular and cerebrovascular diseases and some types of cancer. Glycitin has anti-aging effects and protects skin from photoaging by increasing expression of collagen I in UV-exposed human dermal fibroblasts. In the research database, glycitin has been reported to have an anti-oxidant and anti-carcinogenic activity. Effects of glycitin on MMP-1 and collagens in UV-irradiated human primary dermal fibroblasts were also investigated in some scientific work and their possible anti-inflammatory mechanisms of glycitin were investigated on LPS-induced acute lung injury in mice. Analysis of the research databases have proven the beneficial effect of glycitin in the acute lung injury which could be due to the reduced expressions of IL-1ß, IL-6, TNF-a and NF-κB.

Conclusions: Present investigation highlighted the biological importance of glycitin in the medicine, which could be used for the development of better active pharmaceutical ingredients against various forms of liver disorders.

Keywords: Biological, Glycitin, Medicine, Hepatic disorders, Molecular mechanism

ISALPDC-21

Therapeutic Potential and Protective Role of Delphinidin Against Hepatic Cell Injury: Medicinal Importance through *In-vivo* Experiments and Molecular Mechanism

Kanika Patel[1], Dinesh Kumar Patel[2]

[1]Krishnarpit Institute of Pharmacy, Rewa Rd, Prayagraj, Uttar Pradesh; [2]Shalom Institute of Health and Allied Sciences, Sam Higginbottom University of Agriculture, Technology and Sciences, Payagraj, U.P., India

Aims: Nature is the source of all the materials we need for the betterment of our own health in terms of food and medicine. Anthocyanins are coloured compounds responsible for various attractive colour of plant material and showed wide range of pharmacological activities. Delphinidin were present in all the bright colored fruits and vegetables which have been used in the diet as supplements for the treatment of Hepatic disorders.

Methods: Present research work aim is to describe the medicinal importance and pharmacological activities of delphinidin. To know the medicinal important of delphinidin, various scientific databases have been searched and analyzed for their Health beneficial properties. Hepatoprotective activity of delphinidin has been also analyzed through various *In-vivo* and *In-vitro* experimental works in the present work. All the presented data have been analyzed through statistical method to get significant result of their Hepatoprotective activity. *In-silico* molecular study has been also performed for delphinidin with different ligands to search better molecular mechanism for their Hepatoprotective activity.

Results: From the analysis of the presented data in this work we can reveal the importance of delphinidin in the nature. Delphinidin is an important anthocyanidins which are mainly present in the epidermal tissues of flowers and fruits. Pharmacological study revealed their importance as antioxidant, antimutagenesis, anti-inflammatory and antiangiogenic activity. The mode of mechanism of delphinidin is mainly through the vascular endothelial growth factor receptor-2 phosphorylation inhibition,

platelet-derived growth factor receptor signaling, cancer cell proliferation and modulation of Met receptor phosphorylation. Delphinidin attenuated oxidative stress, increased matrix metalloproteinase-9 and metallothionein I/II expression and restored hepatic cellular damage in the carbon tetrachloride-induced liver fibrosis with strong enhancement of hepatic regenerative power. Delphinidin showed significant scavenging activity against different free radicals.

Conclusions: This work will be benificial to the scientist, manufacturer and consumers in order to explore the Hepatoprotective potential of delphinidin.

Keywords: Delphinidin, Hepatic injury, Hepatoprotective, Molecular mechanism

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수술 또는 국소치료*가 불가능한 진행성 **간세포성암 환자**의 **1차 치료**[1]

Stage Ⅲ 이상 | Child-Pugh Class A | ECOG 수행능력 평가(PS) 0-1

[제품명] 렌비마®캡슐 4 mg, 10 mg (렌바티닙메실산염) [효능 · 효과] 1. 방사능 요오드에 불응한, 국소 재발성 또는 전이성의 진행성 분화 갑상선암 2.절제 불가능한 간세포성암 환자의 1차 치료 [용법 · 용량] 이 약은 매일 같은 시간에 식사와 관계없이 경구로 복용한다. 예정된 투여시간에 복용을 잊은 경우, 다음날 복용시간까지 12시간 미만으로 남았다면 당일 복용을 생략한다. 다음날 두 배로 복용하지 않는다. 1. 분화 갑상선암: 성인에서 이 약의 권장 투여 용량은 1일 1회 24 mg이다. 이상반응 관리를 위하여 1일 투여량은 필요에 따라 조절할 수 있다. 2. 간세포성암: 이 약의 권장 투여용량은 체중을 기준으로 한다. · 60 kg 이상인 환자: 12 mg · 60 kg 미만인 환자: 8 mg 질병이 진행되거나 수용할 수 없는 독성이 나타날 때까지 이 약 1일 1회 투여를 지속한다. 간세포성암에서 10mg 용량의 사용에 대한 임상적 근거는 없다. [이상반응] 1. 분화갑상선암 방사성요오드에 불응인 분화갑상선암환자 452명에서 가장 흔하게 보고된 (30% 이상의 환자에서 발생) 약물이상반응은 고혈압 (68.6%), 설사 (62.8%), 식욕감퇴 (51.5%), 체중감소 (49.1%), 피로 (45.8%), 메스꺼움 (44.5%), 단백뇨 (36.9%), 구내염 (35.8%), 구토 (34.5%), 발음곤란 (34.1%), 두통 (34.1%), 및 손-발바닥 홍반성감각이상증후군 (PPE) (32.7%)이었다. 2. 간세포성암 이 약을 투여 받은 군에서 관찰된 가장 흔한 이상반응 (>20%)은 빈도가 감소하는 순으로 고혈압, 피로, 설사, 식욕 감소, 관절통/근육통, 체중 감소, 복통, 손-발바닥 홍반성 감각이상증후군, 단백뇨, 발음곤란, 출혈사례, 갑상선기능저하증 및 메스꺼움이었다. [사용상의 주의사항] 1.금기 1) 이 약의 주성분 혹은 부형제에 대한 과민증이 있는 환자 2) 모유수유를 하고 있는 환자 2. 신중투여 1) 고혈압환자 2) 혈전색전증 또는 병력이 있는 환자 3) 뇌전이 환자 4) 외과적 수술 후 상처가 치유되지 않은 환자 5) 경동맥, 경정맥 등에 종양 침윤이 있는 환자 3. 임부 수유부 1) 가임 여성 임신가능성이 있는 여성은 임신을 피해야하며, 이 약을 투여 받는 동안 및 이 약의 치료를 중단한 최소 한 달까지 매우 효율적인 피임방법을 사용하여야 한다. 2) 임부 임부에서 이 약의 투여에 대한 정보는 불충분하다. 이 약은 위험성과 임산부에서의 필요성에 대한 신중한 검토 후 반드시 필요하지 않는 한 임산부에게는 투여하지 않는다. 3) 수유부 이 약이 모유를 통해 이행되는지 여부는 밝혀지지 않았다. 4. 소아 만 2세 미만의 소아에서 투여하지 않는다. 만 2세부터 만 18세 미만의 소아에서의 이용 가능한 자료는 없으며, 안전성 및 유효성은 확립되어 있지 않다. 5. 고령자 연령에 따른 초회 용량 조절은 필요하지 않다. 75세 이상 환자에서의 이용 가능한 자료는 제한적이다. [전문의약품] [수입 및 판매자] 한국에자이주식회사 [개정년월일] 2019년 9월 21일.

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* 국소치료라 함은 전신적 항암요법(systemic chemotherapy)을 제외한 TA(C)E, ethanol injection, RFA 등의 치료법을 의미함.

Reference 1. 건강보험심사평가원 공고 제2019-279호 (2019.9.26.)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; RFA, radiofrequency ablation; TA(C)E, transarterial (chemo)embolization; uHCC, unresectable hepatocellular carcinoma

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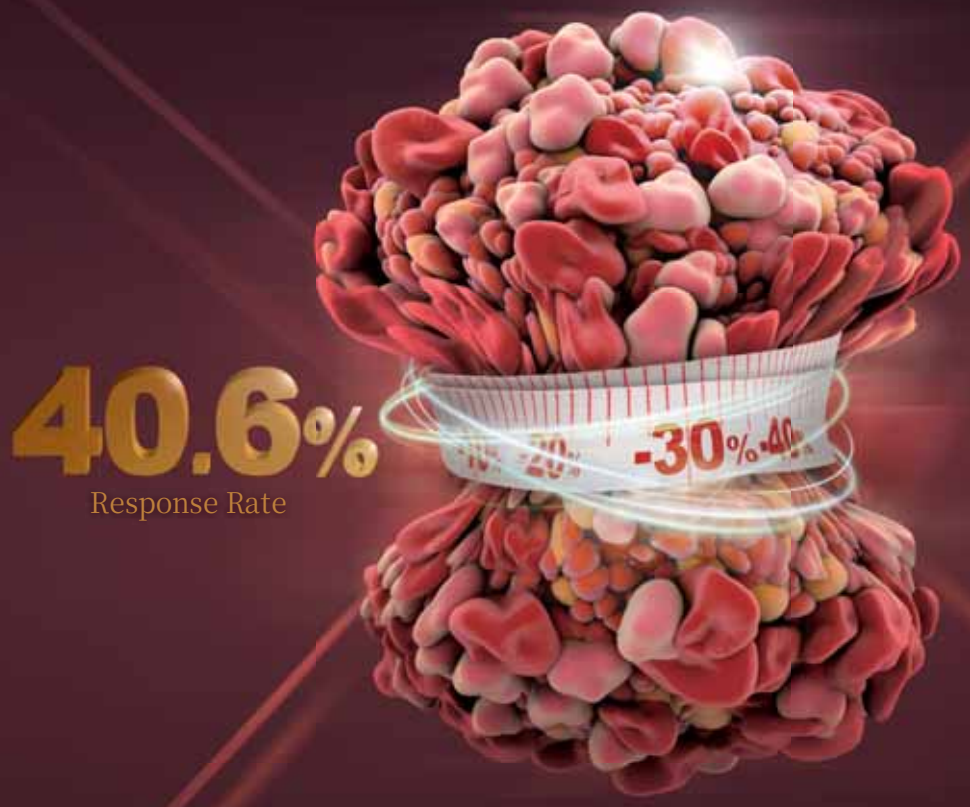
약 41%의 환자*에서 30% 이상의 종양 크기 감소를 보였습니다.[1,2]



* mRECIST에 따른 독립영상검토(Masked IIR) 기준, Lenvatinib군(n=478)의 ORR은 40.6% (n=194; 95% CI:36.2-45.0); Sorafenib군(n=476)의 ORR은 12.4% (n=59; 95% CI: 9.4-15.4)로 통계적으로 유의한 차이가 있었습니다 (P <0.0001).

[Study design] (REFLECT study) 2013년 3월 1일~2015년 7월30일 사이에 등록된 HCC 환자 954명을 대상으로 Lenvatinib (n=478, ≥60 kg 경우 12 mg 하루 한 번, <60 kg 경우 8 mg 하루 한 번)과 Sorafenib (n=476, 400 mg 하루 두 번) 간 1차 항암 요법의 유효성과 안전성을 비교평가한 다국가, 다기관, 1:1 무작위 배정, 공개, 비열등성 3상 임상 시험입니다. Lenvatinib은 소라페닙 대비 1차 평가변수인 전체생존기간에 대한 비열등성을 입증하였습니다.[1]

mRECIST, modified Response Evaluation Criteria in Solid Tumors; IIR, Independent imaging review; ORR, Objective Response Rate; CI, Confidence Interval; HCC, Hepatocellular carcinoma

[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

Product Information [제품명] 렌비마®캡슐 4 mg, 10 mg (렌바티닙메실산염) [효능·효과] 1. 방사능 요오드에 불응한, 국소 재발성 또는 전이성의 진행성 분화 갑상선암 2 절제 불가능한 간세포성암 환자의 1차 치료 3.이전에 전신 치료를 받은 경험이 있고 질병이 진행하였으며 수술적 치료 또는 방사선 치료가 부적합한 , MSI H (microsatellite instability 또는 d MMR (mismatch repair deficient) 상태가 아닌 진행성 자궁내막암 환자의 치료로서 , 펨브롤리주맙과의 병용요법 [용법·용량] 이 약은 항암요법에 충분한 지식과 경험이 있는 전문의에 의해 투여가 시작되고 감독 되어야 한다. 이 약은 환자에게 더 이상 임상적인 유익성이 없거나 수용할 수 없는 독성이 발생할 때까지 계속 투여해야 한다. 이 약은 매일 같은 시간에 식사와 관계없이 경구로 복용한다. 예정된 투여시간에 복용을 잊은 경우, 다음날 복용시간까지 12시간 미만으로 남았다면 당일 복용을 생략한다. 다음날 두 배로 복용하지 않는다. 환자 보호자는 캡슐 안에 든 물질에 반복 노출을 피하기 위해 캡슐을 열지 않아야 한다. 캡슐은 통째로 삼키거나 작은 컵에 녹일 수 있다. 액체에 녹이기 위해 캡슐을 부수거나 분쇄하지 않고 한 큰술의 물에 적어도 10분 동안 넣어두고, 적어도 3분 동안 젓는다. 그 현탁액을 마신 뒤, 한 큰술의 물을 컵에 넣어 몇 번 흔들어 헹군 뒤 그 액을 마신다. 1. 분화 갑상선암: 성인에서 이 약의 권장 투여 용량은 1일 1회 24 mg이다. 이상반응 관리를 위하여 1일 투여량은 필요에 따라 조절할 수 있다. 2. 간세포성암: 이 약의 권장 투여용량은 체중을 기준으로 한다. ·60kg 이상인 환자: 12 mg ·60 kg 미만인 환자: 8 mg 질병이 진행되거나 수용할 수 없는 독성이 나타날 때까지 이 약 1일 1회 투여를 지속한다. 간세포성암에서 10mg 용량의 사용에 대한 임상적 근거는 없다. 3. 자궁내막암:이 약의 권장 투여용량은 1일 1회 20mg을 경구투여 하는 것으로 질병이 진행되거나 수용할 수 없는 독성이 나타날 때까지 투여하며, 병용 투여하는 펨브롤리주맙은 3주마다 30분 동안 200mg을 정맥 점적주입한다. 펨브롤리주맙의 권장 용량 정보는 펨브롤리주맙의 허가사항을 참고한다. [이상반응] 1. 분화갑상선암: 방사성요오드에 불응인 분화갑상선암환자 452명에서 가장 흔하게 보고된 (30% 이상의 환자에서 발생) 약물이상반응은 고혈압 (68.6%), 설사 (62.8%), 식욕감퇴 (51.5%), 체중감소(49.1%), 피로 (45.8%), 메스꺼움 (44.5%), 단백뇨 (36.9%), 구내염 (35.8%), 구토 (34.5%), 발음곤란 (34.1%), 두통 (34.1%), 및 손-발바닥 홍반성감각이상증후군 (PPE) (32.7%)이었다. 2. 간세포성암: 이 약을 투여 받은 군에서 관찰된 가장 흔한 이상반응 (>20%)은 빈도가 감소하는 순으로 고혈압, 피로, 설사, 식욕 감소, 관절통/근육통, 체중 감소, 복통, 손-발바닥 홍반성 감각이상증후군, 단백뇨, 발음곤란, 출혈사례, 감상선기능저하증 및 메스꺼움이었다. 3. 자궁내막암:이 약 1 일 1 회 20mg 경구 투여 과 펨브롤리주맙 (3 주마다 200 mg 정맥 투여 병용 요법의 안전성은 한 가지의 전신 치료 이후 질병 이 진행하였고 MS I H (microsatellite instability high) 또는 dMMR (mismatch repair deficient) 상태가 아닌 자궁내막암 환자 94명에서 발생한 중대한 이상 반응은 이 약과 펨브롤리주맙을 투여 받은 환 자의 52% 에서 발생했다 3% 이상의 환자에서 발생한 중대한 이상 반응은 고혈압 (9%), 복통 (6%), 근육골격통증 (5%), 출혈 4%), 피로 (4%), 메스꺼움 (4%), 작란 상태(4%), 흉막 삼출 (4%), 부신 기능 부전 (3%), 대장염 (3%), 호흡 곤란 (3%) 및 발열 (3%) 이었다. [상호작용] 1. 다른 약물의 영향 이 약을 CYP3A, P-glycoprotein (P-gp), 유방암 저항 단백질(breast cancer resistance protein, BCRP) 억제제 또는 CYP3A, P-gp 유도제의 기질과 병용 시 용량 조절이 요구되지 않는다. 2. 이 약이 다른 약물에 미치는 영향 암 환자에서의 약물 상호작용 임상 시험 결과, 이 약이 미다졸람 (CYP3A 및 Pgp 민감 기질)의 혈장 농도를 변화시키지 않음을 보였다. 따라서 이 약과 다른 CYP3A4/Pgp 기질과의 의미 있는 약물 상호작용이 없을 것으로 예상된다. 3. 기타 항암화학요법 약물 이 약과 카보플라틴 및파클리탁셀을 병용 시, 이 세 가지 성분에서 약물동태학에 유의적인 영향을 주지 않았다. 4. 경구용피임제 현재까지 이 약이 호르몬성 피임제의 효능을 감소시키는지에 대해 알려진 바가 없다. 구용 호르몬성 피임제를 사용하고 있는 여성에서는 장벽 방식을 추가하여야 한다. [사용상의 주의사항] 1.금기 1) 이 약의 주성분 혹은 부형제에 대한 과민증이 있는 환자 2) 모유수유를 하고 있는 환자 2. 신중투여 1) 고혈압환자 2) 혈전색전증 또는 병력이 있는 환자 3) 뇌전이 환자 4) 외과적 수술 후 상처가 치유되지 않은 환자 5) 경동맥, 경정맥 등에 종양 침윤이 있는 환자 [임부 수유부 및 수정능력에 대한 영향] 1) 가임 여성 임신가능성이 있는 여성은 임신을 피해야하며, 이 약을 투여 받는 동안 및 이 약의 치료를 중단한 최소 한 달까지 매우 효율적인 피임방법을 사용하여야 한다. 2) 임부 임부에서 이약의 투여에 대한 정보는 불충분하다. 이 약은 위험성과 임산부에서의 필요성에 대한 신중한 검토 후 반드시 필요하지 않는 한 임산부에게는 투여하지 않는다. 3) 수유부 이 약이 모유를 통해 이행되는지 여부는 밝혀지지 않았다. [소아에 대한 투여] 만 2세 미만의 소아에 투여하지 않는다. 만 2세부터 만 18세 미만의 소아에서의 이용 가능한 자료는 없으며, 안전성 및 유효성은 확립되어 있지 않다. [고령자에 대한 투여] 고령자 연령에 따른 조회 용량 조절은 필요하지 않다. 75세 이상 환자에서의 이용 가능한 자료는 제한적이다. [전문의약품] [수입 및 판매자] 한국에자이주식회사 [개정년월일] 2020년 5월 11일.

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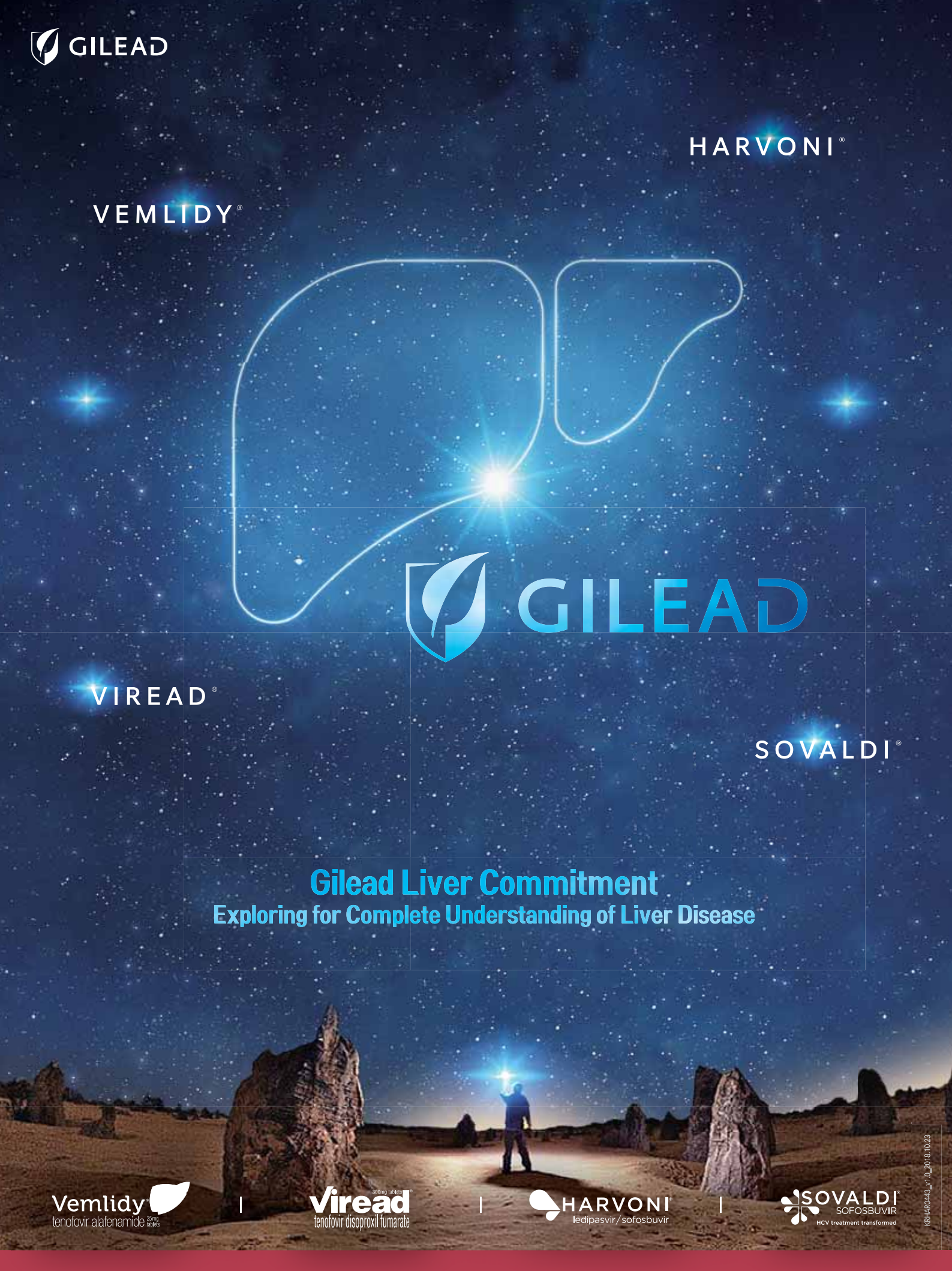
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- Deliver higher rates of ALT normalization vs. VIREAD®[4]
- 0% Detectable resistance at 96 week[4]

Improved safety profile in renal and bone parameters

- Less impact on renal and bone safety parameters as compared to VIREAD®[3,4]

Recommended 1st line treatment option in KASL, EASL and AASLD guideline[5~7]

Provides targeted delivery to the liver reducing systemic exposure with 89% lower plasma concentration of tenofovir compared to VIREAD®[1,4]

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VEMLIDY®Tablet (Equivalent to 25 mg Tenofovir alafenamide)

[PHARMACEUTICAL FORM] Yellow, round, film-coated tablets, debossed with "GSI" on one side of the tablet and "25" on the other side **[INDICATION]** This drug is indicated for the treatment of chronic hepatitis B in adults. **[DOSAGE AND ADMINISTRATION]** The recommended dosage of this drug is one tablet taken orally once daily, with food. **[PRECAUTIONS IN USE]** 1. Warnings 1) Lactic Acidosis/Severe Hepatomegaly with Steatosis. 2) Severe Acute Exacerbation of Hepatitis B after Discontinuation of Treatment 2. Contraindication 1) Patients who are hypersensitive to this drug or other ingredients contained in this drug. 2) Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption. 3. Adverse Reaction The safety assessment of this drug was based on Week 96 pooled data from 1298 subjects in two randomized, double-blind, active-controlled trials, Study 108 and Study 110, in adult subjects with chronic hepatitis B. A total of 866 subjects received one tablet of this drug once daily and the adverse reaction (all Grades) greater than or equal to 5% in this drug group was headache, abdominal pain, cough, back pain, fatigue, nausea, diarrhea, dyspepsia. (Refer to full PI for more safety information) 4. General Precautions 1) Risk of Development of HIV-1 Resistance in Patients Coinfected with HBV and HIV-1. 2) New Onset or Worsening Renal Impairment. 3) The safety and efficacy of this drug in patients with decompensated cirrhosis (Child-Pugh B or C) have not been established; therefore this drug is not recommended in patients with decompensated cirrhosis. 4) This drug is not recommended for coadministration with drugs that contain any of the following: tenofovir alafenamide, tenofovir disoproxil fumarate, adefovir dipivoxil. 5) Resistance (Refer to full PI for more safety information) 5. Drug interactions 1) Potential for Other Drugs to Affect this drug: This drug is a substrate of P-glycoprotein (P-gp) and BCRP. Drugs that strongly affect P-gp and BCRP activity may lead to changes in tenofovir alafenamide absorption. 2) Drugs Affecting Renal Function: Because tenofovir is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of this drug with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of tenofovir and other renally eliminated drugs and this may increase the risk of adverse reactions. 3) Established and Other Potentially Significant Interactions: Anticonvulsants, antimycobacterial, herbal products. 4) Drugs without Clinically Significant Interactions with this drug. (Refer to full PI for more information) 6. Use in Pregnant Women and Nursing Mothers 1) Pregnancy. There are no human data on the use of this drug in pregnant women to inform a drug-associated risks of adverse fetal developmental outcome. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 2) Lactation: It is not known whether this drug and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for this drug and any potential adverse effects on the breastfed infant from this drug or from the underlying maternal condition. 8. Use in specific population Safety and effectiveness of this drug in pediatric patients less than 18 years of age have not been established. Clinical trials of this drug did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. The safety and efficacy of this drug in patients with end stage renal disease (estimated creatinine clearance below 15 mL per minute) have not been established; therefore this drug is not recommended in patients with end stage renal disease. The safety and efficacy of this drug in patients with decompensated cirrhosis (Child-Pugh B or C) have not been established; therefore this drug is not recommended in patients with decompensated hepatic impairment. **[Storage Condition]** Store in a tight container at room temperature (1~30° C)
[Package Unit] 30 tablets **[Manufacture client]** Gilead Sciences International Ltd (Cambridge, CB21 6GT, UK) **[Manufacturer]** Patheon. Inc. (2100 Syntex Court, Mississauga, Ontario, Canada L5N 7K9) Or Gilead Sciences Ireland UC (IDA Business and Technology Park, Carrigtohill, Co. Cork, Ireland)
[Importer] Gilead Sciences Korea Ltd., West Tower 15F, Center 1, 26, Euljiro 5-gil, Jung-gu, Seoul, Korea (Representative phone: 02-6030-3300, Medical information: 0079-814-800-9172) **[Date of Preparation]** 2018. 10. 31 (VEM-1810-01)

※ Please refer to full prescribing information (www.gilead.co.kr or nedrug.mfds.go.kr) before prescription for detailed information. This abridged PI might not include some latest information after the date below.

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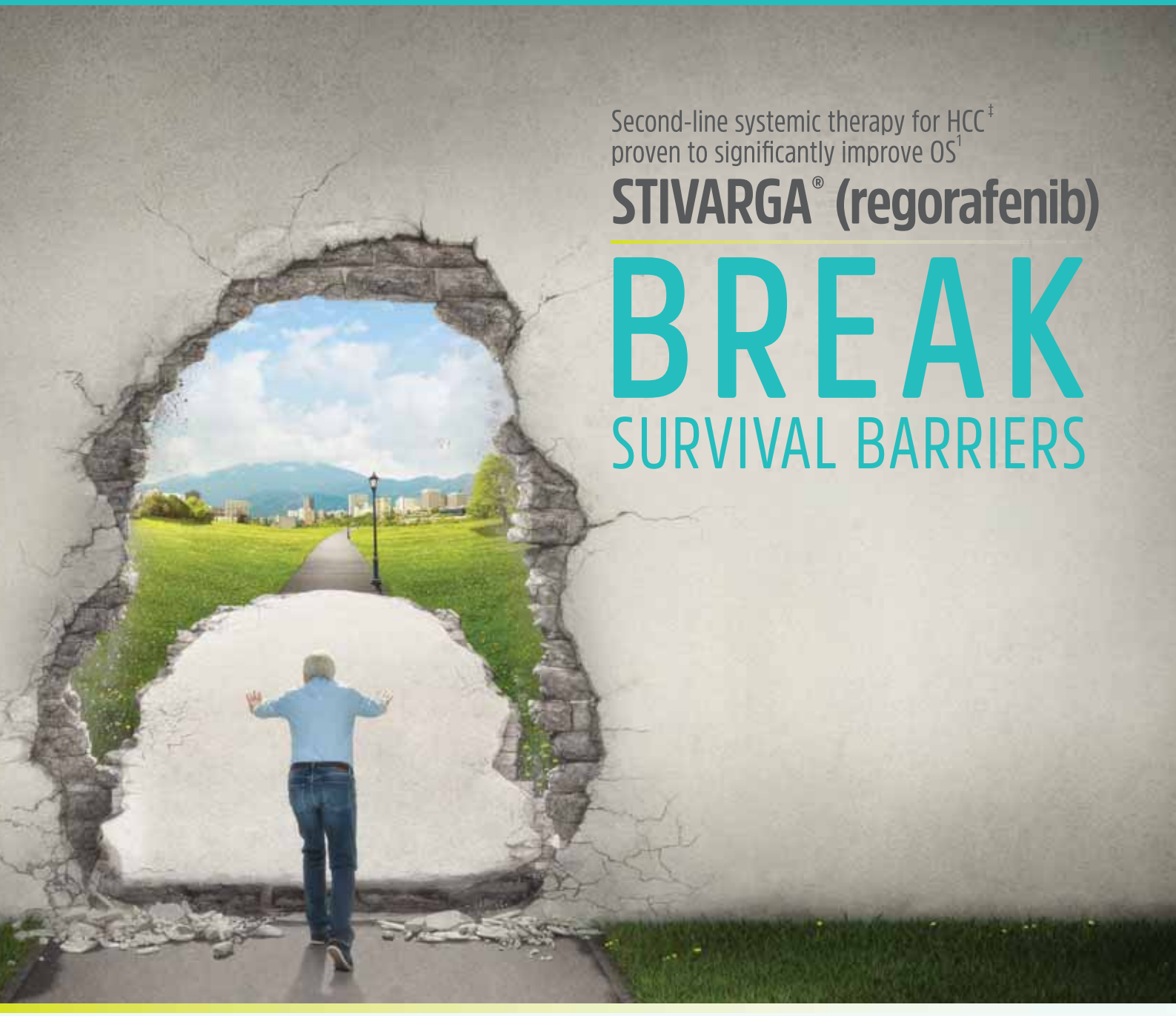

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‡ HCC patients in RESORCE trial: BCLC B or C patients who could not benefit from resection, local ablation or chemoembolization[1]

BCLC, Barcelona Clinic Liver Cancer; RESORCE, REgorafenib after SORafenib in patients with hepatoCEllular carcinoma ; HCC, hepatocellular carcinoma ; OS, Overall Survival

References 1. Bruix J, Qin S, Merle P, et al; on behalf of the RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo controlled, phase 3 trial *Lancet*. 2017;389(10064):56-66

[제품명] 스티바가정40밀리그램(레고라페닙) [주성분] 레고라페닙일수화물(별규) 41.49밀리그램(레고라페닙으로서 40밀리그램) [효능·효과] 1. 이전에 플루오로피리미딘 계열 약물을 기본으로 하는 항암 화학 요법과, 항 VEGF 치료제, 항 EGFR 치료제(RAS 정상형 (wild type)의 경우)로 치료를 받은 적이 있는 전이성 직장결장암 환자의 치료 2. 이전에 이매티닙과 수니티닙으로 치료 받은 적이 있는 전이성 또는 절제불가능한 국소진행성 위장관기질종양(GIST) 환자의 치료 3. 이전에 소라페닙으로 치료 받은 적이 있는 간세포암 환자의 치료 [용법·용량] 1일 권장 투여 용량은 레고라페닙으로서 160 mg (이 약 40 mg 정제 4정에 해당)이며, 1일 1회 경구 복용한다. 투여 주기는 4주로, 3주 투약하고 1주 휴약한다. 이 약은 매일 같은 시간에 가벼운 식사 후 복용한다. 정제를 물과 함께 통째로 삼켜야 한다. 복용을 잊은 것을 기억하는 즉시 이 약을 복용하되, 전날의 투여량을 보충하기 위해 하루에 2회 용량을 복용해서는 안된다. 이 약의 투여는 질병이 진행할 때까지 또는 수용할 수 없는 독성이 발생할 때까지 지속되어야 한다. 환자 개개인의 안전성 및 내약성에 따라, 일시적 투여 중단 및/또는 용량 감소가 필요할 수도 있다. 용량 변경은 40 mg 1정씩 적용한다. 최소 1일 권장 투여 용량은 80 mg이다. 최대 1일 투여 용량은 160 mg이다. 용량 조절에 대한 자세한 내용은 제품설명서 전문을 참고해주시기 바랍니다. [사용상의 주의사항] 1. 경고 1) 임상시험에서 이 약으로 치료 받은 환자에서 치명적인 결과를 동반한 심각한 약물유발 간손상이 발생했다. 대부분의 사례에서, 간 기능 부전은 치료 시작 후 2개월 이내에 발생했으며, 간세포 손상 양상으로 특징지어졌다. 2) 임신한 여성에게 이 약 투여 시 태아에게 해로운 영향을 미칠 수 있다. 랫트 및 토끼에서 이 약은 사람의 권장 노출량보다 적은 용량에서 기형 및 배태자 독성을 유발하는 것으로 나타났다. 임신 가능성이 있는 여성 및 남성은 이 약 투여 중 및 투여 후 8주까지 효과적인 피임법을 실시하여야 한다. 임신 중에 이 약을 사용하거나 이 약을 복용하는 동안 임신이 되면, 태아에 미치는 잠재적 위험에 대해 환자에게 알려주어야 한다. 2. 다음 환자에는 투여하지 말 것 1) 이 약 또는 이 약의 구성성분에 과민증인 환자 3. 다음 환자에는 신중히 투여 할 것 1) 간 기능 장애 환자(1. 경고항 참조) 2) 감염 3) 출혈 4) 심장 허혈 및 경색 4. 이상반응 이 약의 가장 중대한 약물 이상 반응은 중증의 간 손상 및 출혈, 위장관 천공 및 감염이었다. 임상시험에서 매우 흔하게 나타난 약물이상반응(10% 이상): 감염, 저혈소판증, 빈혈, 식욕 및 음식섭취 감소, 출혈, 고혈압, 발성장애, 설사, 구내염, 구토, 오심, 고빌리루빈혈증, 트랜스아미나아제 상승, 손발피부반응, 발진, 무력증/피로, 통증, 고열, 근육염증, 체중감소 흔하게 나타난 약물이상반응(1%이상 10%미만): 백혈구감소증, 감상선기능저하증, 저칼륨혈증, 저칼슘혈증, 저나트륨혈증, 저마그네슘혈증, 고요산혈증, 탈수, 두통, 떨림, 말초신경병증, 미각이상, 입안건조, 위식도역류질환, 위장염, 탈모, 피부건조, 박리성 발진, 근육 경련, 단백뇨증, 아밀라아제 상승, 리파아제 상승, INR치 비정상 [전문의약품] [수입 및 판매자] 바이엘코리아㈜ [개정년월일] 2020.02.22 보다 자세한 사항은 제품설명서 전문 또는 바이엘 웹사이트, http://www.bayer.co.kr/를 참고하시기 바랍니다.

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** 성인 비대상성 간경변 유전자형 1형 환자 및 간 이식 후 유전자형 1형, 4형 환자와 같은 severe한 환자까지 높은 완치율

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**** 음식물과 함께 또는 음식물 없이 경구 투여

Harvoni® Tablet (Ledipasvir 90mg, Sovosbuvir 400mg)
[INDICATION] For the treatment of genotype 1, 2, 4, 5 or 6 chronic hepatitis C (CHC) in adults and paediatrics aged 12 to <18 years, as monotherapy or in combination with other medicinal products. **[DOSAGE AND ADMINISTRATION]** One tablet once daily with or without food. (Refer to full PI for the recommended treatment duration for patient subgroups) **[PRECAUTIONS IN USE]** 1. Warnings 1) Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV. 2) This drug should not be administered concomitantly with other medicinal products containing sofosbuvir. 3) Severe bradycardia and heart block. 4) Pregnancy and concomitant use with ribavirin. 5) The potential risks and benefits associated with co administration with certain HIV antiretroviral regimens should be considered. 6) Co-administration of this drug and HMG CoA reductase inhibitors (statins) can significantly increase the concentration of the statin, which increases the risk of myopathy and rhabdomyolysis. 2. Do not administer to the following patients 1) Hypersensitivity to the active substances or to any of the excipients of this drug. 2) Co administration with rosuvastatin or St. John's wort (Hypericum perforatum). 3) Co-administration with medicinal products that are potent P glycoprotein (P gp) inducers in the intestine will significantly decrease ledipasvir and sofosbuvir plasma concentrations and could result in loss of efficacy of Harvoni. 4) Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption. 5) As this drug is used in combination with other drugs, all contraindications to the combined drugs are also applied to this drug combination therapy. 6) When used in combination with ribavirin, pregnant women and their male partners, or women suspected to be pregnant. 3. Undesirable effects 1) Treatment of patients with prior exposure to HCV direct-acting antivirals. 2) As this drug contains Yellow no. 5 (Sunset yellow FCF), it should be carefully administered to the patients who have hypersensitivity or history of allergic reaction to this ingredient. 4. Undesirable effects 1) In clinical studies, fatigue and headache were more common in patients treated with ledipasvir/sofosbuvir compared to placebo. 2) Cardiac arrhythmias when used with concomitant amiodarone and skin and subcutaneous tissue disorders were identified during post approval use of this drug. (Refer to full PI for more safety information) 5. General precautions 1) Diabetics may experience improved glucose control, potentially resulting in symptomatic hypoglycaemia, after initiating HCV direct-acting antiviral treatment. 2) Medicinal products that are moderate P gp inducers in the intestine (e.g. oxcarbazepine) may decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of this drug. 3) Resistance (Refer to full PI for more information) 6. Drug interactions 1) Ledipasvir is an in vitro inhibitor of drug transporter P gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of co administered substrates for these transporters. 2) Medicinal products that are potent P gp inducers may significantly decrease ledipasvir and sofosbuvir plasma concentrations leading to reduced therapeutic effect of ledipasvir/sofosbuvir and thus are contraindicated with this drug. 3) Clearance of HCV infection with direct acting antivirals may lead to changes in hepatic function, which may require monitoring or dose adjustment of concomitant medication. (Refer to full PI for more information) 7. Use in Pregnant Women and Nursing Mothers 1) Pregnancy: When this drug is used in combination with ribavirin, it must not be used in women who are pregnant or suspected to be pregnant and their partners. 2) Breast feeding: It is unknown whether ledipasvir or sofosbuvir and its metabolites are excreted in human milk. Therefore, this drug should not be used during breast feeding. 8. Use in specific population This drug is not recommended for use in paediatric patients aged < 12 years because the safety and efficacy have not been established in this population. No dose adjustment is warranted for elderly patients. No dose adjustment of this drug is required for patients with renal impairment including end stage renal disease (ESRD) requiring haemodialysis. No dose adjustment of this drug is required for patients with mild, moderate or severe hepatic impairment (Child Pugh Turcotte [CPT] class A, B or C). **[Storage Condition]** Store in a tight container at room temperature (1-30° C) **[Package Unit]** 28 tablets **[Manufacturer]** Patheon, Inc. (Canada) Or Gilead Sciences Ireland UC (Ireland) **[Importer]** Gilead Sciences Korea Ltd., West Tower 15F, Center 1, 26, Euljiro 5-gil, Jung-gu, Seoul, Korea (Representative phone: 02-6030-3300, Medical information: 0079-814-800-9172) **[Date of Preparation]** 2020. 03 (HVN-2003-01)

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Baraclude is **Life-mate** for Life long HBV Treatment

13-years proven real-world efficacy & safety since 2007

Baraclude®
(entecavir) 0.5mg/1mg tablets

Drug Information
Product Name: BARACLUDE® (Entecavir) 0.5mg and 1.0mg **Indication:** This drug is indicated for the treatment of chronic hepatitis B virus infection in adults (above 16 years old) and pediatric patients 2 years of age and older with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. **Dosage and Administration :** This drug should be administered on an empty stomach (at least 2 hours after a meal and 2 hours before the next meal).
*Please refer to full prescribing information on dosage adjustment for patients with renal impairment, child patients

Bristol Myers Squibb™

GC Pharma

686KR20PR00528-01 / Mar 2020

인생친구

Baraclude® (entecavir) 0.5mg/1mg tablets

Baraclude goes along with your long journey

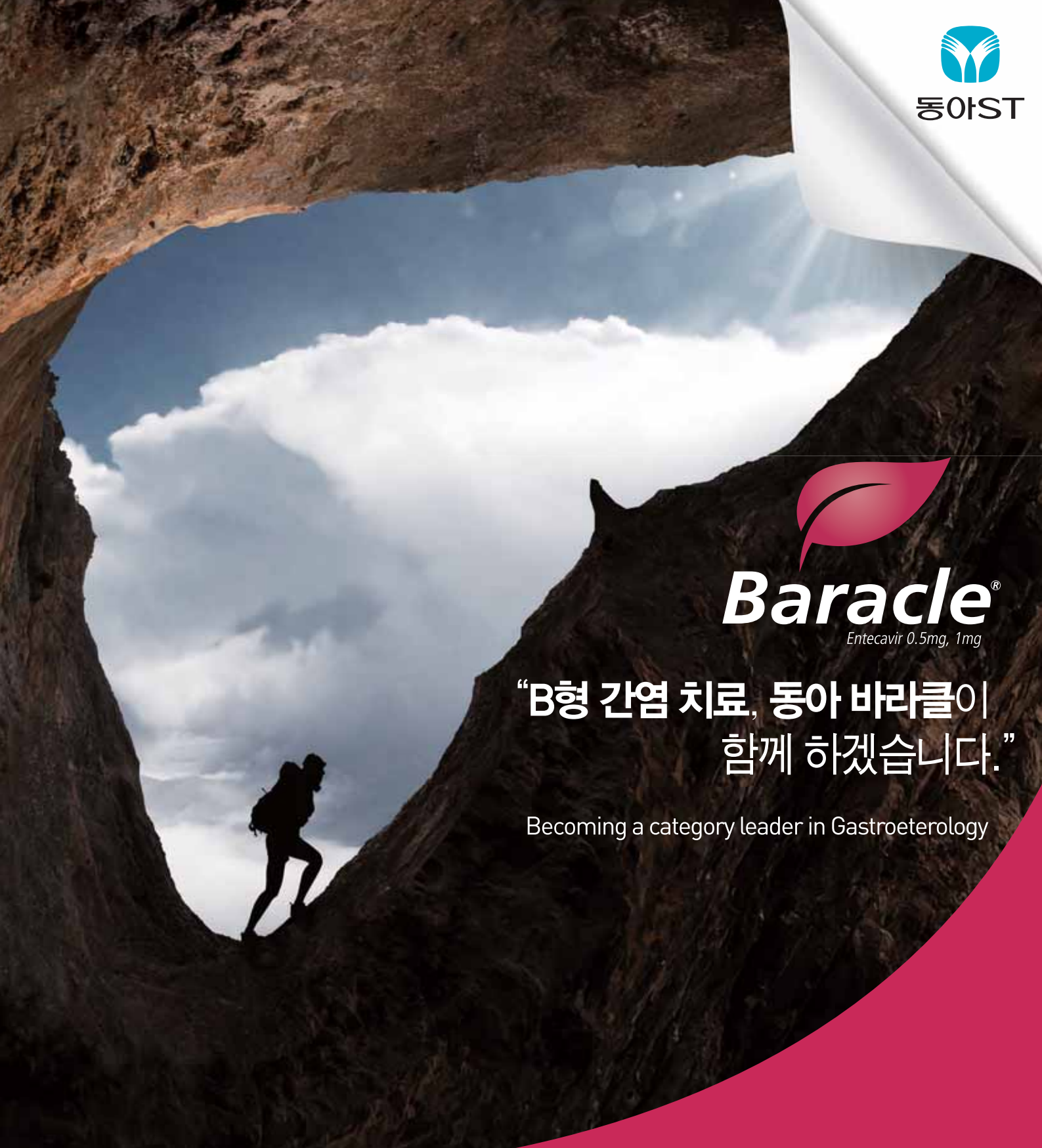
- With or without cirrhosis[1]
- Regardless of HBV DNA levels[2]
- With or at risk of renal or bone diseases[3-5]

[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]** 제품 설명서의 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: 제품 설명서 참조
* 신부전 환자의 용량 조절 및 자세한 내용은 제품설명서를 참조하십시오.

References 1. PC Wang, *et al. European Journal of Gastroenterology&Hepatology* 2017;29:946-950. **2.** Wu IT, *et al. Clin Microbiol Infect* 2017 Jul;23(7):464-469. **3.** EASL. Clinical Practice Guidelines on the management of hepatitis B virus infection. 2017. **4.** AASLD. Practice Guidance. 2018. **5.** 대한간학회. 만성 B형간염 진료 가이드라인 2018.

Bristol Myers Squibb™ GC 녹십자

696KR20PR00723-01 / May 2020



[제품명] 바라클정 0.5mg, 1mg(엔테카비르) **[성분 · 함량]** 바라클정 0.5mg : 이 약 1정(206mg) 중 엔테카비르(별규) 0.53mg(엔테카비르 무수물로서 0.5mg) 바라클정 1mg : 이 약 1정(412mg) 중 엔테카비르(별규) 1.06mg(엔테카비르 무수물로서 1mg) 첨가제(타르색소) : 적색40호 알루미늄레이크, 황색5호 알루미늄레이크, 청색2호 알루미늄레이크 **[성상]** 바라클정 0.5mg : 홍색~회백색의 삼각형 모양의 필름코팅정 바라클정 1mg : 분홍색의 삼각형 필름코팅정 **[효능 · 효과]** 활동성 바이러스의 복제가 확인되고, 혈청 아미노전이효소(ALT 또는 AST)의 지속적 상승 또는 조직학적으로 활동성 질환이 확인된 성인(16세 이상)의 만성 B형 간염바이러스 감염의 치료 **[용법 · 용량]** • 이 약은 공복 시 (식사 2시간 후 또는 최소 2시간 전) 경구투여합니다. • 이 약은 1일 1회 엔테카비르로서 0.5mg 을 경구투여합니다. • 라미부딘 저항성 환자, 즉, 라미부딘 치료에도 불구하고 B형간염바이러스의 지속적 증식을 경험하였거나, 라미부딘저항성 변이가 있는 16세이상의 환자 : 1일1회 공복시 엔테카비어로서 1mg • 신부전환자 : 신부전 환자에서는 크레아티닌 청소율이 감소함에 따라 이 약의 경구 소실율은 감소합니다. 혈액투석이나 복막투석(CAPD)을 받고 있는 환자를 포함하여 크레아티닌 청소율이 50mL/min 미만인 환자에서는 다음과 같이 용량을 조절합니다.

크레아티닌 청소율(mL/min)	엔테카비어 용량	라미부딘 저항성 환자에서의 엔테카비어 용량
≥ 50	1일1회 0.5 mg	1일1회 1 mg
30 – <50	1일1회 0.25 mg [a] 또는 48시간마다 0.5 mg	1일1회 0.5 mg 또는 48시간마다 1 mg
10 – <30	1일1회 0.15 mg [a] 또는 72시간마다 0.5 mg	1일1회 0.3 mg a 또는 72시간마다 1 mg
<10, 혈액투석 b 또는 CAPD	1일1회 0.05 mg [a] 또는 7일마다 0.5 mg	1일1회 0.1 mg a 또는 7일마다 1 mg

a : 0.5mg보다 적은 용량은 시럽제 사용이 권장된다.
b : 혈액투석 일에 투여된다면, 혈액투석 과정 후에 이 약을 투여한다.
(신부전 환자에서의 약동학적 특성 : 상세정보 기타 : 신부전환자에 대한 투여 참조)

[사용상의 주의사항] 1. 경고 1) 뉴클레오시드 유사체 단독사용 또는 엔테카비르를 포함한 항레트로바이러스제와 병용했을때, 치명적인 경우를 포함하여, 유산증 및 지방증이 있는 중증 간종대가 보고되었습니다.이들 대부분은 여성에서 발생했습니다. 비만과 지속된 뉴클레오시드 사용이 위험인자들일수 있습니다. 간질환에 대한 알려진 위험인자 들을 가진 환자에게 뉴클레오시드 유사체를 투여할 때에는 각별한 주의가 요구됩니다. 하지만, 알려진 위험인자들을 가지고 있지 않은 환자에서도 보고된 사례가 있었습니다. 유산증이 보고되었으며, 중증 간대사기능장애, 다른 심각한 의학적 상태(medicalcondition) 또는 약물노출과 관련된 것이었습니다. 간대사기능장애를 가진 환자의 경우 유산증 위험성이 더 높습니다.이 약을 사용한 치료는 유산증이나 명백한 간독성(트랜스아미나제 수치의 상승없는 간종대와 지방증을 포함)을 나타내는 임상적 발견 또는 임상검사치가 나타나면 일시 중지되어야 합니다. 2) 이 약을 비롯한 B형간염 요법을 중단한 환자에서 B형간염의 중증 급성악화가 보고되었습니다. B형B형간염 요법을 중단한 환자에 대해서는 적어도 수 개월간 임상 및 임상검사상 간기능을 면밀하게 추적 관찰해야 합니다. 적절한 경우, 항B형간염 요법을 개시할수 있습니다. 3) 이 약은 효과적인 HIV(인체면역결핍바이러스)치료를 받고 있지 않는 HIV와 HBV에 함께 감염된 환자들을 대상으로 평가되지 않았습니다. HIV에 감염되었지만 아직 치료받지 않은 환자에게 만성 B형감염의 치료로 이 약이 사용된다면 HIV 뉴클레오시드 역전사효소 억제제에 대한 저항성을 나타낼 수 있음이 제한된 임상시험 경험에서 나타났습니다. 그러므로 고효능 항레트로바이러스 치료법(HAART)으로 함께 치료받고 있지 않은 HIV/HBV 동시 감염 환자에게는 이 약을 사용한 치료가 권장되지 않습니다. 이 약을 사용하기 전에 환자들은 HIV 항체 테스트가 필요합니다. 이 약은 HIV감염의 치료목적으로 연구되지 않았고 이러한 목적으로 권장되지 않습니다. 2. 다음 환자에는 투여하지 마십시오. 1) 이 약이나 이 약의 성분에 과민반응이 있는 환자2) 이 약은 유당수화물을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance,Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactosemalabsorption) 등의 유전적인 문제가 있는 환자 3. 다음 환자에는 신중히 투여하십시오. 1) 신부전 : 혈액투석 또는 복막투석(CAPD)을 받고 있는 환자를 포함하여 크레아티닌 청소율이 50 mL/min이하인 환자에서는 용량조절이 권장됩니다. 2) 간이식 수여자 : 싸이클로스포린이나 타크롤리무스와 같이 신장 기능에 영향을 줄 수 있는 약물을 투여 받고 있는 간이식수여자에서 이 약의 요법을 개시하기 전 및 치료 중에 신기능을 주의하여 평가해야 합니다. 3) 이 약은 황색소선(샛별로우 FCF, Sunset Yellow FCF)을 함유하고 있으므로 이 성분에 과민하거나 알레르기 병력이 있는 환자에는 신중히 투여합니다. **※자세한 제품정보는 제품설명서를 참고해 주십시오**

BLT-19J016

DONG-A ST

Tenofovir?
Must be Real,
Must Virreal®

Virreal®
helps with **medication compliance**

Virreal®
is **economical**

Virreal®
conducts **naïve Phase Ⅲ clinical trials**

Virreal® [Tenofovir disoproxil orotate]

Virreal® Tablets (Tenofovir disoproxil orotate) [Indication] 1. In combination with other antiretroviral agents, for the treatment of HIV-1 infection in adult and pediatric patients 12 years of age and older 2. For the treatment of chronic hepatitis B in adults and pediatric patients 12 years of age and older [Dosage & administrations] [1] 1 tablet once daily taken orally, without regard to food [2] Patients with Renal Impairment : Significantly increase drug exposures occurred to subjects with moderate to severe renal impairment. Therefore, the dosing interval of this drug should be adjusted in patients with baseline creatinine clearance below 50mL/min. [Warning] 1. Lactic acidosis/ severe hepatomegaly with Steatosis 2. Worsening of Hepatitis after Discontinuation of Treatment 3. New onset or Worsening of Renal Impairment 4. Coadministration with Other Products 5. Patients Coinfected with HIV-1 and HBV 6. Decreases in Bone Mineral Density 7. Fat Redistribution 8. Immune Reconstitution Syndrome 9. Early Virological Failure [Contraindication] 1.Hypersensitivity to this drug 2. Patients with genetic problems related with lactose [Manufacturer] Dong-A ST Corp. [Distributor] Dong-A ST Corp.
*Please refer to full prescribing information.

Virreal®

VRE-15MD15

ILDONG

Besivo & L-carnitine
For HBV patients liver BETTER!!

Besivo®,
New treatment option for chronic hepatitis B patients

The first developed nucleotide analogue in Korea.
Efficacy, safety and beneficial effects of L-carnitine PLUS!

Antiviral effect of Besivo®

- Besivo has antiviral efficacy comparable to that of TDF after 48 weeks of treatment, with durable effects for 96 weeks.

Tolerance of Besivo®

- Besivo had no drug-resistance mutation for 96 weeks.

Safety data of Besivo®

- Besivo has a better safety profile than TDF, in terms of bone and renal outcomes.

Histological effect of Besivo®

- Besivo showed a significantly higher proportion of patients with improved histological scores* than TDF.

* Ishak modified HAI(hepatic activity index) scoring system
TDF: Tenofovir disoproxil fumarate

REFERENCES
1. Sang Hoon Ahn, et al. Clin Gastroenterol Hepatol. 2018 Nov 15. pii: S1542-3565(18)31244-8. doi: 10.1016/j.cgh.2018.11.001.
2. Besivo Phase III Clinical Trial. Protocol No. ID_BVCL011 Clinical Study Report

Besivo®
Besifovir Dipivoxil 150mg tablets

Besivo® Tab. (Besifovir dipivoxil maleate 183 mg [Besifovir dipivoxil 150 mg])

ETC

[Indication and Usage] Treatment of chronic hepatitis B in adults **[DOSAGE AND ADMINISTRATION]** One tablet containing 150 mg besifovir dipivoxil once daily orally with or without food in adults. When taking this medicine, take 660 mg of L-Carnitine together to prevent a decrease in serum L-Carnitine level. **[WARNINGS AND PRECAUTIONS]** 1) Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. Treatment should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations). 2) Discontinuation of anti-HBV therapy may be associated with severe acute exacerbations of hepatitis. Patients infected with HBV who discontinue Besivo should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, resumption of anti-hepatitis B therapy may be warranted. 3) HIV-1 antibody testing should be offered to all HBV-infected patients before initiating therapy with Besivo. Limited clinical experience suggests there is a potential for the development of resistance to HIV if Besivo is used to treat chronic hepatitis B virus (HBV) infection in patients with HIV infection that is not being treated. Therapy with Besivo is not recommended for HIV/HBV co-infected patients.

BESH-EX04-1906

Besivo & L-carnitine
for your Liver Better!

미토콘드리아 내 지방대사와 당대사 활성을 깨우세요![1]

REFERENCES
1. Altern Med Rev. 2005;10(1):42-50

[제품명] 베시보®정 전문의약품
[원료약품의 분량] 1정 중 베시포비르디피복실말레산염 183mg (베시포비르디피복실로서 150mg)
[효능 · 효과] 만성 B형 간염의 치료 **[용법 · 용량]** 성인 : 1일 1회 1정 (베시포비르디피복실로서 150mg)을 경구투여한다. 이때, 혈청 L-카르니틴의 저하를 막기 위해 L-카르니틴 660mg을 함께 투여한다. 음식물의 섭취와 상관없이 복용할 수 있다. **보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다.**

[제품명] 엘칸®정 일반의약품
[원료약품의 분량] 1정 중 L-Carnitine 330mg (카르니틴(으)로서 300mg)
[효능 · 효과] 1. 1차성, 2차성 카르니틴 결핍증 2. 허혈성 심질환에 의한 심근대사장애 : 협심증, 급성심근경색 **[용법 · 용량]** 성인 : L-카르니틴으로서 1일 2~3g을 2~3회 분할 복용한다. 연령, 증상에 따라 따라 적절히 증감한다. **보다 자세한 사항은 제품설명서 전문을 참고하시기 바랍니다.**

베시보정, 엘칸정 식약처 허가사항(2019.05 기준)

LCARNY-BR01-1905

ILDONG 서울특별시 서초구 바우뫼로 27길 2 (우) 06752 TEL. 080-022-1010(제품문의 및 고객상담), 02-526-3114(본사)

L-CARN® Tab. (L-Carnitine) Besivo® Besifovir Dipivoxil

DAEWOONG

Proven by PEGASUS-D study

(Prevention of Gallstone Formation after Gastrectomy in Patients with Gastric Cancer)

URSA® Tab. 300mg

The World's First Indications

"The Prevention of Gallstone formation after Gastrectomy with Gastric Cancer"

- Displacement of toxic bile acid
- Immunomodulatory effects
- Cytoprotective effects
- Stimulation of bile secretion

Composition

- Each tablet contains – Ursodeoxycholic acid(KP) 300mg

Indication/Dosage and administration

ETC

- 300mg Tab.:

– The Treatment of Patients with Primary Biliary Cirrhosis: 300mg t.i.d
– The Prevention of Gallstone Formation in Obese Patients undergoing Rapid Weight: 300mg b.i.d
– The Prevention of Gallstone Formation after Gastrectomy in Patients with Gastric Cancer: 300mg q.d

URSA®

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

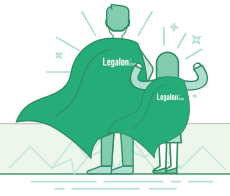
- Proven efficacy in improvement of liver function [5-11]
  * NAFLD, NASH, ALD, cirrhosis

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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- 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

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개인정보동의 확인

References. 1. 카보메틱스® 제품설명서(개정년월일 2019년 10월 11일) 2. Abou-Alfa GK, *et al. New England Journal of Medicine*. 2018; 379(11): 54-63.

[전문/421] 카보메틱스 정 **20mg/ 40mg/ 60mg** **성분:** 카보잔티닙에스말산염 **효능·효과:** 1) 신장세포암의 치료: 이전에 VEGF (Vascular endothelial growth factor) 표적요법의 치료 받은 적이 있는 진행성 신장세포암의 치료 2) 간세포암의 치료 : 이전에 소라페닙으로 치료 받은 적이 있는 간세포암 환자의 치료 **용법·용량:** 이 약을 이용한 치료는 항암제 투여에 숙련된 전문가에 의해 시작되어야 한다. 권장 투여용량은 1일 1회 60mg이다. 이 약은 환자에게 더 이상 임상적 유익성이 없거나 수용할 수 없는 독성이 발생하기 전까지 투여한다. 의심되는 이상반응 관리를 위해 일시적으로 이 약의 투여를 중단하거나 용량 감소가 요구될 수 있다. 투여용량 감소가 필요한 경우, 이 약의 투여용량을 1일 40mg으로 감소시킨 후, 1일 20mg으로 감소시키는 것을 권장한다. 투약 중단은 CTCAE 3등급 또는 그 이상의 독성, 또는 참을 수 없는 2등급 독성의 경우 권장된다. 투여용량 감소는 심각하거나 또는 견딜 수 없는 경우가 지속된다면 권장된다. 만약 환자가 복용을 잊은 경우, 다음 복용 12시간 이내에 누락된 복용량은 투여하지 않아야 한다. (이하 제품설명서 용법·용량 참조) 특수 환자군: <신장애 환자> 이 약은 경증 또는 중등도 신장애 환자에게 주의하여 사용되어야 한다. 이 약은 중증 신장애 환자에게 안전성과 유효성이 입증되지 않았으므로 사용이 권장하지 않는다. <간장애 환자> 경증 간장애 환자에서 용량 조절은 필요하지 않으나, 중등증 간장애 환자에게 추천되는 투여량은 1일 1회 40mg이다. 환자는 약물이상반응이 모니터링 되어야 하며 필요에 따라 용량 조정 또는 투약 중단이 고려되어야 한다(사용상의 주의사항 '10. 전문가를 위한 정보' 참조). 카보잔티닙은 중증 간장애 환자에게 안전성과 유효성이 입증되지 않았으므로 권장되지 않는다. 투여 방법 경구로 투여한다. 이 약은 통째로 삼켜야 하며, 부수어서는 안 된다. 환자는 적어도 이 약을 복용 전 2시간, 복용 후 1시간 동안은 음식물 섭취를 하여서는 안 된다. **사용상의 주의사항:** 1) 이 약의 주성분 또는 첨가제에 과민반응의 병력이 있는 환자 2) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소결핍증 (Lapp lactase deficiency), 또는 포도당-갈락토오스 흡수장애 (glucose-galactose malabsorption)와 같은 유전적 문제가 있는 환자에게는 투여해서는 안 된다. 이상반응: 위장관 천공, 누공, 출혈, 혈전색전증, 설사, 피로, 식욕감소, 손발바닥 홍반성감각이상 증후군, 오심, 고혈압, 구토 등. Please refer to full SmPC for further information * 제품에 관한 보다 자세한 사항은 입센코리아㈜로 문의하여 주십시오. **[저장방법]** 기밀용기, 실온보관(1~30 °C) **[포장단위]** 30정/병 **[제조원]** 수입자: 입센코리아㈜/ 서울시 강남구 강남대로 262 11층. Tel) 02-405-9500 제조의뢰자: Ipsen Pharma/ 65, Quai Georges Gorse, 92100 Boulogne-Billancourt, 프랑스 제조자: Patheon Inc./ 2100 Syntex Court, Mississauga, Ontario L5N 7K9, 캐나다 [개정 연월일] 2019년 10월 11일

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Ref. 1) Kim D et al, Drug Des Devel Ther. 2019 Sep 3 **2)** ESODUO tab, CTD **3)** 보건복지부 고시 제2020-16호(20.02.01 시행)

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제품요약정보[1]

전문의약품 분류번호 : 634

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2018. 8. 21. 개정

※처방하기 전 제품설명서 전문을 참고하십시오. 최신 허가사항에 대한 정보는 '의약품통합정보시스템(nedrug.mfds.go.kr)'에서 확인할 수 있습니다.

References) 1. 에스케이알부민주5%(사람혈청알부민) 허가정보, 의약품통합정보시스템, [Cited 2019 Mar 22] Available from: https://nedrug.mfds.go.kr **2.** Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products [Internet]. WHO; 2004 [cited 2015 Apr 6]. Available from: http://www.who.int/bloodproducts/publications/WHO_TRS_924_A4.pdf

ABM-HA02-201903-01