Joint Symposium
-JKT (Clinical)

New Clinical Insights into the MASLD

Chairpersons

Kyoung-Kon Kim
Gachon University, Korea

Wen-Yuan Lin
China Medical University, Taiwan

Speakers

Jae Seung Lee
Yonsei University, Korea

Chun-Jen Liu
National Taiwan University, Taiwan

Masato Furuhashi
Sapporo Medical University, Japan

Jae Seung Lee

Yonsei University, Korea

• Education

Period	Affiliation	Position
– **2018-2024**	Department of Medicine, The Graduate School, Yonsei University, Seoul, Korea	Ph.D.
– **2004-2010**	Yonsei University College of Medicine, Seoul, Korea	M.D.

• Affiliations / Experience

Period	Affiliation	Position
– **2020-Present**	Department of Internal Medicine, Severance Hospital	Clinical Assistant Professor
– **2014-2020**	Department of Internal Medicine, Severance Hospital	Residency and Fellowship
– **2011-2014**	Republic of Korea Army (ROKA), Korea	Military Medical Officer
– **2010-2011**	Severance Hospital, Yonsei University College of Medicine	Internship

• Committee Memberships

- The Academic Committee of the KASL
- The Research Committee of the KASL
- The Publication Committee of the Korean Association of Clinical Ultrasound
- The Multidisciplinary Committee of the Korean Liver Transplantation Society

• Publications

- Lee JS, Jung CY, Lee JI, Ahn SH, Kim BS, Kim SU. Comparison of decline in renal function between patients with chronic hepatitis B with or without antiviral therapy. *Aliment Pharmacol Ther.* 2023 Jul;58(1):99-109. doi: 10.1111/apt.17532. Epub 2023 Apr 28. PMID: 37114501
- Lee JS, Lee HW, Kim BK, Park JY, Kim DY, Ahn SH, Jang JY, Park SY, Lee HW, Lee CK, Kim SU. Comparison of FibroScan-Aspartate Aminotransferase (FAST) Score and Other Non-invasive Surrogates in Predicting High-Risk Non-alcoholic Steatohepatitis Criteria. *Front Med (Lausanne).* 2022 Apr 14;9:869190. doi: 10.3389/fmed.2022.869190. PMID: 35492369; PMCID: PMC9048204
- Lee JS, Lee HW, Lim TS, Min IK, Lee HW, Kim SU, Park JY, Kim DY, Ahn SH, Kim BK. External Validation of the FSAC Model Using On-Therapy Changes in Noninvasive Fibrosis Markers in Patients with Chronic Hepatitis B: A Multicenter Study. *Cancers (Basel).* 2022 Jan 29;14(3):711. doi: 10.3390/cancers14030711. PMID: 35158982; PMCID: PMC8833581
- Lee JS, Sinn DH, Park SY, Shin HJ, Lee HW, Kim BK, Park JY, Kim DY, Ahn SH, Oh JH, Lee JI, Kim SU. Liver Stiffness-Based Risk Prediction Model for Hepatocellular Carcinoma in Patients with Nonalcoholic Fatty Liver Disease. *Cancers (Basel).* 2021 Sep 11;13(18):4567. doi: 10.3390/cancers13184567. PMID: 34572795; PMCID: PMC8472221
- Baatarkhuu O, Lee JS (Co-primary), Amarsanaa J, Kim DY, Ahn SH, Naranzul N, Enkhtuya D, Choijamts N, Batbayar P, Otgonbayar R, Saruul BU, Gantuul C, Gegeebadrakh B, Tuvshinbayar N, Badamsuren D, Ulzmaa G, Otgonbold J, Han KH. Efficacy and safety of ledipasvir/sofosbuvir in 5,028 Mongolian patients infected with genotype 1 hepatitis C virus: A multicenter study. *Clin Mol Hepatol.* 2021 Jan;27(1):125-135

Joint Symposium-JKT (Clinical)

Noninvasive Approaches to Monitor Liver Fibrosis in Metabolic-Associated Steatotic Liver Disease

Jae Seung Lee (Yonsei University, Korea)

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), is one of the most prevalent causes of chronic liver disease. MASLD covers a spectrum ranging from simple steatosis without inflammation to more severe conditions like steatohepatitis, fibrosis, cirrhosis, and, ultimately, end-stage liver disease. Approximately 25–40% of patients with MAFLD progress to metabolic dysfunction-associated steatohepatitis (MASH), a more severe form characterized by aggressive histological features, including necroinflammatory activity, which increases the risk of liver fibrosis. Identifying patients with advanced inflammation and significant fibrosis is crucial, given their higher risk of progressing to cirrhosis and hepatocellular carcinoma.

Currently, liver biopsy is considered the gold standard for evaluating the severity of steatohepatitis, usually quantified by the NAFLD activity score (NAS), which includes histological assessments of steatosis, ballooning, lobular inflammation, and fibrosis stages ranging from 0 to 4. However, liver biopsy is often impractical due to its invasive nature, cost, sampling errors, and variability between observers.

Consequently, there has been a significant effort to develop noninvasive methods to estimate the histological grade of steatosis, inflammation, and fibrosis using blood-based markers, laboratory test-based scoring systems, and imaging techniques like vibration-controlled transient elastography (VCTE) and magnetic resonance imaging (MRI). Ongoing research aims to determine the superiority of specific tests or to optimize sequential algorithms that provide the most accurate assessment of fibrosis staging.

This lecture will review the currently available noninvasive methods for assessing liver fibrosis.

Chun-Jen Liu

National Taiwan University, Taiwan

• Education

Period	Affiliation	Position
– **2003**	Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine	Ph.D.
– **1992**	Medicine, National Taiwan University	M.D.

• Affiliations / Experience

Period	Affiliation	Position
– **2023-Present**	Division of Gastroenterology & Hepatology (NTUH)	Director
– **2019**	Hepatitis Research Center (NTUH)	Director
– **2018**	Department of Internal Medicine, National Taiwan University College of Medicine	Professor
– **2011**	Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine	Professor

• Committee Memberships

– Taiwan Association for the Study of the Liver (TASL)

• Publications

– Liu CJ, Chuang WL, Sheen IS, Wang HY, Chen CY, Tseng KC, Chang TT, Massetto B, Yang JC, Yun C, Knox SJ, Osinusi A, Camus G, Jiang D, Brainard DM, McHutchison JG, Hu TH, Hsu YC, Lo GH, Chu CJ, Chen JJ, Peng CY, Chien RN, Chen PJ. Efficacy of ledipasvir and Sofosbuvir Treatment of HCV Infection in Patients Coinfected with HBV. *Gastroenterology* 2018;154:989-997

– Liu CJ, Chuang WL, Lee CM, Yu ML, Lu SN, Wu SS, Liao LY, Chen CL, Kuo HT, Chao YC, Tung SY, Yang SS, Kao JH, Liu CH, Su WW, Lin CL, Jeng YM, Chen PJ, Chen DS. Peginterferon alfa-2a plus ribavirin for the treatment of dual chronic infection with hepatitis C and B viruses. *Gastroenterology* 2009;136:496-504

– Liu CJ, Lee PH, Lin DY, Wu CC, Jeng LB, Lin PW, Mok KT, Lee WC, Yeh HZ, Ho MC, Yang SS, Lee CC, Yu MC, Hu RH, Peng CY, Lai KL, Chang SC, Chen PJ. Heparanase inhibitor PI-88 as adjuvant therapy for hepatocellular carcinoma after curative resection: A randomized phase II trial for safety and dose-finding. *J Hepatol* 2009;50:958-968

– Liu CJ, Lo SC, Kao JH, Tseng PT, Lai MY, Ni YH, Yeh SH, Chen PJ, Chen DS. Transmission of occult hepatitis B virus by transfusion to adult and pediatric recipients in Taiwan. *J Hepatol* 2006;44:39-46

– Liu CJ, Chen PJ, Lai MY, Kao JH, Chang CF, Wu HL, Shau WY, Chen DS. A prospective study characterizing full-length hepatitis B virus genomes during acute exacerbation. *Gastroenterology* 2003;124:80-90

Joint Symposium-JKT (Clinical)

Effects of Exercise Intervention in Subjects with Steatotic Liver Disease

Chun-Jen Liu (National Taiwan University, Taiwan)

The objective of this trial was to compare cardiorespiratory fitness and metabolic parameters between individuals diagnosed with metabolic dysfunction-associated steatotic liver disease (MASLD) and matched controls, and to examine the effect of exercise intervention on cardiorespiratory fitness and metabolic derangement. Methods: Individuals diagnosed with MASLD and age-, sex-, body mass index (BMI)-matched healthy volunteers were assessed through cardiopulmonary exercise testing (CPET), biochemical analyses, body composition assessments, and exercise habit surveys. Results: The study included 24 individuals with MASLD (mean age: 45.8 years, standard deviation [SD]: 8.9) and 12 matched controls (mean age: 45.4 years, SD: 6.2). Individuals with MASLD displayed more severe liver steatosis, higher triglyceride levels, worse glycemic profiles, and larger waist circumference compared to the controls (all $p<0.05$). They also showed significantly lower cardiorespiratory performance compared to the controls. Multiple regression analysis identified MASLD was an independent predictor of diminished cardiorespiratory fitness. After 24-week exercise, metabolic derangements improved; and cardiorespiratory fitness also improved. Conclusions: Indivuduals with MASLD exhibited lower cardiorespiratory fitness and poorer metabolic profiles. Exercise improved cardiorespiratory performance.

Masato Furuhashi

Sapporo Medical University, Japan

• Education

Period	Affiliation	Position
– **2002**	Sapporo Medical University	Ph.D.
– **1995**	Sapporo Medical University	M.D.

• Affiliations / Experience

Period	Affiliation	Position
– **2022-Present**	Sapporo Medical University	Professor
– **2015**	Sapporo Medical University	Assistant Professor
– **2013**	Sapporo Medical University	Instructor
– **2004**	Harvard School of Public Health	Postdoctoral Fellow
– **1995**	Sapporo Medical University	M.D.

• Committee Memberships

- Japanese Society of Internal Medicine
- Japan Society for the Study of Obesity
- Japan Diabetes Society
- Japan Endocrine Society
- American Heart Association

• Publications

- Furuhashi M. *J Atheroscler Thromb* 26: 216-232, 2019
- Furuhashi M, *et al*. *Arterioscler Thromb Vasc Biol* 36: 825-834, 2016
- Furuhashi M, *et al*. Nat Rev Drug Discov 7: 489-503, 2008
- Furuhashi M, *et al*. *J Clin Invest* 118: 2640-2650, 2008
- Furuhashi M, *et al*. *Nature* 447: 959-965, 2007

Joint Symposium-JKT (Clinical)

MASLD and Cardio-Renal-Metabolic Syndrome

Masato Furuhashi (Sapporo Medical University, Japan)

New nomenclature of steatotic liver disease (SLD) including metabolic dysfunction-associated SLD (MASLD), MASLD and increased alcohol intake (MetALD), and alcohol-associated liver disease (ALD) has recently been proposed. We investigated the interrelationships among the new nomenclature of SLDs including MASLD, MetALD and ALD as well as the former nomenclature of nonalcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) and explored patient populations categorized within each classification using machine learning (ML) models (*J Gastroenterol Hepatol* 2024). In Japanese individuals who received annual health checkups including abdominal ultrasonography (n=15,788, men/women: 10,250/5,538, mean age: 49 years), the numbers of individuals with SLD, MASLD, MetALD, ALD, NAFLD and MAFLD were 5,603 (35.5%), 4,227 (26.8%), 795 (5.0%), 324 (2.1%), 3,982 (25.8%) and 4,946 (31.3%), respectively. Clustering analyses using t-distributed stochastic neighbor embedding and K-Means to visually represent interconnections in SLDs uncovered 5 cluster formations. MASLD and NAFLD mainly shared 3 clusters including 1) low alcohol intake with relatively low-grade obesity, 2) obesity with dyslipidemia and 3) dysfunction of glucose metabolism. Both MetALD and ALD displayed one distinct cluster intertwined with alcohol consumption. MAFLD widely shared all of the 5 clusters. In ML-based analyses using algorithms of random forest and extreme gradient boosting and receiver operating characteristic curve analyses, fatty liver index (FLI), calculated by body mass index, waist circumference and levels of γ-glutamyl transferase and triglycerides, was selected as a useful feature for SLDs. Next, we showed the associations of SLDs with an increase in blood pressure (*Hypertens Res* 2023) and the development of chronic kidney disease (CKD) (*Nephrol Dial Transplant* 2023, *Hepatol Res* 2024) and ischemic heart disease (IHD) (*J Am Heart Assoc* 2023). Furthermore, we investigated the relationships of FLI with the development of several diseases and showed that a high level of FLI was an independent predictor for new onset of diabetes mellitus (Sci Rep 2021), hypertension (*J Am Heart Assoc* 2021), CKD (*Sci Rep* 2021) and IHD (*Hepatol Res* 2022) during a 10-year follow-up period as well as the validation of FLI in Japan (*Endocr J* 2022). Moreover, ML models incorporating hemoglobin A1c and FLI provided an accurate and straightforward approach for predicting the development of diabetes mellitus (*Diabet Epidemiol Manag* 2024). In addition, the development of hypertension can be simply and accurately predicted by ML models using systolic blood pressure, age and FLI as selected features (*Clin Exp Hypertens* 2024). Lastly, as a possible target for the novel therapy of MASLD, we introduce fatty acid-binding protein 4 (FABP4) (*Nature* 2007, *J Diabetes Investig* 2022), which is mainly expressed in adipocytes and macrophages and acts as an adipokine (*Nat Rev Drug Discov* 2008, *J Atheroscler Thromb* 2019).