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Cardiovascular-Kidney-Metabolic Syndrome and the Risk of Liver Fibrosis Progression and Liver-Related Events in MASLD

Running Title: CKM syndrome in MASLD

Authors' names:

Xiao-Dong Zhou[1¶], Qin-Fen Chen[2,3¶], Qiong-Yue Fan[1¶], Seung Up Kim[4], Terry Cheuk-Fung Yip[5,6], Salvatore Petta[7], Atsushi Nakajima[8], Emmanuel Tsochatzis[9], Jérôme Boursier[10], Elisabetta Bugianesi[11], Hannes Hagström[12,13], Wah-Kheong Chan[14], Manuel Romero-Gomez[15], José Luis Calleja[16], Victor de Lédinghen[17], Laurent Castéra[18], Arun J. Sanyal[19], George Boon-Bee Goh[20], Philip Noel Newsome[21], Jian-Gao Fan[22], Michelle Lai[23], Céline Fournier-Poizat[17], Hye Won Lee[4], Grace Lai-Hung Wong[5,6], Angelo Armandi[11], Ying Shang[12], Grazia Pennisi[7], Elba Llop[16], Masato Yoneda[8], Marc de Saint-Loup[10], Clemence M Canivet[10], Paloma Carrillo-Fernandez[15], Carmen Lara-Romero[15], Rocio Gallego-Durán[15], Amon Asgharpour[19], Kevin Kim-Jun Teh[20], Mandy Sau-Wai Chan[17], Huapeng Lin[25,26,27], Wen-Yue Liu[28], Giovanni Targher[29,30], Christopher D. Byrne[31], Vincent Wai-Sun Wong[5,6*], Ming-Hua Zheng[1,32,33*], VCTE-Prognosis Study Group

Institutions:

[1]MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

[2]Medical Care Center, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325035, China;

[3]Institute of Aging, The Center for Geriatric Medicine, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325035, China;

[4]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea;

[5]Medical Data Analytics Centre, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China;

[6]State Key Laboratory of Digestive Disease, Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, China;

[7]Sezione di Gastroenterologia, Di.Bi.M.I.S., University of Palermo, Italy;

[8]Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan;

[9]University College London Institute for Liver and Digestive Health, Royal Free Hospital, London, United Kingdom;

[10]Hepato-Gastroenterology and Digestive Oncology Department, Angers University Hospital, Angers, France;

[11]Department of Medical Sciences, Division of Gastroenterology and Hepatology, A.O. Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy;

[12]Department of Medicine, Huddinge, Karolinska Institutet, Sweden;

[13]Division of Hepatology, Department of Upper GI Diseases, Karolinska University Hospital, Stockholm, Sweden;

[14]Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, University of Malaya, Malaysia;

[15]UCM Digestive Diseases, Virgen del Rocío University Hospital, Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBEREHD), Institute of Biomedicine of Seville (IBiS), University of Seville, Spain;

[16]Department of Gastroenterology and Hepatology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain;

[17]Echosens, Paris, France;

[18]Université Paris Cité, UMR1149 (CRI), INSERM, Paris, France; Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris (AP-HP), Clichy, France;

[19]Division of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA, USA;

[20]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore;

[21]Institute of Hepatology, Faculty of Life Sciences & Medicine, King's College London and King's College Hospital, London, UK;

[22]Department of Gastroenterology and Hepatology, School of Medicine, Shanghai Jiao Tong University, Shanghai, China;

[23]Division of Gastroenterology & Hepatology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA;

[24]Centre d' Investigation de la Fibrose Hépatique, Haut-Lévêque Hospital, University Hospital of Bordeaux, Pessac, France;

[25]Department of Gastroenterology and Hepatology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China;

[26]Center for Digestive Diseases Research and Clinical Translation of Shanghai Jiao Tong University, Shanghai, China;

[27]Shanghai Key Laboratory of Gut Microecology and Associated Major Diseases Research, Shanghai, China;

[28]Department of Endocrinology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, 325000, China;

[29]Department of Medicine, University of Verona, Verona, Italy;

[30]Metabolic Diseases Research Unit, IRCCS Sacro Cuore - Don Calabria Hospital, Negrar di Valpolicella, Italy;

[31]Southampton National Institute for Health and Care Research Biomedical Research Centre, University Hospital Southampton, and University of Southampton, Southampton General Hospital, Southampton, UK;

[32]Institute of Hepatology, Wenzhou Medical University, Wenzhou, China;

[33]Key Laboratory of Diagnosis and Treatment for the Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China.

[¶]**Co-first authors:** Xiao-Dong Zhou, Qin-Fen Chen and Qiong-Yue Fan

[*]**Corresponding authors:** Vincent Wai-Sun Wong and Ming-Hua Zheng

Prof Vincent Wong, MD, PhD

Department of Medicine and Therapeutics, Prince of Wales Hospital, Shatin, Hong Kong, China

Email: wongv@cuhk.edu.hk; phone: 852-35054205

Ming-Hua Zheng, MD, PhD

MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China.

Email: zhengmh@wmu.edu.cn; phone: (86) 577-55579611; fax: (86) 577-55578522

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Graphical Abstract

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Abstract

Background: Cardio-kidney-metabolic (CKM) syndrome, a new framework integrating cardiovascular, renal, and metabolic dysfunction, remains inadequately characterized in metabolic dysfunction–associated steatotic liver disease (MASLD).

Objective: We investigated the relationships between CKM stages and liver fibrosis severity, progression, and the risk of liver-related events (LREs) in MASLD.

Design: Patients with MASLD from the VCTE-Prognosis cohort were stratified according to CKM stages. Outcomes included the prevalence of advanced liver fibrosis (LSM ≥10 kPa), liver stiffness progression (≥20% increase and Baveno category upshift), and incident LREs. Associations were assessed using multivariable logistic regression and Cox proportional hazards models.

Results: Among 12,097 patients with MASLD, the prevalence of advanced liver fibrosis increased across CKM stages at baseline: 9.6% (CKM stage 0–1), 18.0% (CKM stage 2), and 31.6% (CKM stage 3-4). CKM stage 2 (adjusted-OR=1.663, 95%CI 1.444–1.915) and CKM stage 3-4 (adjusted-OR=2.575, 95%CI 2.109–3.144) were independently associated with advanced fibrosis. During a 4.5-year median follow-up, 716 patients (6.1%) experienced progression of liver stiffness and 352 patients (1.7%) developed LRE. Compared to CKM stage 0–1, the risk of liver

stiffness progression was higher in CKM stage 2 (adjusted-HR=1.321, 95%CI 1.050–1.662; P=0.018) and CKM stage 3-4 (adjusted-HR=1.767, 95%CI 1.339–2.330; P<0.001). In contrast, only CKM stage 3-4 was significantly associated with an increased risk of LREs (adjusted-HR=1.975, 95%CI 1.245–3.133; P=0.004).

Conclusion: CKM stages are independently associated with the severity and progression of liver fibrosis in MASLD. CKM stage 2 significantly increases liver stiffness progression without excess LRE risk, while CKM stage 3-4 confers the highest risk for liver-related outcomes.

Keywords: nonalcoholic fatty liver disease; metabolic dysfunction-associated fatty liver disease; metabolic syndrome, cardiovascular disease; chronic kidney disease, diabetes mellitus, prognosis.

1. WHAT IS ALREADY KNOWN ON THIS TOPIC

Metabolic dysfunction–associated steatotic liver disease (MASLD) commonly coexists with cardiovascular and renal conditions, but liver-related components are not currently part of the cardiovascular-kidney-metabolic (CKM) syndrome framework.

2. WHAT THIS STUDY ADDS

This is the first large-scale cohort study to evaluate the relationship between CKM stages and liver-related outcomes in MASLD. Advanced liver fibrosis increased from 9.6% in CKM stage 0–1 to 31.6% in CKM stage 3–4. Higher CKM stages were

independently associated with greater liver fibrosis progression, and CKM stage 3-4 was associated with an increased risk of liver-related clinical events.

3. HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

These findings support incorporating liver fibrosis assessment into the CKM framework to improve multisystem risk stratification and guide integrated management strategies for individuals with metabolic dysfunction.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver condition globally, affecting more than one-third of adults.[1,2] Closely linked to the worldwide increases in obesity, type 2 diabetes (T2D), and hypertension, MASLD reflects systemic metabolic dysfunction and significantly contributes to cardiovascular and renal morbidity and mortality.[3-6] This has sparked interest in the integrated, multidisciplinary management of metabolic disorders.[7,8] In this context, the cardiovascular-kidney-metabolic (CKM) syndrome was introduced in 2023 by leading cardiovascular and endocrine societies.[9] The CKM framework emphasizes overlapping pathophysiology —such as insulin resistance, endothelial dysfunction, and low-grade inflammation— across cardiovascular, renal and metabolic diseases.[9,10] The CKM framework uses a staged system (CKM stages 0–4) to stratify risk and guide early, coordinated interventions.[11] This approach is increasingly regarded as a pathway toward holistic rather than siloed care for patients at increased cardiometabolic risk.[8,12]

Notably, MASLD has not been incorporated into CKM syndrome, which we believe is a striking omission, given the important role of MASLD in systemic metabolism and cardiometabolic diseases.[13] MASLD alters hepatic lipid and glucose homeostasis, contributing to atherogenic dyslipidemia, insulin resistance, T2D, chronic kidney disease (CKD), and low-grade inflammation.[14,15] Through liver-derived inflammatory mediators and lipotoxic metabolites, MASLD can also exacerbate cardiometabolic injury, reinforcing a vicious cycle of multi-organ dysfunction.[15] To date, despite its systemic adverse effects, MASLD remains isolated within hepatology and is often overlooked by cardiology and nephrology. This disconnect largely reflects an

under-recognition of the liver's integrative metabolic role and its complex, bidirectional interactions with other CKM components.[16,17] MASLD shares multiple key pathophysiological pathways with CKM conditions and acts both as a consequence and a driver of metabolic dysfunction.[18] Progression of MASLD to metabolic dysfunction-associated steatohepatitis (MASH) further amplifies systemic/hepatic insulin resistance and low-grade inflammation, accelerating CVD and renal complications.[19] Yet, the contribution of MASLD to cardiometabolic risk is often subtle and gradual, making it difficult to detect with conventional risk stratification tools. The "silent" progression of liver disease in MASLD may lead to an underestimation of the total disease burden captured by the CKM model.[20] Therefore, MASLD represents a critical risk factor within the CKM continuum. However, the relationship between MASLD severity, disease progression, and prognosis remains poorly understood, with limited current evidence to inform its role in risk stratification and clinical management.

Based on this background of evidence, this international multicenter cohort study involving patients with MASLD aimed: (1) to evaluate the association between CKM stages and liver fibrosis severity; (2) to investigate CKM stages as a determinant of progression or regression of liver stiffness, using serial vibration-controlled transient elastography (VCTE); and (3) to assess the incidence of long-term liver-related events (LREs) across CKM stages.

Methods

Study Design and Participants

The current analysis utilized data from the VCTE-Prognosis cohort, an international, multicenter cohort study involving adult patients with MASLD who underwent longitudinal assessment with VCTE.[21-23] The VCTE-Prognosis cohort includes participants from 16 hepatology centers across North America, Europe, and Asia. Of these, 14 centers collected data prospectively following standardized protocols for clinical, biochemical, and liver imaging evaluations.

Eligible participants for this study were required to have at least two valid VCTE examinations spaced six months or more apart, along with sufficient clinical and laboratory information to classify the CKM stage prior to their final VCTE assessment. Participants were excluded if they were under 18 years of age, had evidence of other chronic liver diseases (e.g., viral hepatitis, autoimmune hepatitis, or inherited liver conditions), reported significant alcohol consumption (greater than 30 g/day for men or greater than 20 g/day for women), or had a previous history of hepatocellular carcinoma (HCC), hepatic decompensation events, liver transplantation, liver resection, or other malignancies either at baseline or within six months of enrollment. Additional exclusion criteria included a follow-up duration of less than 6 months for either VCTE or LRE and missing data on key variables necessary to determine the CKM stages or assess study outcomes.

Ethical approval for this study was obtained from the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (CREC Ref. No.: 2022.255) and from the relevant Ethics Committees of all

participating centers (**Supplement Table 1**, http://links.lww.com/HEP/K337). Due to the retrospective nature of the current analysis, informed consent from participants was waived in accordance with institutional policies. Patients and the public were not involved in the design, conduct, or reporting of this research.

MASLD Diagnosis

MASLD was diagnosed based on the presence of hepatic steatosis, which was identified by imaging methods (ultrasound, computed tomography, or controlled attenuation parameter [CAP] ≥248 dB/m via FibroScan®) or liver histology (steatosis in >5% of hepatocytes).[24] Additionally, at least one of the following five metabolic risk factors was required: (1) body mass index (BMI) ≥25 kg/m² (≥23 kg/m² for Asian individuals), or waist circumference ≥94 cm for men and ≥80 cm for women , with ethnic-specific adjustments; (2) fasting plasma glucose ≥5.6 mmol/L (≥100 mg/dL), or 2-hour post-load glucose ≥7.8 mmol/L (≥140 mg/dL), or HbA1c ≥ 5.7% (≥39 mmol/mol), or diagnosis of type 2 diabetes mellitus or use of glucose-lowering medications; (3) blood pressure ≥130/85 mmHg or use of antihypertensive medications; (4) triglycerides ≥150 mg/dL (≥1.7 mmol/L) or lipid-lowering therapy; (5) HDL cholesterol ≤40 mg/dL (≤1.0 mmol/L) in men or ≤50 mg/dL (≤1.3 mmol/L) in women, or use of lipid-lowering medications.[24]

CKM Syndrome Classification

CKM syndrome staging was defined within a unified framework reflecting the progressive accumulation of cardiometabolic and renal dysfunctions (**Supplement Table 2**, http://links.lww.com/HEP/K337).[9] Participants were classified into five CKM stages (0 to 4). CKM stage 0 referred to individuals without identifiable CKM-related risk factors, including normal body weight, normal blood pressure, normoglycemia, normal lipid profile, and preserved renal function parameters. CKM stage 1 included individuals with one or more cardiometabolic risk factors—such as overweight or obesity (defined as BMI ≥25 or 23 kg/m² for Asian individuals), abdominal obesity (waist circumference ≥90 cm in men or ≥80 cm in women), increased blood pressure (≥130/85 mmHg or treatment), dyslipidemia (HDL-C <40 mg/dL in men or <50 mg/dL in women, or triglycerides ≥150 mg/dL, or treatment), or impaired fasting glucose (100–125 mg/dL)—but without diagnosed metabolic or organ-specific diseases. CKM stage 2 included individuals with established metabolic diseases, including T2D, metabolic syndrome, or CKD. CKM stage 3 included individuals with subclinical CVD abnormalities, such as coronary artery calcium, left ventricular hypertrophy, increased arterial stiffness, or a predicted 10-year CVD risk ≥20% as estimated by the AHA-PREVENT study equation.[25] Subclinical CVD was assessed using standard 10-year CVD risk scores and clinical history. While advanced imaging (e.g., coronary angiography or CT measured calcium scoring) was not available for all participants (because these imaging tests are not extensively used in clinical practice), 10-year CVD risk scores and clinical history allowed classification of CKM stage 3-4 with reasonable accuracy. CKM stage 4 referred to patients with

clinically manifest atherosclerotic cardiovascular diseases, such as coronary artery disease, ischemic stroke, or peripheral artery disease. All patients in this cohort met the diagnostic criteria for MASLD and were classified into CKM stages 0-4 according to available clinical, laboratory, and imaging data. In the current analysis, patients with CKM stage 4 were not analyzed separately because their numbers were very limited in this liver-focused cohort. To maintain statistical robustness, CKM stages 3 and 4 were combined into a single analytical group (CKM stage 3–4) to reflect advanced CKM stages. Similarly, CKM stage 0 cases were rare due to the requirement of at least one metabolic abnormality for a MASLD diagnosis, and were, therefore, combined with CKM stage 1 for the analysis.

Study Outcomes

Study outcomes included the prevalence of advanced liver fibrosis, longitudinal changes in liver stiffness, and the incidence of long-term LREs. Advanced fibrosis was defined as a liver stiffness measurement (LSM) ≥10 kPa. Liver stiffness outcomes were evaluated and categorized as either progression or regression based on temporal changes in LSM obtained through serial VCTE. Liver stiffness progression was defined as a ≥20% relative increase in LSM accompanied by a transition to a higher liver fibrosis risk category, using the following LSM thresholds: <10.0 kPa, 10.0–14.9 kPa, 15.0–19.9 kPa, 20.0–24.9 kPa, and ≥25.0 kPa, in accordance with the Baveno VII and AASLD recommendations.[26] Liver stiffness regression was defined similarly as a ≥20% relative decrease in LSM with a corresponding downward shift in

the liver fibrosis risk category.[26] The 20% threshold of LSM was selected based on its previously demonstrated clinical relevance for predicting the risk of long-term LREs. To ensure valid VCTE assessments, participants with a baseline LSM ≥25.0 kPa were excluded from progression analyses while those with a LSM <10.0 kPa at baseline were excluded from regression analyses. For participants with multiple VCTE assessments, the earliest scan temporally aligned with baseline CKM data was defined as the index measurement and the final available scan was used for the follow-up. A minimum interval of six months was required between the two VCTE assessments. LRE occurrence was defined as a composite outcome that included incident HCC, cirrhosis-related complications (ascites, spontaneous bacterial peritonitis, variceal hemorrhages, hepatic encephalopathy, or hepatorenal syndrome), liver transplantation, or liver-related deaths.

Statistical Analysis

Continuous variables were presented as means ± standard deviations (SD) or medians with interquartile ranges (IQR), while categorical variables were presented as percentages. Comparisons across CKM stages were performed using one-way analysis of variance (ANOVA), or the Kruskal–Wallis test for normally and non-normally distributed continuous variables, and the chi-square test for categorical variables. Cox proportional hazards models were used to examine the associations between CKM stages and liver stiffness progression, regression, and the long-term risk of developing incident LREs in patients with MASLD. These models were

adjusted for age, sex, race/ethnicity, BMI, baseline LSM, baseline controlled attenuation parameter (CAP), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), PLT count, and use of medications (such as lipid-lowering and/or glucose-lowering drugs). Kaplan–Meier survival curves were performed to evaluate time-to-event outcomes (liver stiffness progression and LRE) by CKM stages, and group differences were assessed using the log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) were reported. All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS Statistics for Mac, version 23.0.

To assess the robustness of our findings, multiple sensitivity analyses and subgroup analyses were also performed. First, to reduce bias from short observation periods and ensure sufficient time to detect meaningful changes in liver stiffness, statistical analyses were restricted to participants who had at least one year of follow-up and at least two valid VCTE examinations spaced ≥12 months apart. This approach allowed robust assessment of liver stiffness changes and risk of long-term LRE. Second, we excluded participants with advanced liver fibrosis (baseline LSM ≥10 kPa) and examined whether CKM stages were associated with liver stiffness progression or the risk of long-term LRE among participants with a baseline LSM <10 kPa. Third, competing risk regression models were performed to account for non-liver-related deaths, which could bias the estimates of LRE risk. Fourth, given that LSM 10–15 kPa represents a “gray zone” potentially influenced by transient factors such as body weight changes, we repeated the analyses using a stricter cutoff of LSM of ≥15 kPa. This allowed us to confirm whether the associations between CKM stages,

liver stiffness progression, and LREs remained consistent among MASLD patients with more definitively advanced fibrosis. Fifth, to evaluate whether pre-existing type 2 diabetes alone could account for the observed associations between CKM stages (particularly CKM stage 3-4) and liver stiffness progression and long-term LREs, we performed additional analyses adjusting for the presence of type 2 diabetes, both alone and in combination with other covariates (AST, ALT, PLT count, baseline LSM, and CAP).

Results

Baseline Characteristics

A total of 12,097 adult patients with MASLD and serial VCTE assessments were included in the current analysis (**Figure 1**). According to the CKM staging, 3,753 (31.0%) patients were at CKM stage 0–1, 7,026 (58.1%) at CKM stage 2, and 1,318 (10.9%) at CKM stage 3-4 (**Table 1**). Higher CKM stages were associated with older age, higher BMI, and a greater proportion of males (all P<0.001). Liver-related parameters also worsened with increasing CKM stage: LSM rose from 6.4 ± 4.6 kPa in CKM stage 0–1 to 10.3 ± 9.1 kPa in CKM stage 3-4, and CAP increased from 296.0 ± 37.3 to 304.7 ± 43.7 dB/m. Platelet count and albumin levels declined while circulating levels of AST, ALT, and GGT increased progressively across CKM stages (all P<0.001).

Association Between Prevalence of Advanced Fibrosis and CKM Stages

Among the 12,097 patients with MASLD included, advanced liver fibrosis (defined as LSM ≥10 kPa) was observed in 2,042 (21.9%) individuals and increased across CKM stages: 9.6% in CKM stage 0–1, 18.0% in CKM stage 2, and 31.6% in CKM stage 3-4 (P<0.001), respectively (**Figure 2**). After adjustment for potential confounders, the risk of having advanced liver fibrosis was significantly higher in both CKM stage 2 (adjusted OR 1.663, 95% CI 1.444–1.915, P<0.001) and CKM stage 3-4 (adjusted OR 2.575, 95% CI 2.109–3.144, P<0.001) compared to CKM stage 0–1 (**Table 2**). Histologic assessment in a subset of 2,358 patients with MASLD confirmed similar trends: advanced fibrosis (fibrosis stage F3-4) occurred in 22.8% of individuals at CKM stage 0–1, 32.4% of those at CKM stage 2, and 55.3% of those at CKM stage 3-4 (P<0.001), respectively. In adjusted logistic regression analyses, CKM stage 2 (adjusted OR 1.343, 95% CI 1.027–1.757, P=0.031) and CKM stage 3-4 (adjusted OR 1.673, 95% CI 1.165–2.402, P=0.005) were independently associated with a higher risk of having histologic severe liver fibrosis.

Association Between Incidence of Liver Stiffness Progression and Regression and CKM Stages

During a median follow-up of 2.7 years (IQR: 1.4–4.3 years) based on serial VCTE assessments, the progression of liver stiffness occurred in 716 patients (6.1%) among the 1,218 patients with MASLD and a baseline LSM <25 kPa. The incidence rates significantly increased across CKM stages: 1.22 per 100 person-years in CKM stage 0–1, 1.91 per 100 person-years in CKM stage 2, and 3.52 per 100 person-years in CKM stage 3-4, respectively. After adjustment for potential confounders, the risk of

liver stiffness progression was significantly higher in both CKM stage 2 (adjusted HR 1.314, 95% CI 1.073–1.610, P=0.008) and CKM stage 3-4 (adjusted HR 1.767, 95% CI 1.339–2.330, P<0.001) compared to CKM stage 0–1 (**Table 3**).

Among the 2,042 patients with MASLD and a baseline LSM ≥ 10 kPa, the regression of liver stiffness occurred in 52.2% of those at CKM stage 0–1, 55.3% of those at CKM stage 2, and 50.1% of those at CKM stage 3-4 patients. No significant differences were observed among the three groups (all P >0.05). Kaplan–Meier analysis confirmed these trends, showing a significantly higher cumulative incidence rate of liver stiffness progression in CKM stages 2 and 3 than in CKM stage 0–1 (P<0.001 by log-rank test, **Figure 3A**).

Association Between the Incidence of LREs and CKM Stages

A total of 208 (1.7%) cases of LREs occurred during the mean follow-up of 4.5 years (IQR: 2.5-6.8). The most frequent LREs were new-onset hepatocellular carcinoma (94, 45.2%), ascites (56, 26.9%), and variceal hemorrhages (37, 17.8%) (**Supplement Table 3**, http://links.lww.com/HEP/K337). The incidence of long-term LREs significantly increased across CKM stages: 0.22 per 100 person-years in CKM stage 0–1, 0.29 per 100 person-years in CKM stage 2, and 1.01 per 100 person-years in CKM stage 3-4, respectively. In multivariable Cox regression analyses, only CKM stage 3-4 was significantly associated with a higher risk of long-term LRE (adjusted HR 1.975, 95% CI 1.245–3.133, P=0.004), whereas CKM stage 2 was not (adjusted HR 1.135, 95% CI 0.770–1.672, P=0.523). Kaplan–Meier analyses revealed

significantly higher cumulative incidence rates of both liver stiffness progression and LREs across increasing CKM stages (P<0.001 by log-rank test) (**Figure 3B**).

Sensitivity Analyses

To evaluate the robustness of our findings, several sensitivity and subgroup analyses were conducted. First, restricting the analysis to participants who had at least one year of follow-up and a minimum VCTE interval of 12 months, we found that higher CKM stages were significantly associated with liver stiffness progression (CKM stage 2: adjusted HR 1.350, 95% CI 1.086–1.678, P=0.007; CKM stage 3-4: adjusted HR 1.809, 95% CI 1.347–2.428, P<0.001) **(Supplement Figure 1**, http://links.lww.com/HEP/K337). For long-term LREs, only CKM stage 3-4 remained significantly associated with a higher risk of events (HR 1.898, 95% CI 1.170–3.078, P = 0.009). Second, in patients without advanced fibrosis (LSM <10 kPa at baseline), both CKM and CKM stages 2 and 3 were significantly associated with liver stiffness progression (CKM stage 2: HR 1.369, 95% CI 1.064–1.761, P = 0.015; CKM stage 3-4: HR 1.846, 95% CI 1.287-2.646, P < 0.001) (**Supplement Figure 2**, http://links.lww.com/HEP/K337). For long-term LREs, Kaplan-Meier analysis revealed a significant difference across CKM stages, although the associations were not statistically significant in adjusted Cox regression models, likely due to the limited number of LREs. Third, competing risk models accounting for non-liver-related deaths confirmed the significant association between higher CKM stages and liver stiffness progression (CKM stage 2: SHR 1.336, 95% CI 1.092-1.635,

P=0.005; CKM stage 3-4: SHR 1.826, 95% CI 1.365-2.442, P<0.001) (**Supplement Figure 3**, http://links.lww.com/HEP/K337). Conversely, for long-term LREs, only CKM stage 3-4 remained significantly associated with an increased risk of this outcome (SHR 1.923, 95% CI 1.180-3.134, P=0.009). Fourth, using a stricter cutoff of LSM ≥15 kPa to define advanced liver fibrosis, the prevalence of advanced fibrosis was lower (as expected), but the associations with CKM stages for both liver stiffness progression and LRE remained consistent with the primary analysis, thus further confirming the robustness of our findings (**Supplement Table 4**, http://links.lww.com/HEP/K337). Fifth, to evaluate whether the presence of type 2 diabetes alone could explain these associations, we conducted additional analyses adjusting for diabetes status. Notably, CKM stage 3-4 remained independently associated with liver stiffness progression (HR 1.919, 95% CI 1.433–2.569, P<0.001) and long-term LREs (HR 2.088, 95% CI 1.247–3.498, P=0.005), indicating that these associations are not solely driven by the coexistence of type 2 diabetes (**Supplement Table 5**, http://links.lww.com/HEP/K337).

Discussion

In this multinational VCTE-Prognosis cohort, we examined the relationships between CKM stages and the burden of liver fibrosis, its progression, and the incidence of LREs in over 12,000 adult patients with MASLD. Our main and novel findings are as follows: (1) higher CKM stages are associated with a greater prevalence of significant liver fibrosis; (2) the progression of liver stiffness begins at CKM stage 2, indicating

early hepatic involvement; and (3) higher CKM stages are independently associated with both an increased risk of liver stiffness progression and incident long-term LREs during the follow-up.

The first key finding of the study is that liver fibrosis is common in early stages of CKM and steadily increases as the disease progresses, with CKM stage 2 emerging as a critical turning point. However, despite its prognostic relevance, liver assessment is not included in CKM management, unlike the standardized monitoring of cardiovascular and renal complications.[18,27] Our study suggests that liver fibrosis progression begins earlier than anticipated and occurs silently as metabolic dysfunction advances. This pattern supports the concept of a shared pathophysiological axis that links the liver, heart, and kidneys through biological mechanisms, such as low-grade inflammation, insulin resistance, and endothelial dysfunction.[28-30] While MASLD is viewed as a consequence of systemic metabolic dysfunction, recent data suggest that liver fibrosis severity may also contribute to worsening CVD and renal outcomes.[31,32] In this context, the severity of liver fibrosis is more than just a hepatic issue, it can serve as a reliable marker of multisystem disease and a potential amplifier of cardiometabolic risk.[29,33,34] Evidence indicates that liver fibrosis reflects systemic low-grade inflammation, endothelial dysfunction, and metabolic derangement, all of which contribute to the pathogenesis of CVD. Therefore, liver fibrosis deserves attention from a broader clinical community, including cardiologists, endocrinologists, and primary care physicians, rather than

being regarded merely as a concern for hepatologists. Our study reinforces this integrative view by emphasizing that liver fibrosis assessment provides actionable information within the multisystem framework of CKM.[35]

The second key finding of our study is that patients with CKM stage 3-4 have a significantly higher risk of liver stiffness progression and incidence of long-term LREs over time. Importantly, these associations between higher CKM stages and advanced liver fibrosis, liver stiffness progression, and incident LREs remained significant even after adjustment for diabetes status, suggesting that the observed relationships are not solely driven by diabetes but rather reflect broader multisystem metabolic dysfunction. While CVD and renal risks are routinely monitored in CKM patient population, liver-related outcomes often receive less attention. Because liver damage can develop slowly without obvious symptoms or diagnosis, it can go unnoticed while other cardiometabolic disorders worsen, adding to the overall disease burden. Historically, treatment options specifically targeting both MASLD and CVD risk have been limited. However, newer antihyperglycemic agents, such as incretin-based therapy and sodium-glucose cotransporter-2 (SGLT2) inhibitors, are showing potential benefits across multiple organ systems.[36] Accumulating evidence shows that these antihyperglycemic agents reduce not only CVD events but also liver-related outcomes in individuals with MASLD and T2D.[37-41] Wider use of these drugs could support a more integrated management approach for this patient population. Taken together, these findings support the need for greater clinical

recognition of liver-related risks within the CKM framework. Incorporating liver-related outcomes into cardio-renal-metabolic care, particularly in patients with advanced metabolic impairment, can help improve long-term outcomes across the heart, kidneys, and liver. Looking ahead, further evidence may justify reframing this paradigm entirely, perhaps toward a more inclusive "cardiovascular-liver-kidney-metabolic" (CLKM) syndrome. In line with this, we have developed a preliminary framework (**Supplement Table 6**, http://links.lww.com/HEP/K337), integrating MASLD and liver fibrosis into the CKM staging system (named CLKM syndrome). This framework proposes CLKM stages that incorporate metabolic risk factors, chronic kidney disease, subclinical or clinical CVD, and the presence of MASLD with advanced liver fibrosis or long-term LREs, providing a structured approach to identify patients at higher multisystem risk who may benefit from closer monitoring or early therapeutic interventions.

Our study has important strengths. It leveraged a large, multi-ethnic, real-world cohort with standardized longitudinal liver stiffness assessments via serial VCTE, enabling a dynamic evaluation of hepatic fibrosis trajectories across the CKM spectrum. The integration of comprehensive clinical, biochemical, and imaging data allowed for robust phenotyping of CKM stages and MASLD severity. Nonetheless, important limitations should also be acknowledged. First, variability in follow-up duration and the number of VCTE assessments could have influenced the accuracy of liver stiffness trajectory modeling. Second, although LSM is a validated surrogate for liver

fibrosis, non-invasive measures, such as VCTE and FIB-4 index, have limitations in detecting subtle histological changes, and liver biopsy data were not available for most of our participants. Third, the relatively low incidence of LREs, particularly in subgroup analyses, limited the statistical power to detect modest associations. Fourth, residual confounding from unmeasured lifestyle, genetic, or environmental factors cannot be fully excluded due to the observational design. Fifth, the classification of CKM stage 3-4 relied on standard CVD risk scores and clinical history rather than systematic imaging for subclinical CVD, such as coronary CT angiography or calcium scoring, which are not routinely performed in clinical practice. Consequently, some misclassification is possible, potentially leading to under- or overestimation of associations in this patient group. Finally, since the cohort of the study was drawn from tertiary academic centers, there could be referral bias, which limits the generalizability to broader primary care or community-based populations. Future prospective studies in diverse clinical settings, incorporating standardized longitudinal assessments and advanced biomarkers, including omics, VCTE, and imaging-derived signatures, will be needed to further validate these findings. Additionally, embedding the MASLD assessment within the CKM framework could improve early detection, multidisciplinary management, and prevention of downstream liver-related and CVD complications.

Conclusions

In patients with MASLD, advanced liver fibrosis becomes more prevalent as CKM stages worsen. Higher CKM stages are significantly and independently associated with an increased risk of liver stiffness progression and incidence of long-term LREs. These findings highlight a close interconnection between the progression of cardiometabolic, renal, and liver diseases. Therefore, assessing and monitoring liver fibrosis should be integrated into routine care for all patients with MASLD and advanced CKM stages. Emerging pharmacotherapies (such as incretin-based therapies and SGLT2 inhibitors) show promise for improving both liver-related and cardiovascular-renal outcomes, thus supporting the potential value of a more integrated management approach for this patient population.

Author Contributions: Ming-Hua Zheng is the guarantor of the article. Xiao-Dong Zhou, Qin-Fen Chen, and Ming-Hua Zheng contributed to the study concept and design; data acquisition involved all authors. Xiao-Dong Zhou, Qin-Fen Chen, and Qiong-Yue Fan performed the statistical analysis and drafted the manuscript. All authors critically revised the manuscript for important intellectual content. Administrative, technical, or material support was provided by Xiao-Dong Zhou, Qin-Fen Chen, and Ming-Hua Zheng. Supervision was provided by Xiao-Dong Zhou and Ming-Hua Zheng. All authors approved the final version of the manuscript.

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Emmanuel Tsochatzis advises and is on the speakers' bureau for Novo Nordisk and Boehringer Ingelheim. He advises Madrigal, Pfizer, MSD, and Siemens. He is on the speakers' bureau for Echosens, AbbVie, AstraZeneca, and Gilead. Jérôme Boursier received grants from Echosens outside the submitted work. Elisabetta Bugianesi consults for and advises Novo Nordisk and MSD. She consults for Boehringer Ingelheim, Eli Lilly, and Madrigal. Hannes Hagström received grants from AstraZeneca, BMS, MSD, Novo Nordisk, Boehringer Ingelheim, Kowa, Echosens, Gilead, Intercept, and GW Pharma outside the submitted work. Wah-Kheong Chan consults for, advises, and is on the speakers' bureau for Novo Nordisk. He advises, is on the speakers' bureau for, and received grants from Abbott and Roche. He consults for and advises Boehringer Ingelheim. He advises AbbVie, Ipsen, and Zuellig. He is on the speakers' bureau for Echosens, Hisky Medical, and Viatris. Manuel Romero-Gómez consults for Ipsen, Gilead, and UCB Pharma. He received grants from Novo Nordisk, Siemens, Theratechnologies, and Echosens. José Luis Calleja consults for and is on the speakers' bureau for Echosens. He received grants from Roche and Gilead outside the submitted work. Victor de Lédinghen is employed by Echosens. Laurent Castéra consults for and is on the speakers' bureau for Boehringer Ingelheim, Echosens, Gilead, Madrigal, GSK, and Novo Nordisk. He consults for Boston Pharmaceuticals, MSD, Pfizer, Sagimet, and Siemens. He is on the speakers' bureau for Inventiva and AstraZeneca. Arun J. Sanyal consults for and received grants paid to the institution from AstraZeneca, Boehringer Ingelheim, HistoIndex, Novo Nordisk, BMS, Gilead, MSD, Salix, Genfit, and Novartis. He consults for Eli Lilly,

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Boehringer Ingelheim, Echosens, Inventiva, Pfizer, Sagimet, and TARGET PharmaSolutions. He consults for Intercept and Visirna. He is on the speakers' bureau for Abbott and . He is a confounder and owns stock in Illuminatio. Ming-Hua Zheng consults for Boehringer Ingelheim and Eieling Technology. He is on the speakers' bureau for AstraZeneca, Hisky Medical, and Novo Nordisk. The remaining authors have no conflicts to report.

Group Information: The VCTE-Prognosis Study Group consists of the following authors: Arun J. Sanyal, MD (Virginia Commonwealth University), Atsushi Nakajima, MD (University of Yokohama), Elisabetta Bugianesi, MD (University of Torino), Emmanuel Tsochatzis, PhD (Royal Free Hospital), George Boon-Bee Goh, MD (Singapore General Hospital), Hannes Hagström, PhD (Karolinska University Hospital), Jérôme Boursier, MD (Angers University Hospital), José Luis Calleja, MD (Hospital Puerta de Hierro), Manuel Romero-Gomez, MD (University of Seville), Ming-Hua Zheng, MD (Wenzhou Medical University), Philip N. Newsome, MD (University of Birmingham), Salvatore Petta, PhD (University of Palermo), Seung Up Kim, PhD (Yonsei University School of Medicine), Victor de Lédinghen, MD (University of Bordeaux), Vincent Wai-Sun Wong, MD (The Chinese University of Hong Kong), and Wah-Kheong Chan, MD (University of Malaya).

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Figure 1. Flowchart of the study participants.

Abbreviations: CKM, cardiometabolic-renal syndrome; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

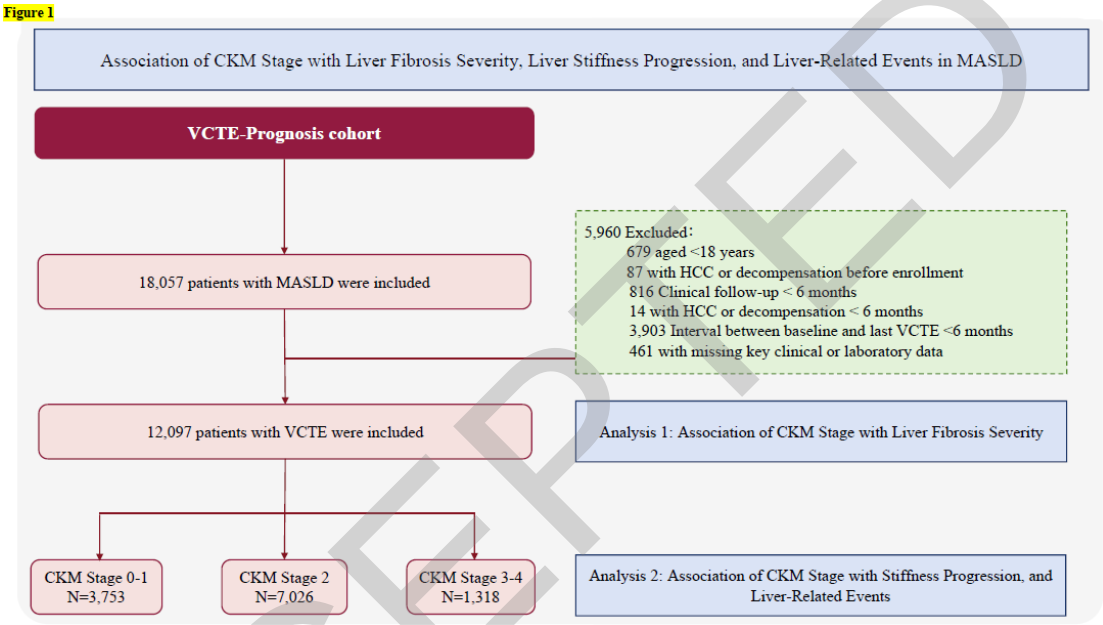

Figure 2. Prevalence rates of Advanced Fibrosis Assessed by either Vibration-Controlled Transient Elastography (VCTE) or Liver Histology, Stratified by CKM Stages in Patients with MASLD.

Abbreviations: CKM, cardiometabolic-renal syndrome; VCTE, vibration-controlled transient elastography.

Figure 2

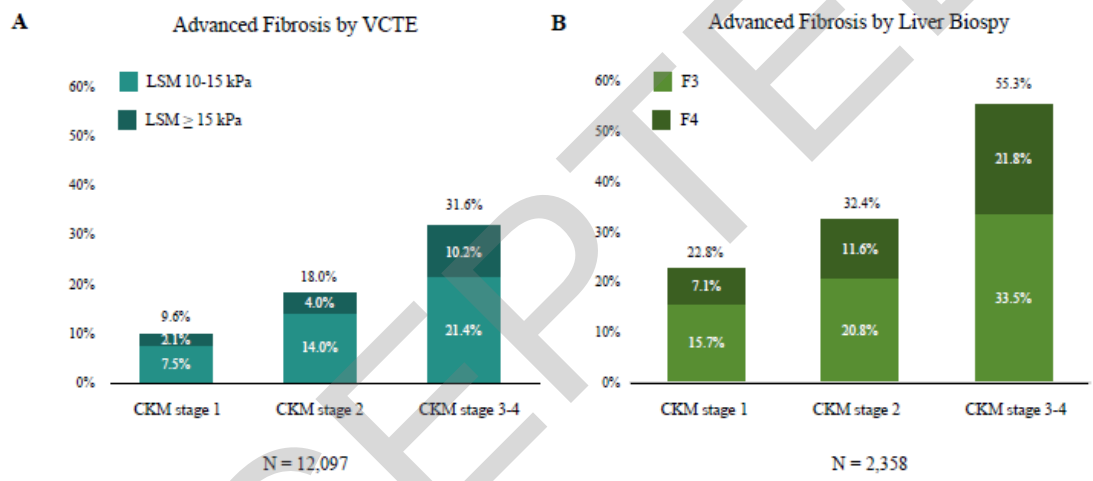

Figure 3. Cumulative Incidence rates of (A) Liver Stiffness Progression, and (B) long-term LREs, Stratified by CKM Stages in Patients with MASLD.

Abbreviations: CKM, cardiometabolic-renal syndrome; LRE, liver-related events.

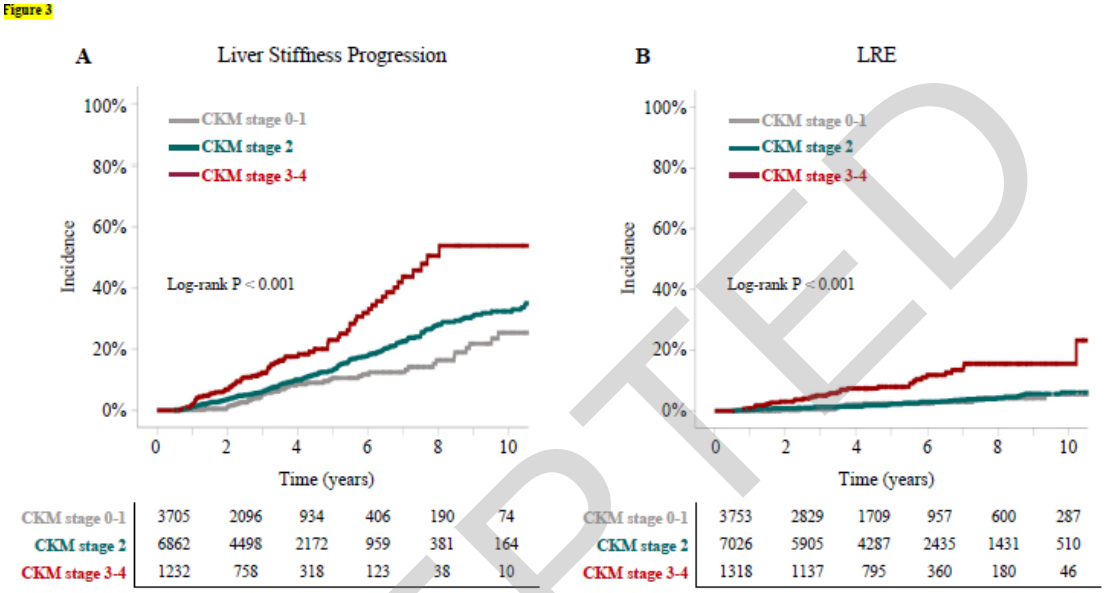

Table 1. Baseline Clinical and Demographic Characteristics Stratified by CKM Stages in MASLD.

Characteristics	Overall N = 12,097	CKM Stage 0-1 N = 3,753	CKM Stage 2 N = 7,026	CKM Stage 3-4 N = 1,318	P-value
Age, years	52.9 ± 13.4	48.8 ± 13.1	52.3 ± 12.4	67.8 ± 8.5	<0.001
Male sex, n (%)	7,131 (58.9%)	2,264 (60.3%)	4,087 (58.2%)	780 (59.2%)	0.094
BMI, kg/m^2	27.7 ± 5.4	26.5 ± 3.9	28.1 ± 4.9	29.1 ± 9.8	<0.001
Obesity, n (%)	10,705 (88.5%)	3,124 (83.2%)	6,368 (90.6%)	1,213 (92.0%)	<0.001
Hypertension, n (%)	5,201 (43.0%)	0 (0.0%)	4,003 (57.0%)	1,198 (90.9%)	<0.001
Type 2 diabetes, n (%)	5,073 (41.9%)	0 (0.0%)	3,913 (55.7%)	1,160 (88.0%)	<0.001
Dyslipidemia, n (%)	9,616 (79.5%)	2,343 (62.4%)	6,119 (87.1%)	1,154 (87.6%)	<0.001
ALT, U/L	37 (23, 61)	35 (22, 61)	38 (24, 62)	35 (22, 58)	<0.001
AST, U/L	31 (23, 46)	30 (22, 42)	32 (23, 46)	33 (24, 49)	<0.001
GGT, U/L	45 (28, 75)	41 (26, 68)	47 (30, 76)	49 (28, 87)	<0.001
HbA1c, %	6.3 ± 1.8	5.4 ± 0.6	6.6 ± 2.0	7.4 ± 2.2	<0.001
Fasting glucose, mmol/L	6.3 ± 1.1	5.7 ± 0.3	6.6 ± 1.2	7.1 ± 1.2	<0.001
TG, mmol/L	1.8 ± 1.1	1.6 ± 0.6	2.0 ± 1.2	1.9 ± 1.4	<0.001
TC, mmol/L	4.9 ± 1.1	5.1 ± 1.0	4.8 ± 1.1	4.5 ± 1.1	<0.001
HDL-C, mmol/L	1.3 ± 0.3	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	<0.001
LDL-C, mmol/L	2.9 ± 0.9	3.1 ± 0.8	2.8 ± 1.0	2.6 ± 0.9	<0.001
Creatinine, μmol/L	71.6 (60.1, 82.2)	71.6 (60.1, 81.3)	70.7 (60.0, 82.0)	76.0 (64.5, 90.2)	0.697
eGFR, mL/min/1.73 m²	93.9 ± 16.3	98.1 ± 13.8	94.5 ± 15.6	79.1 ± 18.5	<0.001

Platelet count, $\times 10^9$/L	241.8 ± 65.1	246.8 ± 61.2	243.9 ± 66.8	216.6 ± 61.3	<0.001
Albumin, g/L	44.6 ± 3.4	45.1 ± 3.2	44.7 ± 3.4	43.2 ± 3.6	<0.001
Total bilirubin, μmol/L	13.7 ± 7.3	14.6 ± 7.6	13.3 ± 7.4	12.6 ± 6.1	<0.001
LSM, kPa	7.6 ± 6.1	6.4 ± 4.6	7.8 ± 5.9	10.3 ± 9.1	<0.001
CAP, dB/m	302.8 ± 39.8	296.0 ± 37.3	306.1 ± 39.9	304.7 ± 43.7	<0.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI: body mass index; CAP, controlled attenuation parameter; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transpeptidase; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes; TC, total cholesterol, TG, triglycerides.

Table 2. Prevalence Rates of Advanced Fibrosis Assessed either by VCTE or by Histology According to CKM Stages in MASLD.

	Prevalence (n, %)	**Unadjusted OR (95% CI)**	**P-value**	**Adjusted OR* (95% CI)**	**P-value**
Advanced fibrosis (LSM ≥10 kPa)					
CKM Stage 0-1	362 (9.6%)	*Ref.*		*Ref.*	
CKM Stage 2	1263 (18.0%)	2.053 (1.813-2.325)	<0.001	1.663 (1.444-1.915)	<0.001
CKM Stage 3-4	417 (31.6%)	4.335 (3.699-5.082)	<0.001	2.575 (2.109-3.144)	<0.001
Advanced fibrosis (histologic F3-4 stage)					
CKM Stage 0-1	100 (22.8%)	*Ref.*		*Ref.*	
CKM Stage 2	512 (32.4%)	1.627 (1.271-2.082)	<0.001	1.343 (1.027-1.757)	0.031
CKM Stage 3-4	188 (55.3%)	4.193 (3.078-5.711)	<0.001	1.673 (1.165-2.402)	0.005

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; CKM, cardio-kidney-metabolic; HbA1c, hemoglobin A1c; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; OR, odds ratio; PLT, platelet count.

*Data adjusted for age, sex, BMI, AST, ALT, PLT count, and medication use (i.e., glucose-lowering and/or lipid-lowering agents).

Table 3. Incidence Rates of Liver Stiffness Progression, Regression and Liver-related Events According to CKM Stages in MASLD.

	Events (n, %)	Events (100 person-years)	Unadjusted HR (95% CI)	P-value	Adjusted HR* (95% CI)	P-value
Liver stiffness progression						
CKM Stage 0-1	133 (3.6%)	1.22	*Ref.*		*Ref.*	
CKM Stage 2	446 (6.5%)	1.91	1.519 (1.251-1.844)	<0.001	1.314 (1.073-1.610)	0.008
CKM Stage 3-4	137 (11.1%)	3.52	3.233 (2.546-4.106)	<0.001	1.767 (1.339-2.330)	<0.001
Liver stiffness regression						
CKM Stage 0-1	189 (52.2%)	17.70	*Ref.*		*Ref.*	
CKM Stage 2	699 (55.3%)	16.22	0.961 (0.818-1.129)	0.688	0.914 (0.771-1.084)	0.300
CKM Stage 3-4	209 (50.1%)	15.89	1.102 (0.905-1.343)	0.344	0.983 (0.783-1.235)	0.884
LRE						
CKM Stage 0-1	38 (1.0%)	0.22	*Ref.*		*Ref.*	
CKM Stage 2	106 (1.5%)	0.29	1.241 (0.857-1.799)	0.253	1.135 (0.770-1.672)	0.523
CKM Stage 3-4	64 (4.9%)	1.01	4.475 (2.991-6.694)	<0.001	1.975 (1.245-3.133)	0.004

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; CKM, cardio-kidney-metabolic; HbA1c, hemoglobin A1c; HR, hazards ratio; LSM, liver stiffness measurement; LRE, liver-related events; MASLD, metabolic dysfunction-associated steatotic liver disease; PLT, platelet count.
*Data adjusted for age, sex, BMI, AST, ALT, PLT count, baseline LSM, baseline CAP, and medication use (i.e., glucose-lowering and/or lipid-lowering medications).