

ORIGINAL ARTICLE

Cardiovascular–kidney–metabolic syndrome and the risk of liver fibrosis progression and liver-related events in MASLD

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Abstract

Background: Cardiovascular-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 ($\geq 20\%$ increase and Baveno category upshift), and incident LREs. Associations were assessed using multi-variable 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 with 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

Abbreviations: BMI, body mass index; CAP, controlled attenuation parameter; CKD, chronic kidney disease; CKM, Cardiovascular-kidney-metabolic; CKLM, cardiovascular-kidney-liver-metabolic; CVD, cardiovascular disease; LRE, liver-related event; LSM, liver stiffness measurement; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; SGLT2, sodium-glucose cotransporter-2; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.

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were significantly associated with an increased risk of LREs (adjusted HR = 1.975, 95% CI 1.245–3.133; $p = 0.004$).

Conclusions: 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 confer the highest risk for liver-related outcomes.

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

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 stage 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 cardiovascular disease (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 2 valid VCTE examinations spaced 6 months or more apart, along with sufficient clinical and laboratory information to classify the CKM stage

before their final VCTE assessment. Participants were excluded if they were under 18 years of age, had evidence of other chronic liver diseases (eg, viral hepatitis, autoimmune hepatitis, or inherited liver conditions), reported significant alcohol consumption (>30 g/day for men or >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 6 months of enrollment. Additional exclusion criteria included a follow-up duration of <6 months for either VCTE or LRE and missing data on key variables necessary to determine the CKM stages or assess study outcomes.

All research involving human participants was conducted in accordance with the principles of the Declaration of Helsinki and the Declaration of Istanbul. 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 S1, <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] In addition, at least one of the following 5 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 $\geq 5.7\%$ (≥ 39 mmol/mol), or diagnosis of type 2 diabetes mellitus or use of glucose-lowering medications; (3) blood pressure $\geq 130/85$ mm Hg 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 (Supplemental Table S2, <http://links.lww.com/HEP/K337>).^[9] Participants were classified into 5 CKM stages (0–4). 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 ($\geq 130/85$ mm Hg 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 $\geq 20\%$ 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 (eg, 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 stages 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 $\geq 20\%$ 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 $\geq 20\%$ 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 6 months was required between the 2 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 $\pm$ SD or medians with IQR, while categorical variables were presented as percentages. Comparisons across CKM stages were performed using one-way 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 CAP, serum ALT, serum AST, platelet (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. HR and 95% CIs 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 1 year of follow-up and at least 2 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 T2D 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 T2D, 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, 3753 (31.0%) patients were at CKM stage 0–1, 7026 (58.1%) at CKM stage 2, and 1318 (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 stages 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 2042 (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 with CKM stage 0–1 (Table 2). Histologic assessment in a subset of 2358 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 the incidence of liver stiffness progression and regression and CKM stages

During a median follow-up of 2.7 years (IQR: 1.4–4.3 y) based on serial VCTE assessments, the progression of liver stiffness occurred in 716 patients (6.1%) among the 1218 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 with CKM stage 0–1 (Table 3).

Among the 2042 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. No significant differences were observed among the 3 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%) (Supplemental Table S3,

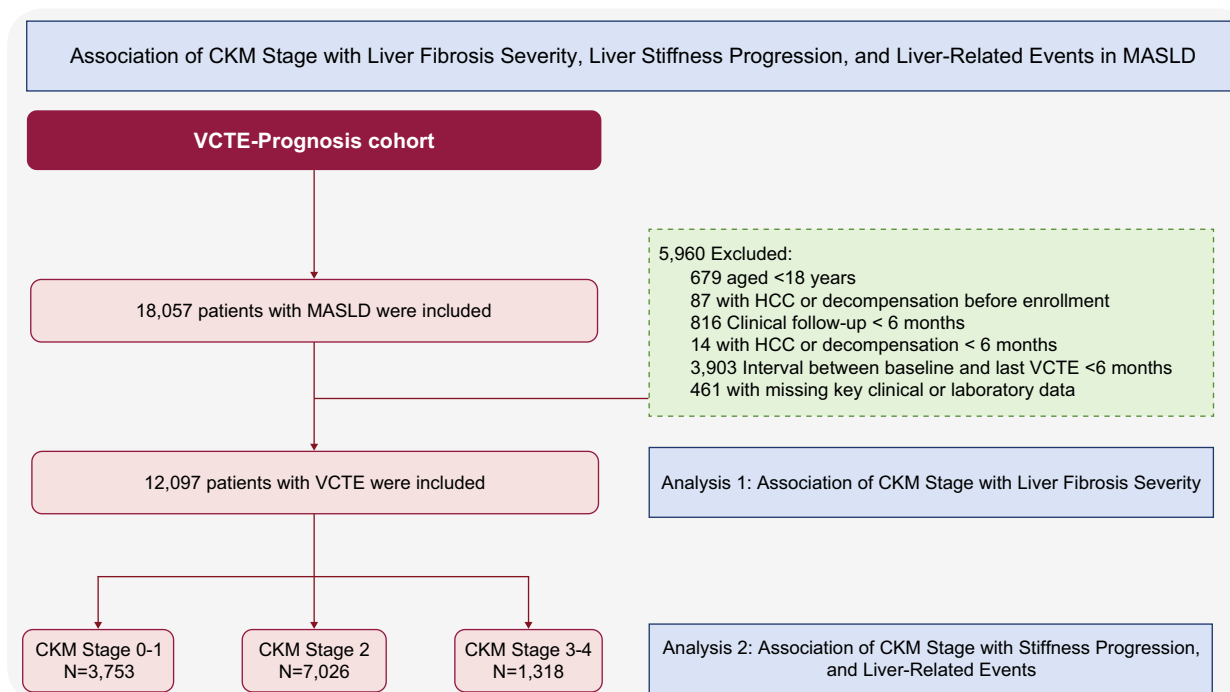


FIGURE 1 Flowchart of the study participants. Abbreviations: CKM, cardiometabolic-renal syndrome; MASLD, metabolic dysfunction–associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

TABLE 1 Baseline clinical and demographic characteristics stratified by CKM stages in MASLD

Characteristics	Overall N = 12,097	CKM stage 0–1 N = 3753	CKM stage 2 N = 7026	CKM stage 3–4 N = 1318	p
Age, y	52.9 ± 13.4	48.8 ± 13.1	52.3 ± 12.4	67.8 ± 8.5	<0.001
Male sex, n (%)	7131 (58.9%)	2264 (60.3%)	4087 (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%)	3124 (83.2%)	6368 (90.6%)	1213 (92.0%)	<0.001
Hypertension, n (%)	5201 (43.0%)	0 (0.0%)	4003 (57.0%)	1198 (90.9%)	<0.001
Type 2 diabetes, n (%)	5073 (41.9%)	0 (0.0%)	3913 (55.7%)	1160 (88.0%)	<0.001
Dyslipidemia, n (%)	9616 (79.5%)	2343 (62.4%)	6119 (87.1%)	1154 (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 m ²	93.9 ± 16.3	98.1 ± 13.8	94.5 ± 15.6	79.1 ± 18.5	<0.001
Platelet count, ×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.

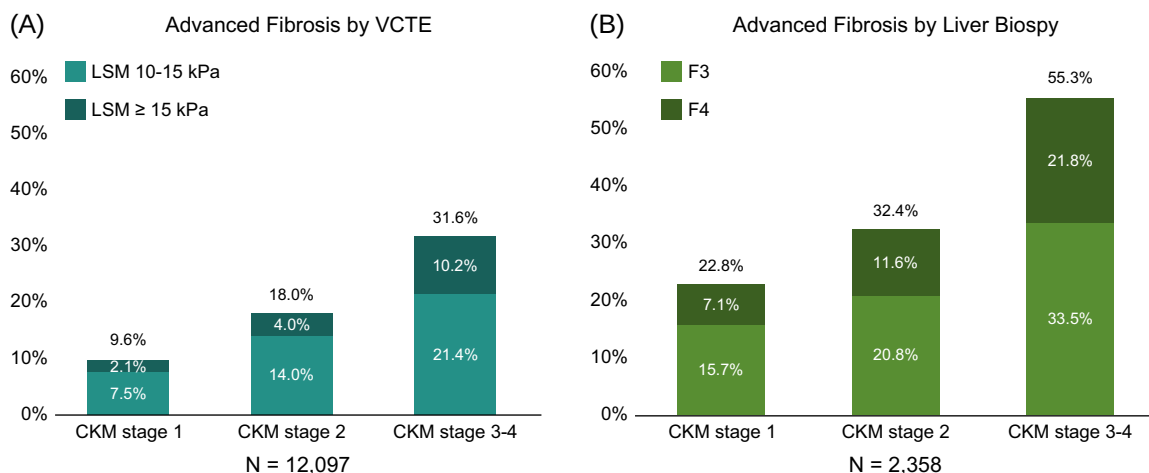


FIGURE 2 Prevalence rates of advanced fibrosis assessed by either vibration-controlled transient elastography or liver histology, stratified by CKM stages in patients with MASLD. Abbreviations: CKM, cardiometabolic–renal syndrome; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; VCTE, vibration-controlled transient elastography.

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)	<i>p</i>	Adjusted OR ^a (95% CI)	<i>p</i>
Advanced fibrosis (LSM $\geq$ 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

^aData adjusted for age, sex, BMI, AST, ALT, PLT count, and medication use (ie, glucose-lowering and/or lipid-lowering agents).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CKM, cardiovascular-kidney-metabolic; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; OR, odds ratio; PLT, platelet count.

<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 1 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, $p<0.001$) (Supplemental Figure S1, <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, $p<0.001$) (Supplemental Figure S2, <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, $p<0.001$) (Supplemental Figure S3, <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 $\geq$ 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 (Supplemental Table S4, <http://links.lww.com/HEP/K337>). Fifth, to evaluate whether the presence of T2D 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 T2D (Supplemental Table S5, <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

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	Adjusted HR ^a (95% CI)	p
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

^aData adjusted for age, sex, BMI, AST, ALT, PLT count, baseline LSM, baseline CAP, and medication use (ie, glucose-lowering and/or lipid-lowering medications).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; CKM, cardiovascular-kidney-metabolic; HR, hazards ratio; LRE, liver-related events; LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; PLT, platelet count.

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 the 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

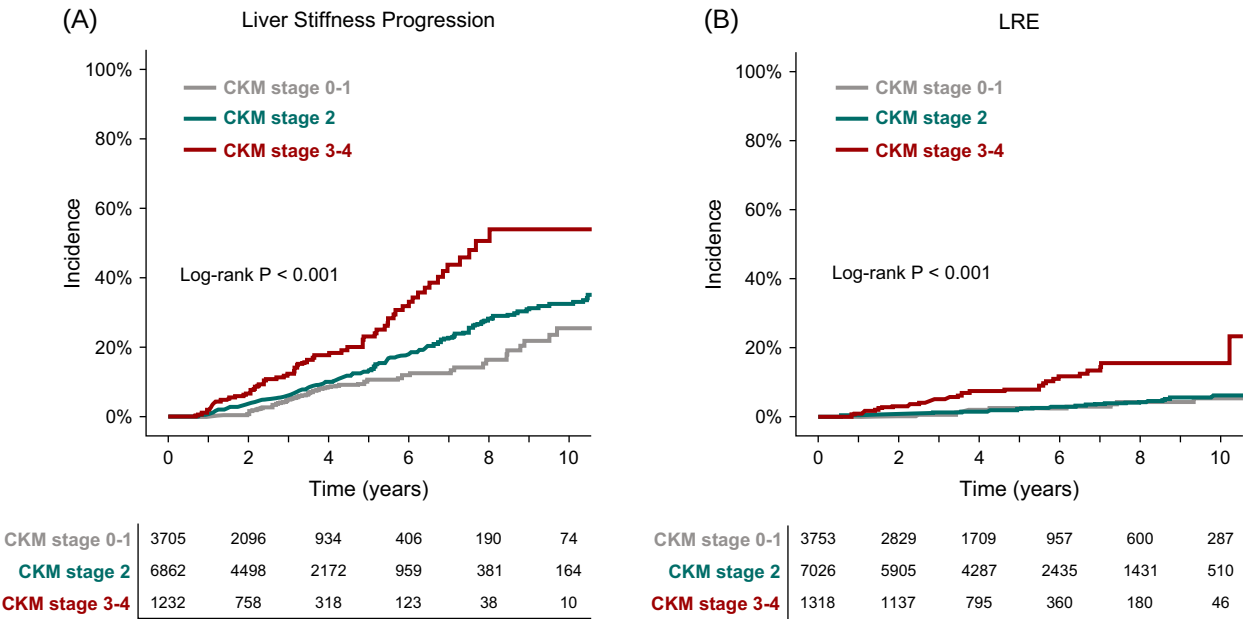


FIGURE 3 Cumulative Incidence rates of (A) liver stiffness progression, and (B) long-term LREs, stratified by CKM stages in patients with MASLD. Abbreviations: CKM, cardiometabolic-renal syndrome; LRE, liver-related events; MASLD, metabolic dysfunction–associated steatotic liver disease.

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-kidney-liver-metabolic” (CKLM) syndrome. In line with this, we have developed a preliminary framework (Supplemental Table S6, <http://links.lww.com/HEP/K337>), integrating MASLD and liver fibrosis into the CKM staging system (named CKLM syndrome). This framework proposes CKLM stages that incorporate metabolic risk factors, CKD, 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, noninvasive 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 underestimation 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. In addition, 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 cardio-metabolic, 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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CONFLICTS OF INTEREST

Terry Cheuk-Fung Yip consults for, advises, and received grants from Gilead. Seung Up Kim received grants from Gilead, GSK, Bayer, Eisai, AbbVie, Echosens, MSD, BMS, and AstraZeneca outside the submitted work. 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

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