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Impact of cardiometabolic risk factors on hepatic fibrosis and clinical outcomes in MASLD: A population-based multi-cohort study

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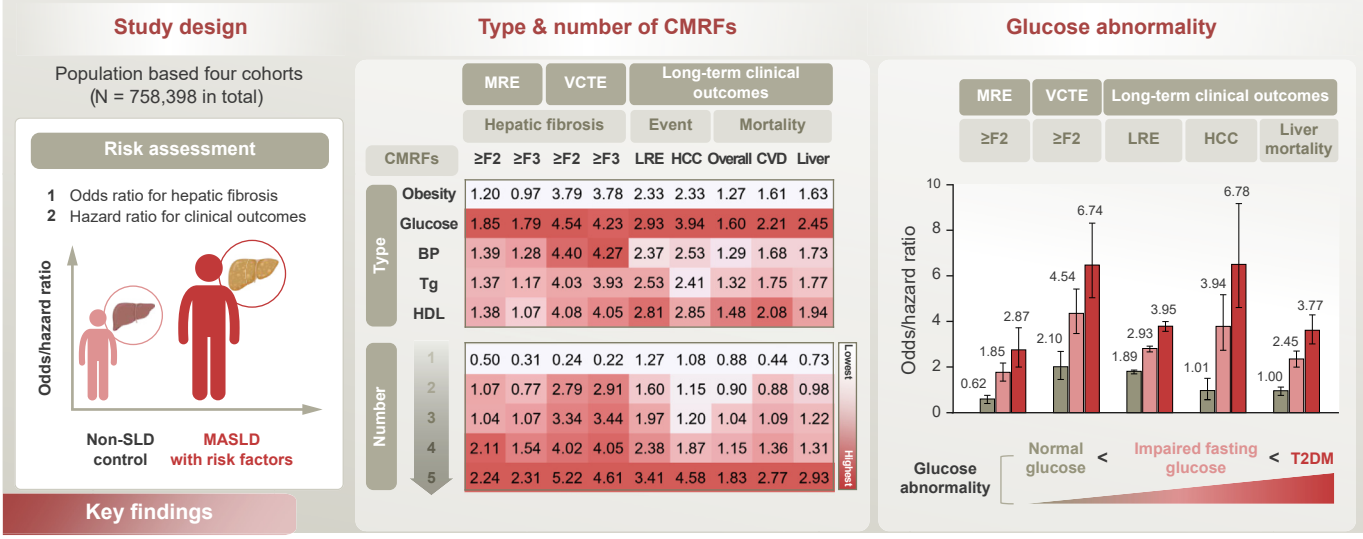
Graphical abstract



- Impaired fasting glucose (CMRF2) was identified as the most significant risk factor for MASLD-related clinical outcomes
- The risks increased in proportion to the number of CMRFs present
- MASLD -related clinical outcomes correlate highly with glucose severity

Highlights:

- CMRFs strongly link to hepatic fibrosis and clinical outcomes.
- MASLD-related clinical outcomes correlate highly with glucose severity.
- The impact of each of the five CMRFs varied depending on the type of clinical outcome and the characteristics of the population.
- Impaired fasting glucose (CMRF2) consistently posed the highest risk.
- Patients with MASLD with CMRF2 had a 2-4-fold higher risk of hepatic fibrosis and liver-related events.

Impact and implications:

Understanding the impact of the five cardiometabolic risk factors (CMRFs) used in the diagnosis of metabolic dysfunction-associated steatotic liver disease (MASLD) on hepatic fibrosis and long-term clinical outcomes can improve the quality of care in the general population by facilitating the identification of at-risk individuals with MASLD. In our results, although the impact of each of the five CMRFs on hepatic fibrosis and long-term clinical outcomes varied depending on the type of clinical outcomes and the characteristics of the population, impaired fasting glucose (CMRF2) consistently showed the highest risk. Patients with MASLD and CMRF2 exhibited a two-to-four times higher risk of hepatic fibrosis and liver-related events compared with those without impaired fasting glucose levels, similar to MASLD accompanied by any four CMRFs. The utilization of impaired fasting glucose (CMRF2) can raise awareness among primary care providers regarding high-risk groups at the time of MASLD diagnosis.

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Research article

JHEP|Reports

Impact of cardiometabolic risk factors on hepatic fibrosis and clinical outcomes in MASLD: A population-based multi-cohort study

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Background & Aims: Evaluating five cardiometabolic risk factors (CMRFs) is crucial for diagnosing metabolic dysfunction-associated steatotic liver disease (MASLD). This study investigated the impact of CMRFs on hepatic fibrosis and long-term clinical outcomes in patients with MASLD.

Methods: Two cross-sectional cohorts (Korean magnetic resonance elastography [n = 6,684] and US vibration-controlled transient elastography [n = 6,230]) were included to assess the impact of five CMRFs and their combinations on hepatic fibrosis. Two longitudinal cohorts (UK Biobank [n = 408,544; mean follow-up, 14.3 years] and Korea National Health Insurance data [n = 355,640; mean follow-up, 11.7 years]) were included to evaluate long-term outcomes, including liver-related events, hepatocellular carcinoma events, and overall, cardiovascular, and liver-related death. The risk of MASLD associated with CMRFs was assessed using logistic or Cox regression analysis, referencing participants without steatotic liver disease.

Results: Across all four cohorts, patients with type 2 diabetes mellitus had the highest risk of hepatic fibrosis and long-term clinical outcomes. Among the five CMRFs, impaired fasting glucose (CMRF2) was the most significant risk factor for both hepatic fibrosis and long-term clinical outcomes. High blood pressure (CMRF3) was the second most significant risk factor for hepatic fibrosis, following CMRF2. Low high-density lipoprotein cholesterol level (CMRF5) exhibited comparable significance for long-term clinical outcomes. These clinical outcomes worsened with increasing severity of glucose abnormalities (normal and impaired fasting glucose levels and type 2 diabetes mellitus). Patients with MASLD and CMRF2 exhibited a two-to-four times higher risk of hepatic fibrosis and liver-related events compared with those without impaired fasting glucose levels, similar to MASLD accompanied by any four CMRFs.

Conclusions: The impact of the five CMRFs on hepatic fibrosis and long-term clinical outcomes varied across different clinical outcomes and population characteristics. However, impaired fasting glucose (CMRF2) consistently demonstrated the highest risk.

Introduction

In recent years, international societies have endorsed a new nomenclature, definition, and classification system for steatotic liver disease (SLD).[1–6] Metabolic dysfunction-associated SLD (MASLD) affects ~30% of the population, although its prevalence varies across countries.[3–6] The new definition of MASLD emphasizes the role of five cardiometabolic risk factors (CMRFs): overweight/obesity, impaired fasting glucose level, high blood pressure, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol level. The diagnosis of MASLD requires the presence of at least one of these five CMRFs. The effect of each CMRF on hepatic fibrosis and long-term clinical outcomes, including the overall and specific causes of mortality, varies considerably. Among these factors, type 2 diabetes mellitus (T2DM) is believed to be the strongest independent risk factor for hepatic fibrosis and adverse long-term outcomes.[7–9]

Raising awareness regarding the risk of hepatic fibrosis and adverse long-term clinical outcomes of MASLD is crucial. In this new era of MASLD, assessing the five CMRFs is vital not only for accurate diagnosis, but also for predicting the stage of associated hepatic fibrosis and the risk of adverse long-term outcomes. A deeper understanding of the impact of CMRFs on fibrosis can promote the broader use of non-invasive testing (NIT) in primary care settings, enabling earlier detection and improved management of fibrosis.

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A question often asked is what the ranking should be of the various CMRFs for predicting the severity of fibrosis and prognosis, although these factors are primarily used as diagnostic criteria and not as severity or prognostic criteria. Kanwal *et al.*[10] highlighted that metabolic traits increase the risk of cirrhosis and hepatocellular carcinoma (HCC) in patients with MASLD. The presence of CMRFs in patients with MASLD also increases the risk of cirrhosis and HCC, and this risk escalates with an increase in the number of CMRFs. Among these factors, T2DM is associated with the highest risk of progression to HCC. The authors stressed the importance of assessing CMRFs in MASLD, highlighting that patients with MASLD with T2DM, along with other CMRFs, represent a crucial target population for the secondary prevention of liver cancer. Similarly, Marchesini *et al.*[11] eported that both the number of metabolic risk factors and the presence of T2DM are significant determinants of hepatic fibrosis and long-term clinical outcomes in patients with non-alcoholic fatty liver disease.

Although previous studies examined the influence of various types of CMRF, there is a lack of research on the impact of the five individual or combined CMRFs included in the newly defined MASLD on fibrosis and long-term clinical outcomes of MASLD. Therefore, in this study, we investigated the impact and relative importance of the five CMRFs included in the diagnosis of MASLD on hepatic fibrosis and long-term liver disease-related clinical outcomes in MASLD. Specifically, we focused on the clinical significance of impaired fasting glucose (CMRF2), including impaired fasting glucose levels and T2DM. We also explored the role of the five CMRFs, alone and in combination, in hepatic fibrosis and long-term clinical outcomes of metabolic dysfunction and alcohol-related liver disease (MetALD).

Patients and methods

Research design and cohorts

This study included four large cohorts of ~758,000 patients. Two cross-sectional cohorts assessed the effect of the five CMRFs and their combinations on the risk of hepatic fibrosis: the magnetic resonance elastography (MRE) health check-up cohort from South Korea (n = 6,684) and the vibration-controlled transient elastography (VCTE) cohort from the US National Health and Nutrition Examination Survey (NHANES; n = 6,230). Two longitudinal cohorts evaluated the prognostic significance of the proposed CMRF classification: the UK Biobank (n = 408,544) and the Korea National Health Insurance (KNHIS) data (n = 355,640). This research has been conducted using the UK Biobank Resource under Application Number 99573. Approved by the institutional review board of Hanyang University (HY-2021-04-001-001, HY-2023-10-006, and HY-2023-10-007), the study adhered to the Declaration of Helsinki and Istanbul, with informed consent waived because of its retrospective design.

Inclusion and exclusion criteria

Individuals aged ≥0 years who were evaluated for hepatic steatosis were eligible for inclusion. Patients with missing data on CMRFs, liver health status (*e.g.* history of HBV or HCV or other chronic liver diseases), and clinical outcomes, such as hepatic fibrosis, in the training/validation cohort or mortality in the longitudinal cohort, were excluded. In addition, individuals with significant alcohol consumption (>140 and >210 g/week in women and men, respectively) were excluded (Fig. 1).[1]

Definition of hepatic steatosis in the cohorts

In the four cohorts, hepatic steatosis was defined as follows: MRE health check-up cohort, steatosis diagnosed via abdominal ultrasound; NHANES cohort, a controlled attenuation parameter of ≥263 dB/m; and the UK Biobank and KNHIS data cohorts, a hepatic steatosis index (HSI) score ≥36.[12]

MRE health check-up cohort from Korea

A risk assessment of each of the five CMRFs and their combinations for significant hepatic fibrosis was performed in the MRE health check-up cohort (n = 6,684). Patients who underwent abdominal ultrasonography and MRE on the same day as part of their health examinations at centers that solely offered health evaluation programs were included (Fig. 1).[13] SLD was diagnosed using ultrasonography. Cut-off values of ≥3.0 and ≥3.6 kPa indicated significant hepatic fibrosis (≥F2) and advanced hepatic fibrosis (≥F3), respectively, in the MRE cohort.[14] The mean age of the participants in the training cohort was 46.8 ± 10.3 years. The prevalence rates of hypertension, T2DM, metabolic syndrome, and MASLD in the MRE cohort were 15.6%, 8.0%, 22.8%, and 35.3%, respectively (Table S1). The proportions of CMRF1, 2, 3, 4, and 5 in patients with MASLD were 93.6%, 45.7%, 37.7%, 55.2%, and 25.7%, respectively (Table 1). The prevalence of significant and advanced hepatic fibrosis was 9.0% and 2.3%, respectively.

Transient elastography cohort from the NHANES

The VCTE cohort from NHANES 2017 to 2020 (Fig. 1) was used to externally validate the risk assessment of significant hepatic fibrosis using a combination of CMRFs. A controlled attenuation parameter of ≥263 dB/m indicated SLD in the US NHANES cohort.[15] Cut-off values of ≥8.2 and ≥9.7 kPa indicated significant (≥F2) and advanced hepatic fibrosis (≥F3), respectively, in the VTCE cohort.[16,17] In total, 6,230 patients were analyzed. The mean age of the patients in the VTCE cohort was 50.2 ± 17.0 years. The prevalence rates of hypertension, T2DM, metabolic syndrome, and MASLD in the VTCE cohort were 43.5%, 18.2%, 57.1%, and 46.6%, respectively (Table S1). The proportions of CMRF1, 2, 3, 4, and 5 in patients with MASLD were 97.7%, 66.9%, 61.5%, 62.2%, and 66.3%, respectively (Table 1). The prevalence of significant and advanced hepatic fibrosis was 14.7% and 9.1%, respectively.

Two longitudinal cohorts for long-term clinical outcomes

The association between the severity of MASLD and cause of mortality was assessed in two large community-based cohorts: the UK Biobank and KNHIS (Fig. 1). Although the two cohorts had different population coverage rates (UK: ~5%; South Korea: almost the entire population), both datasets encompassed extensive health information, medical and death records, and socioeconomic factors (*e.g.* income). These datasets represent real-world data; consequently, they have been used to analyze prescriptions, procedures, and surgeries, and to identify trends in the medical field. The prevalence rate of MASLD in the UK Biobank and KNHIS cohorts was 27.7% and 27.2%, respectively. Clinical events and causes of death were defined according to International Classification of Diseases (ICD)-10 code at the time of the first diagnosis and death, respectively. Clinical events were classified as liver-related or HCC events.

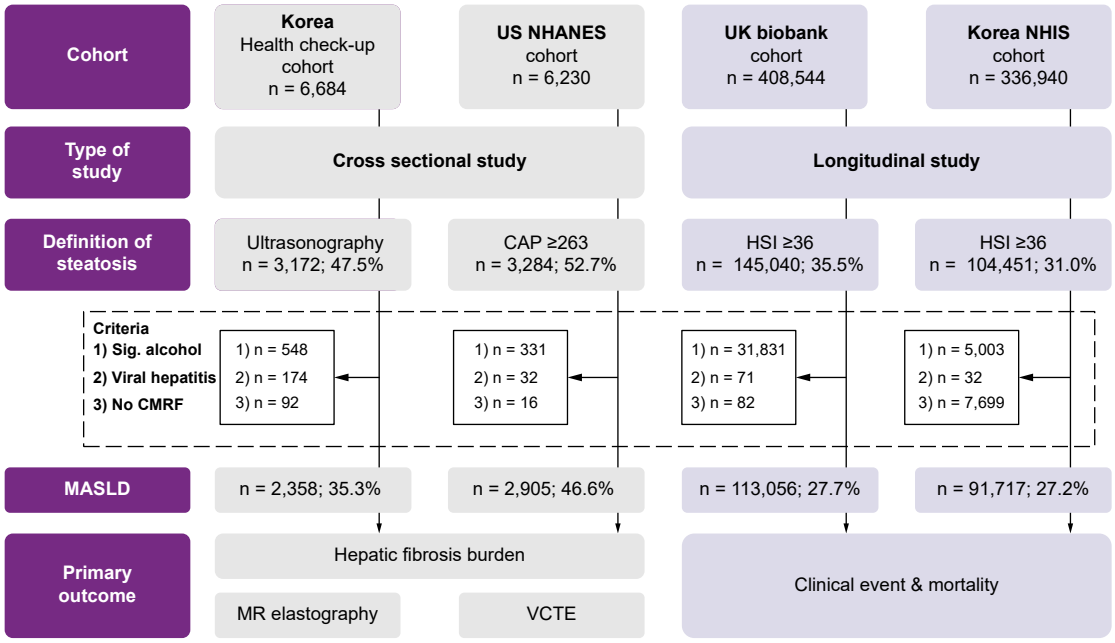

Fig. 1. Study flowchart. CAP, controlled attenuation parameter; CMRF, cardiometabolic risk factor; HSI, hepatic steatosis index; MASLD, metabolic dysfunction-associated steatotic liver disease; MR, magnetic resonance; NHIS, National Health Insurance Service; NHANES, National Health and Nutrition Examination Survey; VCTE, vibration-controlled transient elastography.

Causes of death were classified as overall, cardiovascular, liver-related, and extrahepatic cancer-related (EHCD) deaths. The ICD-10 codes used in this study are detailed in Table S2. The mean follow-up duration was 14.3 years and 11.7 years in the UK Biobank and KNHIS cohorts, respectively. In the UK Biobank cohort, the rates of liver-related and HCC events and the overall, cardiovascular, liver-related, and EHCD deaths during the follow-up period were 5.2%, 0.08%, 10.2%, 2.4%, 0.35%, and 4.5%, respectively (Table 1). In the KNHIS database, the corresponding values were 0.8%, 0.26%, 8.2%, 1.4%, 0.46%, and 2.3%, respectively.

Definition of cardiometabolic risk factors

To provide primary care physicians with clinical information regarding risk assessment and long-term prognosis in conjunction with the diagnosis of MASLD in a more comprehensible manner, this study focused on only the five CMRFs used for diagnosis in newly defined MASLD: (1) CMRF1 (overweight/obesity): BMI ≥25 kg/m^2 (≥23 kg/m^2 for Asians) or waist circumference (WC) >94 cm in men and >80 cm in women, or adjusted based on ethnicity; (2) CMRF2 (impaired fasting glucose regulation or T2DM): fasting serum glucose level ≥100 mg/dl (≥5.6 mmol/L), 2-h post-load glucose level ≥140 mg/dl (≥7.8 mmol/L), HbA1c ≥5.7%, or on specific drug treatment; (3) CMRF3 (high blood pressure): blood pressure ≥130/85 mmHg or taking specific antihypertensive treatment; (4) CMRF4 (hypertriglyceridemia): plasma triglyceride level ≥150 mg/dl (≥1.70 mmol/L) or use of specific lipid-lowering treatment; and (5) CMRF5 (low HDL cholesterol): plasma HDL cholesterol level <40 mg/dl (<1.0 mmol/L) for men and <50 mg/dl (<1.3 mmol/L) for women or on specific treatment to increase HDL level.[2]

There are considerations in defining CMRFs. For CMRF1, prevalence differed based on WC and BMI diagnostic criteria; therefore, in addition to current criteria considering both, indicators considering WC (CMRF1 [WC criteria]) and BMI (CMRF1 [BMI criteria]) were included in the analysis. For CMRF2, fasting was required in HNANES, KHNIS, and health check-up cohorts, but was not mandatory in the UK Biobank cohort. Consequently, there is potential for overestimation of CMRF2 within the UK Biobank cohort.

Calculation of the FIB-4 score, MAF-5 score, and triglyceride glucose index

The Fibrosis-4 index (FIB-4) score was calculated, and the cut-off values were selected according to the method described by McPherson *et al.*[18] The Metabolic Dysfunction-Associated Fibrosis-5 (MAF-5) score was calculated, and the cut-off values were selected according to the method described by van Kleef *et al.*[19] The triglyceride glucose index, a surrogate marker of insulin resistance, was calculated according to the method described by Guerrero-Romero *et al.*[20]

Statistical analysis

Continuous and categorical variables are presented as mean ± SD and as numbers and percentages, respectively. Student independent *t* test and Chi-square test were used to analyze continuous and categorical variables, respectively. The odds ratios (ORs) of the five CMRFs, their various combinations, and the presence of T2DM in patients with MASLD were calculated and assessed using logistic regression analysis to determine the severity of MASLD based on hepatic fibrosis as a reference for participants without SLD (non-SLD), after adjusting for age and sex. The hazard ratios (HRs) of the five CMRFs among patients with MASLD were used to report the results of Cox regression analysis (the cause-specific method) for long-term clinical outcomes, such as liver-related and HCC events and

Table 1. Baseline characteristics of patients with MASLD in various cohorts.

Variable	Cohort			
	Korea health check-up MRE cohort (n = 2,358; 35.3%)	US NHANES VCTE cohort (n = 2,905; 46.6%)	UK Biobank cohort (n = 113,056; 27.7%)	Korea NHIS cohort (n = 91,717; 27.2%)
Age (years	47.6 ± 9.8	53.1 ± 16.0	56.8 ± 7.9	53.3 ± 14.0
Male sex	2,124 (90.1)	1,532 (52.7)	57,083 (50.5)	25,495 (27.8)
BMI (kg/m^2)	26.6 ± 2.9	33.1 ± 6.9	32.3 ± 4.3	26.1 ± 10.8
Waist circumference (cm)	90.5 ± 7.3	109.2 ± 15.0	102.0 ± 11.1	84.0 ± 9.1
Systolic blood pressure (mmHg)	119 ± 13	125 ± 18	142 ± 18	126.1 ± 15.8
Diastolic blood pressure (mmHg)	76 ± 9	75 ± 11	85 ± 10	77.8 ± 10.3
Glucose (mg/dl)	104 ± 24	108 ± 42	97 ± 30	101.2 ± 26.9
Triglyceride (mg/dl)	185 ± 130	166 ± 121	189 ± 100	138.7 ± 102.7
HDL (mg/dl)	48 ± 10	48 ± 13	48 ± 11	55.5 ± 33.4
Platelet (10^3/μl)	251 ± 51	249 ± 65	255 ± 61	–
Hypertension	538 (22.8)	1,524 (52.5)	49,137 (43.5)	33,859 (36.9)
T2DM	313 (13.3)	823 (28.3)	18,657 (16.5)	14,552 (15.9)
FIB-4 score	1.11 ± 0.64	1.07 ± 0.68	1.27 ± 1.89	–
MAF-5 score	−0.07 ± 1.76	0.83 ± 2.33	0.66 ± 1.74	–
Metabolic syndrome	935 (39.7)	2,198 (75.7)	85,343 (75.5)	32,986 (36.0)
Cardiometabolic risk factors				
Overweight/obesity (CMRF1)	2,208 (93.6)	2,837 (97.7)	112,459 (99.5)	79,079 (86.2)
Impaired glucose regulation/T2DM (CMRF2)	1,077 (45.7)	1,943 (66.9)	45,830 (40.5)	39,137 (42.7)
High blood pressure (CMRF3)	890 (37.7)	1,788 (61.5)	96,629 (85.5)	51,542 (56.2)
Hypertriglyceridemia (CMRF4)	1,302 (55.2)	1,806 (62.2)	78,373 (69.3)	30,722 (33.5)
Low HDL cholesterol level (CMRF5)	606 (25.7)	1,927 (66.3)	59,359 (52.5)	30,801 (33.6)
Clinical outcomes				
Significant hepatic fibrosis	213 (9.0)	427 (14.7)	–	–
Advanced hepatic fibrosis	55 (2.3)	265 (9.1)	–	–
Liver-related event	–	–	5,741 (5.2)	776 (0.8)
Hepatocellular carcinoma	–	–	94 (0.08)	234 (0.26)
Overall mortality	–	–	11,579 (10.2)	7,541 (8.2)
Cardiovascular mortality	–	–	2,666 (2.4)	1,288 (1.4)
Liver-related death	–	–	401 (0.35)	421 (0.46)
Extrahepatic cancer-related death	–	–	5,074 (4.5)	2,072 (2.3)

Data are presented as n (%) or mean ± SD.

The percentages in the cohort column headings represent the proportion of MASLD in each cohort.

CMRF, cardiometabolic risk factor; FIB-4, fibrosis-4 score; HDL, high-density lipoprotein; KNHIS, Korean National Health Insurance Service; MAF-5, metabolic dysfunction-associated fibrosis-5; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; NHANES, National Health and Nutrition Examination Survey; T2DM, type 2 diabetes mellitus; SLD, steatotic liver disease; VTCE, vibration-controlled transient elastography.

the overall, cardiovascular, liver-related, and EHCD deaths, as a reference for participants without SLD after adjusting for age and sex. The HRs for long-term clinical outcomes in patients with MASLD with an FIB-4 score >1.3, MAF-5 score >0, and T2DM were also evaluated. All statistical analyses were performed using SPSS (version 26.0; IBM, Armonk, NY, USA). Statistical significance was set at p <0.05.

Results

Effects of each of the five CMRFs on hepatic fibrosis and long-term clinical outcomes

The ORs of each of the five CMRFs for hepatic fibrosis in patients with MASLD were assessed using the non-SLD group as a reference in the Korean MRE and US NHANES VCTE cohorts (Table 2 and Fig. 2A). Both the Korean MRE and NHANES VCTE cohorts exhibited high ORs for hepatic fibrosis in the following order: CMRF2 > CMRF3 > CMRF5 > CMRF4 > CMRF1 (Fig. 2A). The ORs for significant and advanced hepatic fibrosis showed slight variations. However, CMRF2 consistently presented the highest OR in both the Korean and US cohorts, followed by CMRF3. Among the five CMRFs, CMRF1 exhibited the lowest OR for hepatic fibrosis in both cohorts. When comparing the prevalence of CMRFs across the four cohorts, 86–99% of patients with MASLD had CMRF1 and 40–67% had CMRF2 (Table S3). This observation, combined with the lowest OR for CMRF1, could result from the fact that >90% of MASLD cases occurred in both the South Korea and the US cohorts, suggesting that CMRF1 exerts a relatively minor influence on MASLD-induced fibrosis.

The adjusted HRs (aHRs) of each of the five CMRFs for long-term clinical outcomes, including liver-related events (LREs), HCC events, overall mortality, liver-related death (LRD), cardiovascular disease (CVD), and EHCD, were assessed in the UK Biobank and KNHIS cohorts after adjusting for age and sex (Tables 3 and 4, and Fig. 2). Consistently, CMRF2 demonstrated the highest aHR, followed by CMRF5, regardless of the cohort type or clinical outcome. Across all four cohorts, CMRF2 was identified as the most significant risk factor for hepatic fibrosis and poor clinical outcomes. However, in the case of hepatic fibrosis, CMRF3 was the second most significant risk factor after CMRF2. CMRF5 demonstrated similar significance in liver-related clinical outcomes.

Joint associations of CMRFs with hepatic fibrosis

As the number of CMRFs increased, the risk (OR and aHR) of hepatic fibrosis and adverse clinical outcomes also increased. The OR and aHR of patients with MASLD with all five CMRFs were higher than those of patients with MASLD presenting with only CMRF2. However, the risk of hepatic fibrosis and clinical outcomes remained lower than those in patients with both MASLD and T2DM. This tendency was not observed, particularly for LREs, LRDs, and EHCDs, in the KNHIS cohort, where the incidence of these diseases was low. This finding resulted in a small difference in ORs and aHRs between patients with MASLD accompanied by one and five CMRFs, with most values overlapping the CIs.

The ORs of the combination of the five CMRFs for hepatic fibrosis in patients with MASLD are detailed in Table S4. Overall, as the number of combined CMRFs increased, the risk

Table 2. Age and sex-adjusted logistic and Cox regression analysis of hepatic fibrosis in Korea Health check-up MRE and US NHANES VTCE cohorts.

Subgroup in MASLD	Cohort											
	Korea Health check-up MRE cohort (n = 2,358)						US NHANES VTCE cohort (n = 2,905)					
	Significant fibrosis (total cases: 213)			Advanced fibrosis (total cases: 55)			Significant fibrosis (total cases: 427)			Advanced fibrosis (total cases: 265)		
	%	OR	95% CI	%	OR	95% CI	%	OR	95% CI	%	OR	95% CI
Non-SLD (reference)	6.8	1.000	1	2.1	1.000	1	4.1	1.000	1	2.4	1.000	1
CMRF												
CMRF1	9.1	1.202	0.985–1.467	2.2	0.967	0.667–1.402	15.0	3.785	3.064–4.675	9.3	3.775	2.880–4.948
CMRF1 (WC criteria)	11.0	1.530	1.227–1.907	2.8	1.223	0.814–1.839	15.4	3.914	3.167–4.837	9.6	3.903	2.977–5.117
CMRF1 (BMI criteria)	9.2	1.211	0.992–1.479	2.2	0.975	0.673–1.414	15.3	3.890	3.147–4.807	9.5	3.893	2.969–5.104
CMRF2	14.2	1.846	1.481–2.301	4.5	1.787	1.224–2.609	18.1	4.536	3.638–5.656	11.0	4.226	3.190–5.598
CMRF3	11.3	1.385	1.078–1.779	3.4	1.281	0.825–1.987	18.0	4.404	3.518–5.514	11.3	4.266	3.209–5.673
CMRF4	10.2	1.367	1.090–1.715	2.6	1.165	0.766–1.771	16.7	4.030	3.220–5.044	10.4	3.934	2.957–5.234
CMRF5	10.6	1.383	1.031–1.856	2.6	1.074	0.618–1.865	16.3	4.078	3.267–5.090	10.2	4.050	3.054–5.469
MASLD	9.0	1.182	0.972–1.438	2.3	1.006	0.703–1.441	14.7	3.688	2.986–4.555	9.1	3.678	2.806–4.820
T2DM	22.0	2.874	2.119–3.899	9.6	3.625	2.301–5.711	25.3	6.744	5.261–8.645	16.0	6.306	4.628–8.593
Number of CMRF(s)												
Any 1 CMRF	3.8	0.498	0.301–0.824	0.7	0.307	0.096–0.980	0.9	0.243	0.060–0.991	0.5	0.223	0.031–1.619
Any 2 CMRFs	7.9	1.065	0.784–1.447	1.7	0.772	0.415–1.435	10.2	2.787	1.950–3.984	6.2	2.905	1.848–4.568
Any 3 CMRFs	8.2	1.044	0.768–1.420	2.5	1.071	0.624–1.838	12.9	3.339	2.485–4.486	8.1	3.442	2.375–4.989
Any 4 CMRFs	16.0	2.106	1.559–2.845	3.9	1.542	0.882–2.696	15.6	4.015	3.046–5.293	9.9	4.045	2.863–5.715
Any 5 CMRFs	17.8	2.242	1.331–3.777	6.5	2.309	1.026–5.193	21.0	5.218	4.046–6.730	12.9	4.605	3.351–6.328

ORs for significant and advanced hepatic fibrosis were calculated as a reference for subjects without SLD. In addition, age and sex were also adjusted for.
CMRF, cardiometabolic risk factor; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; VTCE, vibration-controlled transient elastography; WC, waist circumference.

	Cohort	Korea health check-up		US NHANES		UK biobank						Korea NHIS					
	Clinical outcomes	Significant fibrosis	Advanced fibrosis	Significant fibrosis	Advanced fibrosis	LRE	HCC	Overall death	CVD death	LRD	EHCD	LRE	HCC	Overall death	CVD death	LRD	EHCD
		OR	OR	OR	OR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR
A Kinds of CMRFs	CMRF 1	1.202	0.967	3.785	3.775	2.325	2.334	1.268	1.613	1.634	1.156	1.425	1.378	1.014	1.053	1.563	1.070
	CMRF 1 (WC criteria)	1.530	1.223	3.914	3.903	2.383	2.483	1.304	1.674	1.700	1.181	1.537	1.505	1.080	1.100	1.721	1.121
	CMRF 1 (BMI criteria)	1.211	0.975	3.890	3.893	2.324	2.338	1.269	1.614	1.637	1.157	1.414	1.383	1.006	1.040	1.542	1.070
	CMRF 2	1.846	1.787	4.536	4.226	2.934	3.943	1.600	2.212	2.453	1.315	1.751	1.583	1.220	1.243	1.984	1.234
	CMRF 3	1.385	1.281	4.404	4.266	2.370	2.525	1.288	1.682	1.729	1.156	1.411	1.282	1.080	1.203	1.512	1.051
	CMRF 4	1.367	1.165	4.030	3.934	2.530	2.405	1.324	1.754	1.773	1.176	1.141	0.803	1.111	1.159	1.265	1.094
	CMRF 5	1.383	1.074	4.078	4.050	2.807	2.848	1.484	2.081	1.938	1.261	1.423	1.396	1.171	1.196	1.625	1.135
B Number of CMRFs	Any 1 of CMRF	0.498	0.307	0.243	0.223	1.274	1.077	0.883	0.438	0.731	0.975	1.51	1.41	1.007	0.914	1.759	1.201
	Any 2 of CMRF	1.065	0.772	2.787	2.905	1.599	1.15	0.903	0.876	0.979	0.951	1.529	1.492	1.016	1.043	1.781	1.127
	Any 3 of CMRF	1.044	1.071	3.339	3.442	1.967	1.199	1.04	1.094	1.224	1.057	1.449	1.325	1.052	1.161	1.469	1.039
	Any 4 of CMRF	2.106	1.542	4.015	4.045	2.377	1.874	1.148	1.363	1.311	1.153	1.453	1.185	1.17	1.287	1.569	1.137
	Any 5 of CMRF	2.242	2.309	5.218	4.605	3.405	4.58	1.827	2.774	2.933	1.369	1.371	1.327	1.251	1.196	1.705	1.258

Lowest

Highest

Fig. 2. ORs and HRs for various clinical outcomes according to (A) type and (B) number of CMRFs. ORs and HRs were evaluated as references for the non-steatotic liver disease group in various cohorts. The degree of OR and HR within the comparison group is expressed as a pink gradient (lowest, white; highest, deep pink). CMRF, cardiometabolic risk factor; CVD, cardiovascular disease; EHCD, extrahepatic cancer-related death; HCC, hepatocellular carcinoma; HR, hazard ratio; LRD, liver-related death; LRE, liver-related event; NHIS, National Health Insurance Service; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; WC, waist circumference.

of hepatic fibrosis and clinical outcomes also increased. However, the presence of all five CMRFs did not necessarily result in the highest OR. Only in the case of advanced fibrosis in the Korean MRE cohort did the combination of all five CMRFs show the highest OR (2.289; 95% CI 1.017–5.149). In the other three cases, different combinations of CMRFs showed the highest OR: significant fibrosis (CMRF1, 2, 3, and 4: OR, 2.469; 95% CI:1.794–3.400) in the Korean MRE cohort and significant fibrosis (CMRF 2, 3, and 5: OR, 5.812; 95% CI 4.055–6.622) and advanced fibrosis (CMRF 1, 2, 3, and 5: OR, 4.780; 95% CI 3.510–6.511) in the NHANES VCTE cohort.

Significance of CMRF2 for hepatic fibrosis and long-term clinical outcomes

When comparing the prevalence of CMRFs across the four cohorts, ∼50% (40.5–66.9%) of patients with MASLD had CMRF2. This percentage was similar to that in patients with MASLD accompanied by three or more CMRFs in the Korean cohort and four or more CMRFs in the UK BioBank and US cohort (Table S3).

The degree of hepatic fibrosis and long-term liver-related clinical outcomes increased proportionally with the severity of abnormal glucose homeostasis (normal and impaired fasting glucose levels and T2DM) (Fig. 3A; Table S5). In terms of significant fibrosis in the Korean MRE cohort, patients with MASLD accompanied by CMRF2 (CMRF2 [+]) and T2DM had 2.96-fold and 4.61-fold higher risks of significant hepatic fibrosis, respectively, compared with those without impaired fasting glucose levels (CMRF2 [–]). This trend was consistently observed regardless of the type of cohort and clinical outcomes, and patients with MASLD accompanied by CMRF2 (impaired fasting glucose levels) had a two-to-four times higher risk of developing hepatic fibrosis and LREs. Moreover, when stratified according to the number of CMRFs, the severity of MASLD remained elevated in proportion to the severity of glucose abnormalities (Fig. 3B–F).

The spectrum of glucose abnormalities, ranging from normal to impaired fasting glucose levels and T2DM, is closely related to insulin levels. To evaluate the independent contribution of insulin resistance, an additional logistic regression analysis for hepatic fibrosis was conducted, adjusting for BMI, which demonstrated the strongest correlation with insulin resistance (Table S6), and the triglyceride glucose index (Table S7), which is a surrogate marker of insulin resistance. These analyses revealed that only CMRF2 consistently increased the risk of hepatic fibrosis. These findings imply that the severity of MASLD correlates well with glucose abnormalities, including CMRF2.

Comparison of risk between MASLD with CMRF2 and FIB-4 >1.3 or MAF-5 >0

The proportion of patients with CMRF2 in the MASLD group ranged from 45.7% to 66.9% (KHNIS, 45.7%; NHANES, 66.9%; UK Biobank, 40.5%; Fig. 4). These proportions did not significantly differ from the percentage of individuals with a high MAF-5 score (MAF-5 >0) in the MASLD group (40.7–59.3%). However, this proportion was significantly higher than the percentage of patients with MASLD with a high FIB-4 score (FIB-4 >1.3), which ranged from 15.5% to 24.7%. The presence of CMRF2 was associated with an increased risk of

Table 3. Age and sex-adjusted logistic and Cox regression analysis of long-term clinical outcomes in UK Biobank cohort.

	UK Biobank cohort (n = 113,056)																			
	Liver-related events (total cases: 5,741; previous events: n = 2,409)			Hepatocellular carcinoma (total cases: 94; previous events: n = 1,247)			Overall death (total cases: 11,579)			Cardiovascular death (total cases: 2,666)			Liver-related death (total cases: 401)			Extrahepatic cancer-related death (total cases: 5,074)		
Subgroup in MASLD	%	HR	95% CI	%	HR	95% CI	%	HR	95% CI	%	HR	95% CI	%	HR	95% CI	%	HR	95% CI
Non-SLD (reference)	2.2	1.000	1	0.03	1.000	1	8.0	1.000	1	1.4	1.000	1	0.20	1.000	1	3.9	1.000	1
CMRFs																		
CMRF1	5.1	2.325	2.241–2.411	0.08	2.334	1.743–3.126	10.3	1.268	1.240–1.297	2.4	1.613	1.535–1.695	0.35	1.634	1.436–1.859	4.5	1.156	1.118–1.196
CMRF1 (WC criteria)	5.2	2.383	2.297–2.473	0.08	2.483	1.852–3.329	10.6	1.304	1.274–1.334	2.5	1.674	1.592–1.760	0.36	1.700	1.493–1.937	4.6	1.181	1.141–1.222
CMRF1 (BMI criteria)	5.1	2.324	2.241–2.411	0.08	2.338	1.745–3.131	10.3	1.269	1.240–1.298	2.4	1.614	1.536–1.697	0.35	1.637	1.439–1.862	4.5	1.157	1.119–1.197
CMRF2	6.5	2.934	2.806–3.067	0.15	3.943	2.880–5.398	14.5	1.600	1.556–1.644	3.7	2.212	2.088–2.343	0.56	2.453	2.116–2.844	5.7	1.315	1.260–1.373
CMRF3	5.3	2.370	2.282–2.461	0.09	2.525	1.891–3.397	11.1	1.288	1.259–1.319	2.6	1.682	1.600–1.769	0.39	1.729	1.516–1.971	4.7	1.156	1.116–1.197
CMRF4	5.6	2.530	2.432–2.632	0.09	2.405	1.764–3.277	11.6	1.324	1.291–1.357	2.8	1.754	1.664–1.849	0.41	1.773	1.544–2.035	4.9	1.176	1.133–1.220
CMRF5	6.2	2.807	2.693–2.926	0.10	2.848	2.061–3.935	12.9	1.484	1.446–1.523	3.3	2.081	1.970–2.198	0.43	1.938	1.671–2.247	5.2	1.261	1.212–1.313
MASLD	5.1	2.320	2.237–2.406	0.08	2.322	1.733–3.110	10.2	1.265	1.237–1.294	2.4	1.610	1.532–1.692	0.35	1.634	1.436–1.859	4.5	1.153	1.115–1.193
T2DM	8.5	3.954	3.739–4.181	0.28	6.776	4.817–9.531	18.4	1.985	1.915–2.058	5.3	3.051	2.844–3.273	0.90	3.769	3.168–4.484	5.8	1.321	1.241–1.407
Number of CMRF(s)																		
Any 1 CMRF	2.6	1.274	1.035–1.113	0.02	1.077	0.149–7.772	3.8	0.883	0.717–0.967	0.3	0.438	0.264–0.727	0.11	0.731	0.303–1.767	2.3	0.975	0.804–1.182
Any 2 CMRFs	3.4	1.599	1.479–1.728	0.03	1.150	0.531–2.489	6.0	0.903	0.853–0.956	1.0	0.876	0.763–1.007	0.18	0.979	0.707–1.356	3.1	0.951	0.879–1.030
Any 3 CMRFs	4.3	1.967	1.851–2.091	0.04	1.199	0.655–2.197	7.6	1.040	0.995–1.086	1.4	1.094	0.990–1.210	0.25	1.224	0.961–1.559	3.7	1.057	0.993–1.125
Any 4 CMRFs	5.3	2.377	2.252–2.508	0.07	1.874	1.192–2.947	10.1	1.148	1.107–1.191	2.2	1.363	1.259–1.476	0.30	1.311	1.059–1.625	4.8	1.153	1.093–1.216
Any 5 CMRFs	7.5	3.405	3.232–3.587	0.19	4.580	3.227–6.499	18.1	1.827	1.770–1.887	5.1	2.774	2.604–2.956	0.72	2.933	2.478–3.471	6.4	1.369	1.299–1.443

HRs for significant and advanced hepatic fibrosis were calculated as a reference for subjects without SLD.
In addition, age and sex were adjusted for CMRF, cardiometabolic risk factor; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; WC, waist circumference.

hepatic fibrosis and adverse liver-related clinical outcomes (Fig. 4; Table S8).

Although patients with a high MAF-5 score exhibited a higher risk of hepatic fibrosis compared with those with CMRF2, the risks of LREs, HCC, and LRD were comparable (LREs and LRDs) or even higher (HCC incidence) in patients with CMRF2 than in those with a high MAF-5 score. Given that the positivity rate of FIB-4 was lower than that of CMRF2 or MAF-5, patients with MASLD with a high FIB-4 score demonstrated the highest risk of hepatic fibrosis and liver-related clinical outcomes among the three groups. However, patients with MASLD and CMRF2 showed a higher risk of overall and CVD-related deaths than those with MASLD and high FIB-4 or MAF-5 scores.

Effects of each of the five CMRFs on hepatic fibrosis in MetALD

The prevalence of MetALD in all participants ranged from 3.9% to 5.7% (Korean MRE cohort, 5.4%; NHANES, 3.9%; UK Biobank, 5.7%; Table S9). CMRF2 demonstrated the strongest association with the occurrence of significant hepatic fibrosis in both the Korean and US VCTE cohorts (Table S10A). However, CMRF3 exhibited the highest OR for the development of advanced hepatic fibrosis. In the UK Biobank cohort, CMRF2 demonstrated the strongest association with liver-related clinical outcomes (LREs, HCC, and LRDs; Table S10B). These results show that CMRF has an important role in the clinical course of MetALD, with the degree of insulin resistance involved in glucose metabolism being particularly important.

Discussion

This study demonstrated that the five CMRFs used in the diagnosis of MASLD were associated with an increased risk of hepatic fibrosis and adverse long-term clinical outcomes, with this risk increasing as the number of CMRFs increased. T2DM exhibited the strongest correlation with the risk of developing significant hepatic fibrosis. Among the five CMRFs, CMRF2 was identified as the most significant risk factor, irrespective of the type of clinical outcome or cohort.

To date, several studies have investigated the impact of CMRFs, including T2DM, on MASLD-related clinical outcomes.[10,21,22] Nevertheless, this study has several unique characteristics that distinguish it from prior investigations. First, although previous studies examined the influence of various cardiometabolic risk factors, this study emphasizes the significance of CMRFs that were incorporated into the newly defined MASLD diagnostic criteria. Second, although T2DM has been established as the most crucial independent risk factor for intrahepatic fibrosis and long-term prognosis, this study compared the relative importance of each of the five CMRFs. Third, this study primarily focused on the clinical significance of CMRF2, which encompasses impaired fasting glucose levels and T2DM. In summary, our study aimed to enhance awareness regarding liver fibrosis screening in primary care settings when diagnosing MASLD and to improve the understanding of the pathophysiology of MASLD.

This study clearly demonstrated that a spectrum of glucose abnormalities, ranging from normal to impaired fasting glucose levels and T2DM, is closely associated with the severity of MASLD (Figs 3 and 4). The severity of glucose abnormalities

Table 4. Long-term clinical outcomes in KNHIS cohort.

	KNHIS cohort (n = 91,717)																			
	Liver-related events (total cases: 776)				Hepatocellular carcinoma (total cases: 234)				Overall death (total cases: 7,541)				Cardiovascular death (total cases: 1,288)				Liver-related death (total cases: 421)				Extrahepatic cancer death (total cases: 2,027)			
Subgroup in MASLD	%	HR	95% CI		%	HR	95% CI		%	HR	95% CI		%	HR	95% CI		%	HR	95% CI		%	HR	95% CI	
Non-SLD (reference)	0.57	1.000		1	0.21	1.000		1	5.3	1.000		1	0.75	1.000		1	0.28	1.000		1	1.55	1.000		1
CMRFs																								
CMRF1	0.83	1.425	1.29–1.574		0.26	1.378	1.160–1.637		7.64	1.014	0.981–1.048		1.27	1.053	0.969–1.144		0.44	1.563	1.362–1.794		2.16	1.070	1.007–1.138	
CMRF1 (WC criteria)	1.03	1.537	1.362–1.734		0.33	1.505	1.220–1.857		9.89	1.080	1.038–1.123		1.65	1.100	0.997–1.214		0.58	1.721	1.461–2.027		2.72	1.121	1.041–1.207	
CMRF1 (BMI criteria)	0.82	1.414	1.279–1.562		0.26	1.383	1.164–1.644		7.50	1.006	0.973–1.039		1.23	1.040	0.957–1.131		0.44	1.542	1.342–1.771		2.14	1.070	1.006–1.138	
CMRF2	1.22	1.751	1.568–1.956		0.36	1.583	1.300–1.929		11.76	1.220	1.177–1.264		1.97	1.243	1.137–1.359		0.71	1.984	1.711–2.301		3.17	1.234	1.153–1.321	
CMRF3	1.00	1.411	1.265–1.573		0.29	1.282	1.054–1.558		11.03	1.080	1.044–1.117		2.05	1.203	1.108–1.306		0.55	1.512	1.302–1.756		2.79	1.051	0.984–1.122	
CMRF4	0.74	1.141	0.986–1.32		0.17	0.803	0.601–1.075		9.63	1.111	1.064 –1.158		1.66	1.159	1.044–1.287		0.40	1.265	1.036–1.546		2.54	1.094	1.009–1.187	
CMRF5	0.81	1.423	1.226–1.65		0.25	1.396	1.074–1.815		9.74	1.171	1.121–1.224		1.73	1.196	1.074–1.331		0.43	1.625	1.322–1.997		2.45	1.135	1.041–1.237	
MASLD	0.85	1.475	1.342–1.622		0.26	1.358	1.150–1.604		8.22	1.078	1.045–1.111		1.40	1.127	1.043–1.218		0.46	1.633	1.433–1.861		2.26	1.123	1.059–1.19	
T2DM	1.84	2.199	1.915–2.526		0.60	2.223	1.748–2.827		16.67	1.373	1.313–1.437		2.83	1.398	1.251–1.564		1.07	2.427	2.021–2.916		4.25	1.310	1.199–1.431	
Number of CMRF(s)																								
Any 1 CMRF	0.57	1.510	1.251–1.822		0.18	1.410	1.012–1.965		4.09	1.007	0.940–1.079		0.57	0.914	0.761–1.098		0.30	1.759	1.356–2.282		1.35	1.201	1.065–1.355	
Any 2 CMRFs	0.82	1.529	1.320–1.772		0.26	1.492	1.154–1.929		7.07	1.016	0.967–1.068		1.18	1.043	0.922–1.18		0.46	1.781	1.461–2.17		2.08	1.127	1.029–1.236	
Any 3 CMRFs	0.98	1.449	1.254–1.674		0.29	1.325	1.022–1.719		9.80	1.052	1.004–1.101		1.77	1.161	1.039–1.296		0.50	1.469	1.201–1.797		2.54	1.039	0.950–1.135	
Any 4 CMRFs	1.02	1.453	1.221–1.728		0.27	1.185	0.850–1.652		11.66	1.170	1.111–1.233		2.13	1.287	1.135–1.458		0.55	1.569	1.237–1.989		2.95	1.137	1.026–1.261	
Any 5 CMRFs	1.02	1.371	1.053–1.786		0.31	1.327	0.824–2.136		14.07	1.251	1.164–1.345		2.27	1.196	0.998–1.433		0.64	1.705	1.218–2.387		3.63	1.258	1.091–1.449	

HRs for significant and advanced hepatic fibrosis were calculated as a reference for subjects without SLD.
Age and sex were also adjusted for. CMRF, cardiometabolic risk factor; HR, hazard ratio; KNHIS, Korean National Health Insurance Service; MASLD, metabolic dysfunction-associated steatotic liver disease; SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; WC, waist circumference.

correlates well with insulin resistance. T2DM is not only an indicator of insulin resistance, but also a well-known key player in the development of liver diseases and CVDs.[23,24] By contrast, the clinical significance of CMRF2 has been largely overshadowed compared with T2DM. In this study, when evaluating the OR for hepatic fibrosis or aHR for long-term clinical outcomes, although its impact was smaller than that of T2DM, CMRF2 was the most powerful risk factor among the other five CMRFs. Furthermore, its impact was two-to-four times higher than that of MASLD without impaired fasting glucose levels and was similar to that of patients with MASLD accompanied by any four CMRFs. As a standalone indicator, it is considered the second most powerful marker after T2DM.

The key factor to consider in terms of risk level is prevalence. The prevalence of CMRF2 was approximately half that of MASLD (Table S3). Considering that the prevalence of T2DM in patients with MASLD ranged from 13.3% to 28.3%, this is a significant advantage in terms of careful management of many at-risk patients. Further economic evaluations using this approach are necessary to enhance our understanding of this risk.

Numerous studies have reported the different effects of various metabolic traits on the long-term clinical outcomes of MASLD.[9,10,21] Building on past research, this study compared the influence of five CMRFs on cohorts from both Eastern and Western populations, as well as various clinical outcomes. In addition, the study revealed that the effects of each metabolic trait on clinical outcomes varied. The risk of significant hepatic fibrosis also varied according to the combination of CMRFs (Table S4), with the highest risk observed when CMRFs 1, 2, 3, and 4 were combined (OR = 2.46) in cases of significant fibrosis in the Korean MRE cohort. However, when the evaluation criteria were based on advanced hepatic fibrosis or assessed using the US NHANES VCTE cohort, different combinations exhibited the highest risk. Many studies have consistently shown that an increasing number of metabolic traits are associated with poor clinical outcomes in various diseases. The risk of significant hepatic fibrosis increases with an increase in the number of CMRFs. However, because the influence of each CMRF varies depending on the type of clinical outcome and the characteristics of the population, we believe that it is impossible to identify a critical number of CMRFs that universally separate high- and low-risk groups. Furthermore, liver fibrosis should be evaluated in all patients with MASLD. Therefore, the risk of MASLD cannot be stratified using a specific number or combination of CMRFs and any efforts to do so may encounter numerous challenges.

MASLD is associated with increased rates of liver-related and cardiovascular mortality. Therefore, risk assessment should be performed using NITs, such as FIB-4 and MAF-5, in all patients at the time of diagnosis.[25] However, NITs are not widely used in real-world settings because they require additional tests or complicated calculations. Considering the comparable ability of CMRF2 to predict the risk of hepatic fibrosis and liver-related clinical outcomes to that of MAF-5 and the lack of additional tests or calculation processes beyond the MASLD diagnostic process, CMRF2 could be an attractive option for assessing the risk of patients with MASLD in clinical practice. Although CMRF2 does not provide sufficient evidence to replace or omit NIT, it can raise awareness among primary care providers regarding high-risk groups at the

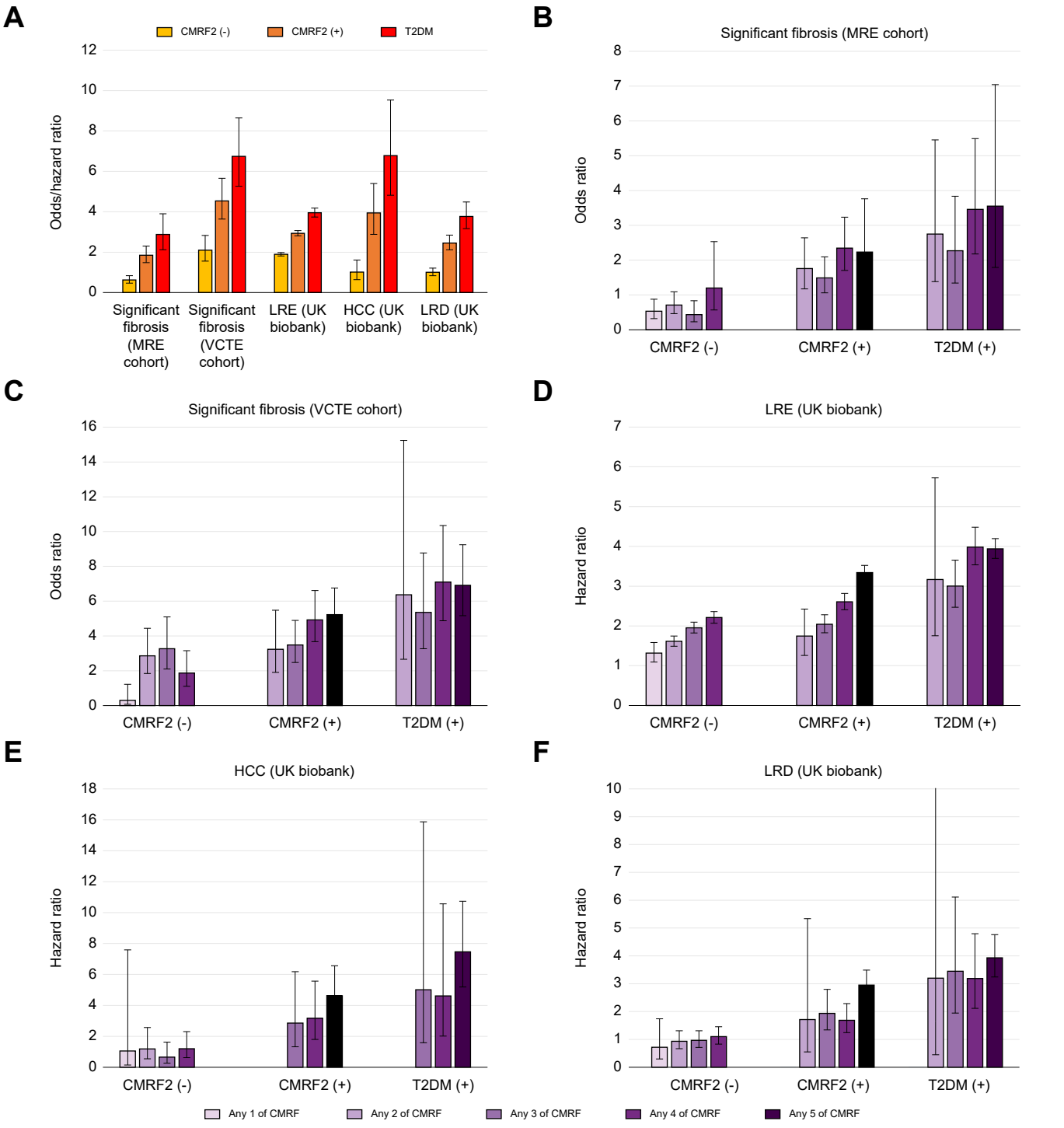

Fig. 3. ORs and HRs of patients with MASLD with CMRF2 (–), CMRF2 (+), and T2DM for clinical outcomes according to the number of CMRFs in various cohorts. The ORs and HRs were evaluated as references for the non-steatotic liver disease group. Age and sex are also adjusted for. CMRF, cardiometabolic risk factor; CVD, cardiovascular disease; EHCD, extrahepatic cancer-related death; HCC, hepatocellular carcinoma; HR, hazard ratio; LRD, liver-related death; LRE, liver-related event; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; OR, odds ratio; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

time of diagnosis. This could increase screening rates using NITs and improve the overall quality of care.

The results shown in Fig. 3 and Table S5 demonstrate other noteworthy findings. In patients with MASLD with CMRF2, the ORs for hepatic fibrosis and the risk of liver-related long-term clinical outcomes exhibited a dose-dependent increase as the number of other CMRFs increased. However, in patients with MASLD without CMRF2, although the ORs for hepatic fibrosis and the risk of liver-related long-term clinical outcomes tended to increase with the number of other CMRFs, the pattern was

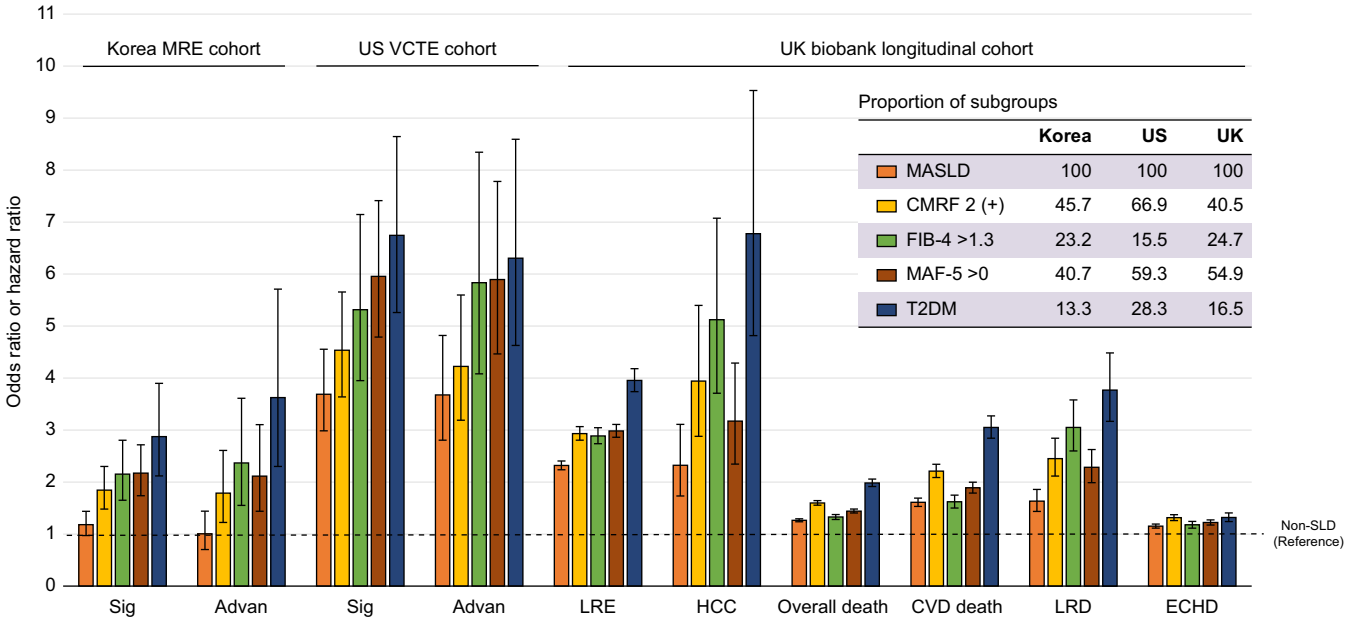

Fig. 4. ORs and HRs of the risk group defined by CMRF2, FIB-4, and MAF-5 among patients with MASLD for various clinical outcomes in different cohorts. The ORs and HRs were evaluated as references for the non-steatotic liver disease group. Age and sex are also adjusted for. CMRF, cardiometabolic risk factor; FIB-4, Fibrosis-4 Index; HR, hazard ratio; LRD, liver-related death; LRE, liver-related event; MAF-5, Metabolic Dysfunction-Associated Fibrosis-5; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; OR, odds ratio; VCTE, vibration-controlled transient elastography.

not linear. In patients with MASLD and T2DM, the additional increase in the risk of liver fibrosis and liver disease-related complications associated with an increasing number of other CMRFs was minimal. These findings suggest that the degree of underlying glucose homeostasis has a significant role in the association between the number of CMRFs and the severity of liver disease in patients with MASLD.

Notably, overweight/obesity (CMRF1: OR, 1.202; 95% CI 0.985–1.467) showed no statistically significant association with significant hepatic fibrosis in the Korean MRE cohort. However, when WC was considered, the significance of CMRF1 (OR, 1.530; CI, 1.227–1.907) increased as the prevalence of CMRF1 in patients with MASLD decreased from 93.3% to 55.5%. WC and BMI are the most important indicators of overall metabolic health. However, when MASLD is present, almost all patients also have CMRF1. This characteristic was particularly prominent in cohorts from the USA (97.7%) and UK (99.5%). CMRF1 is undoubtedly the most critical risk factor for the development and progression of MASLD. However, within the MASLD group, which is almost universally associated with obesity, or in situations where the prevalence of obesity is overwhelmingly high, the ability of CMRF1 to predict hepatic fibrosis and adverse long-term clinical outcomes of MASLD is limited.

The findings of this study have several advantages over those of previous studies. First, the influence of each metabolic trait on long-term mortality can differ according to ethnicity, region, or cohort. However, the present study leveraged a vast cohort of 758,000 participants and conducted analyses across diverse regional populations, encompassing Eastern and Western cohorts, to address this limitation. Second, the use of community-based cohorts, such as the NHANES and KNHIS databases (which closely mirror the environment of a primary care clinic) lends credibility to our findings. Third, the classification of the severity of MASLD was based on liver fibrosis data obtained from large-scale MRE and VCTE cohorts.

Careful consideration is necessary when interpreting this paper. The objective of our study was to compare the relative significance of the five CMRFs on MASLD-related clinical outcomes. In our results, the importance of the five CMRFs varied depending on the cohort type and clinical outcomes under consideration. A definitive conclusion from our findings is that, among the five CMRFs, impaired fasting glucose (CMRF2) consistently demonstrated the most substantial impact, irrespective of the cohort type and clinical outcomes. This impact is approximately half of that observed with T2DM alone and is comparable to that seen with a FIB-4 >1.3 or MAF-5 >0 (Figure 4). Although CMRF2 accounts for approximately half of all MASLD cases, its risk level is comparable to that of patients with MASLD with a FIB-4 >1.3 or MAF-5 >0, underscoring its clinical significance. Given that all patients with MASLD are candidates for hepatic fibrosis screening, the use of CMRF2 is not intended solely to identify individuals for fibrosis screening or to replace other non-invasive tests. In the current context, where the assessment of CMRFs has become essential in diagnosing MASLD, our results emphasize the need to recognize individuals with MASLD accompanied by CMRF2 as a particularly significant patient group.

This study had some limitations. First, the gold standards for diagnosing steatosis and hepatic fibrosis, such as magnetic resonance proton density fat fraction or liver biopsy, were not used in any of the four cohorts. Hepatic steatosis was diagnosed using the HSI in the UK Biobank and KNHIS cohorts. In particular, the HSI incorporates BMI and diabetes status, and potential confounding factors might arise if the sample selection is based on the HSI and if subsequent analyses are focused on BMI and diabetes status. This methodological approach could result in over- or underestimation of the association between these variables and the outcome, because

these factors are already components of the HSI. However, imaging tests, such as abdominal ultrasound and VCTE, were performed in the Korean MRE and US NHANES VCTE cohorts, with consistent results. Second, there was a lack of analysis using direct indicators, such as fasting insulin levels or Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), which are considered the most important pathophysiological factors, specifically insulin resistance. Most large cohorts lack data on insulin levels. To address this, we adjusted the triglyceride glucose index (a surrogate marker of insulin resistance) according to the severity of glucose abnormalities, from normal glucose to impaired fasting glucose levels, and T2DM. Further studies using direct indicators are required.

In conclusion, the five CMRFs demonstrated a strong association with significant hepatic fibrosis. However, the magnitude of their effects varied depending on the type of CMRF used. The results also varied depending on the type of clinical outcome and characteristics of the population. Nevertheless, CMRF2 consistently exhibited the highest risk of hepatic fibrosis and MASLD-related clinical outcomes among the five CMRFs in both the Eastern and Western populations. Considering the need to evaluate CMRFs at the time of MASLD diagnosis and the substantial impact of CMRF2 on MASLD-related clinical outcomes, implementing CMRF2 in clinical practice could facilitate the identification of at-risk patients among those diagnosed with MASLD.

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Abbreviations

aHR, adjusted hazard ratio; CAP, controlled attenuation parameter; CMRF, cardiometabolic risk factor; CVD, cardiovascular disease; EHCD, extrahepatic cancer-related death; FIB-4, Fibrosis-4 Index; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HR, hazard ratio; HSI, hepatic steatosis index; ICD, International Classification of Diseases; KNHIS, Korea National Health Insurance Service; LRD, liver-related death; LRE, liver-related event; MAF-5, Metabolic Dysfunction-Associated Fibrosis-5; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-related liver disease; MRE, magnetic resonance elastography; NHANES, National Health and Nutrition Examination Survey; NIT, non-invasive testing; OR, odds ratio; SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography; WC, waist circumference.

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Conflicts of interest

The authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Guarantor of the article: DWJ. Concept and design: DWJ. Data collection and management: TC-FY, ELY, GL-HW, HSL., JC-TL. Data interpretation: DWJ., HP. writing of the manuscript: HP. Supervision: DWJ, JC-TL, VW-SW. All authors approved the final version of the manuscript.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

Supplementary data

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