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Research Paper

Impact of cardiometabolic risk factors for metabolic dysfunction-associated steatotic liver disease on mortality

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ABSTRACT

Background and aims: Metabolic dysfunction–associated steatotic liver disease (MASLD) is a potential independent risk factor for cardiovascular disease (CVD)-associated and all-cause mortalities as they share common risk factors. We investigated the association between cardiometabolic risk factors for MASLD and CVD-associated and all-cause mortality risks in middle-aged and older Korean adults.

Methods and results: We used data from the Korean Genome and Epidemiology Study, a population-based prospective cohort study. Five cardiometabolic risk factors were assessed. MASLD was defined as liver steatosis with a fatty liver index (FLI) ≥60 and at least one cardiometabolic risk factor. The non-MASLD group included individuals with a FLI <60 or FLI ≥60 without cardiometabolic risk factors. The primary outcomes were CVD-associated and all-cause mortalities. Cox proportional hazard models were used to evaluate the association between cardiometabolic risk factors for MASLD and mortalities, adjusting for covariates. Multivariable Cox regression analysis revealed that the MASLD group had increased CVD-associated and all-cause mortality risks compared to the non-MASLD group. The presence of three or more and one or more cardiometabolic risk factors significantly increased the CVD-associated and all-cause mortality rate, respectively. The combination of hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), and high glucose concentrations significantly increased both CVD-associated (hazard ratio [HR] 3.64; 95 % confidence interval [CI] 1.44–9.22; p = 0.006) and all-cause (HR 4.57; 95 % CI: 1.74–12.05; p = 0.002) mortality risks.

Conclusion: Cardiometabolic risk factors for MASLD are strongly associated with higher CVD-associated and all-cause mortality risks, highlighting the need to manage hypertriglyceridemia, low HDL-C, and high glucose concentrations.

1. Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD), the newly proposed nomenclature replacing "nonalcoholic fatty liver disease (NAFLD)" [1], affects a substantial portion of the global population and poses a growing public health concern [2]. Cardiovascular disease (CVD) is a leading cause of death among patients with MASLD, accounting for approximately one-third of all-cause mortality [3]. Hepatic steatosis affects approximately 32 % of the global population, reaching 40 % in America and Southeast Asia and approximately 30 % in Korea [4–6]. To highlight the close association with metabolic syndrome, MASLD encompasses the presence of liver steatosis and at least one of five cardiometabolic risk factors [7]. Liver fibrosis is independently associated with poor cardiovascular outcomes and mortality [8,9]. Since the definition of MASLD includes at least one risk factor for CVD, it implies that patients with MASLD are at an increased risk of CVD. This association is supported by the observed higher prevalence of CVD among patients with MASLD [10].

In a previous study involving 28,000 individuals from the UK Biobank, patients with MASLD experienced more cardiovascular events

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than did those without MASLD [10]. A recent analysis of data from the National Health and Nutrition Examination Survey in the United States found that patients with MASLD have higher CVD-associated and all-cause mortality rates than do those without MASLD [11]. However, data regarding whether MASLD can exacerbate CVD-associated and all-cause mortalities in response to cardiometabolic risk factors are lacking.

Therefore, we aimed to assess the incidence of CVD-associated and all-cause mortalities in relation to the number and combinations of cardiometabolic risk factors associated with MASLD to understand the comprehensive impact of cardiometabolic risk factors in patients with MASLD and inform more effective management strategies for individuals with these risk factors.

2. Methods

2.1. Study population

We used data from the Korean Genome and Epidemiology Study (KoGES), a large, population-based, prospective, longitudinal cohort study analyzing the environmental causes and prevalence of non-communicable diseases in Korea [12]. Baseline data of participants aged ≥40 years were evaluated in the KoGES, Ansan/Ansung Study (2001–2002), KoGES Health Examinee Study (2004–2013), and KoGES Cardiovascular Disease Association Study (2005–2011). The complete dataset of the KoGES is available from https://nih.go.kr/ko/main/contents.do?menuNo=300569 (accessed on May 4, 2024).

Of the 211,562 participants with baseline data (2001–2013), we excluded 65,371 who lacked data on mortality (n = 54,529) and laboratory examination of the fatty liver index (FLI) (n = 10,842) (Fig. 1). Thus, 146,191 individuals were included in the study. Informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of the Korean Centre for Disease Control and the Institutional Review Board of the College of Medicine (approval number: 4-2024-0634).

2.2. Anthropometric and laboratory measurements

Trained medical professionals measured the anthropometric variables, including weight (to the nearest 0.1 kg), height (to the nearest 0.1 cm, with participants wearing light clothing and no shoes), and waist circumference (WC [cm], measured at the midpoint between the iliac crest and lowest rib). Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). WC (cm) was measured at the midpoint between the iliac crest and lowest rib. Blood pressure (BP) was assessed with participants in a seated position, recorded twice at 1-min intervals using a mercury sphygmomanometer according to standardized protocols. Blood samples were collected after ≥8 h of fasting, and analyzed by a central laboratory (Seoul Clinical Laboratory, Seoul, Korea). Fasting plasma glucose (FPG), HbA1c, insulin, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (γGTP), total cholesterol, triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were enzymatically analyzed using a Chemistry Analyzer (Hitachi 7600, Tokyo, Japan, until August 2002; ADVIA 1650, Siemens, Tarrytown, NY, from September 2002). Self-reported questionnaires contained items concerning smoking, alcohol consumption, and physical activity. Non-smokers were defined as never having smoked in their lifetime, and smokers as having smoked at any point in their lifetime or currently smoking. Alcohol consumption was defined as consuming >20 g/day and >10 g/day in men and women, respectively. Detailed study protocols are available at https://nih.go.kr/ko/main/contents.do?menuNo=300563.

2.3. Definitions of variables

2.3.1. Definition of MASLD

A diagnosis of MASLD was established based on the presence of blood biomarker evidence of hepatic steatosis (FLI ≥60) [13] and having one of the following five cardiometabolic risk factors [14].

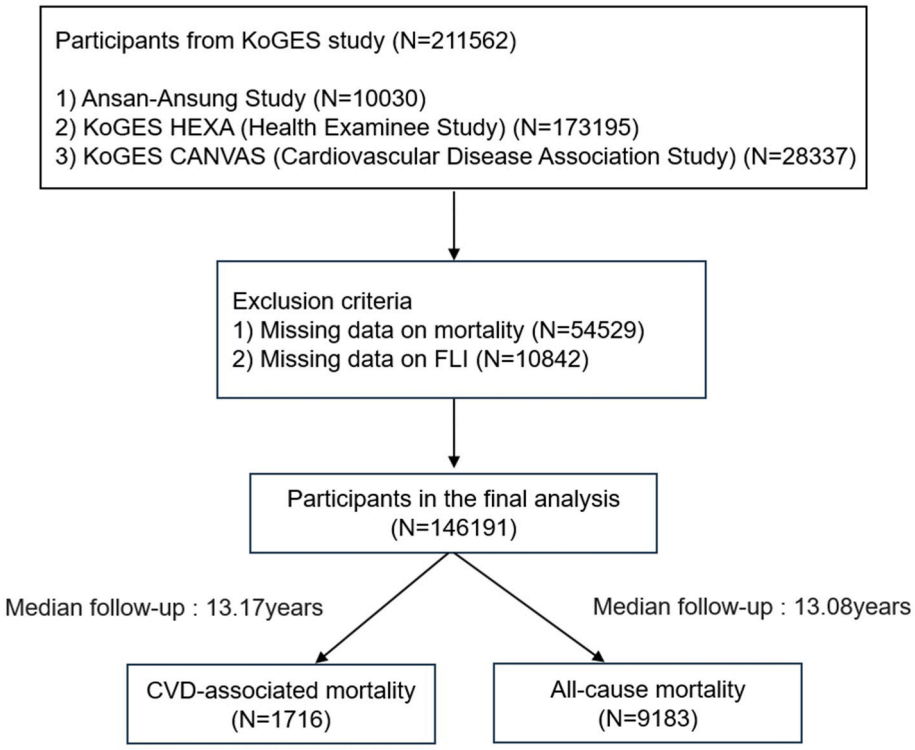

Fig. 1. Flowchart of the study population
CVD, Cardiovascular disease; KoGES, Korean Genome and Epidemiology Study.

① Overweight or obesity: BMI ≥23 kg/m^2 or WC ≥ 90 cm in men and ≥80 cm in women
② High BP: systolic BP (SBP) ≥130 mmHg, diastolic BP (DBP) ≥85 mmHg, or antihypertensive drug treatment
③ Hypertriglyceridemia: TG ≥150 mg/dL or antihyperlipidemic drug treatment
④ Low HDL-C: <40 mg/dL in men and <50 mg/dL in women
⑤ High glucose: FPG ≥100 mg/dL, 2-h post load glucose concentration ≥140 mg/dL, HbA1c ≥5.7 %, or antihyperglycemic drug treatment

FLI was calculated as follows [15].

$$FLI = [e^{\wedge}(0.953 \times \ln(TGs) + 0.139 \times BMI + 0.718 \times \ln(\gamma GTP) + 0.053 \times WC - 15.745)] / [1 + e^{\wedge}(0.953 \times \ln(TGs) + 0.139 \times BMI + 0.718 \times \ln(\gamma GTP) + 0.053 \times WC - 15.745)] \times 100$$

The non-MASLD group was defined as having an FLI <60 or an FLI ≥60 without any cardiometabolic risk factors.

2.3.2. Definition of CVD-associated and all-cause mortalities

The KoGES data are linked to national sources of information, such as the Korea National Statistics Office, which includes mortality records. To determine the participants' mortality status, an individual keycode identification system was used for information linkage. Participants were tracked from the time of enrollment to their death, completion of the study, or the last time they were contacted. The International Classification of Diseases (ICD) codes in the National Mortality Index were used to classify cause of death, which was monitored from January 2001 to December 2019. ICD-10 codes I00–I99 were used to classify CVD-associated mortality, and all-cause mortality included known and unidentified causes of death [16].

2.4. Statistical analysis

Data are expressed as mean ± standard deviation or number (percentage). For demographic and biochemical participant characteristics, analysis of variance and the chi-squared test were used to compare continuous and categorical variables, respectively. We used a Cox proportional hazard spline curve to determine the dose-response relationship between the number of cardiometabolic risk factors for MASLD and the hazard ratio (HR) for incident CVD-associated and all-cause mortalities. Cox proportional hazard models were built to estimate the HR and its 95 % confidence interval (CI) for the incidence of CVD-associated and all-cause mortalities across categories based on the number and combination of cardiometabolic risk factors for MASLD, adjusting for the certain variables. Three models were used in the analysis—Model 1 was unadjusted, Model 2 was adjusted for age and sex, and Model 3 was additionally adjusted for alcohol consumption and smoking status.

Covariates were selected based on statistical and clinical significance, which included variables with $p < 0.05$ in the baseline comparison across groups and univariate analysis. Statistical significance was set at $p < 0.05$ for all tests. All analyses were conducted using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics based on MASLD status and number of cardiometabolic risk factors

Of the 146,191 participants, 129,935 (88.9 %) were included in the non-MASLD group. In the MASLD group, 392 participants (0.3 %) had one risk factor, 2072 (1.4 %) had two risk factors, 5043 (3.4 %) had three risk factors, 6028 (4.1 %) had four risk factors, and 2721 (1.9 %) had five risk factors. Participants in the group with five risk factors were older and exhibited the highest BMI and WC compared to those in the other groups. They also had the highest SBP and DBP; HbA1c; TG, insulin, and FPG concentrations; and FLI. Moreover, this group had the highest proportion of patients with hypertension, diabetes, dyslipidemia, CVD-associated mortality, and all-cause mortality. In the group with one risk factor, overweight or obesity was the most prevalent cardiometabolic risk factor, followed by hypertriglyceridemia, high BP, high glucose, and low HDL-C (Table 1).

3.2. Association between MASLD status, number of cardiometabolic risk factors, and CVD-associated mortality

In the univariable analysis, the HRs for incident CVD-associated mortality were not statistically significant for participants with one or two cardiometabolic risk factors compared to those in the non-MASLD group. However, for participants with three, four, and five cardiometabolic risk factors, the HRs for incident CVD mortality were statistically significant at 1.43 (95 % CI: 1.15–1.79), 1.51 (95 % CI: 1.24–1.83), and 2.14 (95 % CI: 1.69–2.71), respectively, compared to those in the non-MASLD group. Similarly, in **Model 3**, after adjusting for age, sex, alcohol consumption, and smoking status, the HRs for participants with one or two cardiometabolic risk factors remained non-significant. After adjusting for age, sex, alcohol consumption, and smoking status, the HRs for CVD-associated mortality were significantly higher for individuals with three, four, or five cardiometabolic risk factors at 1.43 (95 % CI: 1.14–1.79), 1.36 (95 % CI: 1.11–1.66), and 1.72 (95 % CI: 1.36–2.18), respectively, all showing significant associations with CVD-associated mortality (Table 2).

3.3. Association between MASLD status, number of cardiometabolic risk factors, and all-cause mortality

In the univariable analysis, the HRs for all-cause mortality were statistically significant for participants with one, two, three, four, and five cardiometabolic risk factors compared to those in the non-MASLD group. The HRs were 1.99 (95 % CI: 1.50–2.65) for those with one risk factor, 1.43 (95 % CI: 1.23–1.66) for those with two risk factors, 1.42 (95 % CI: 1.29–1.56) for those with three risk factors, 1.43 (95 % CI: 1.31–1.56) for those with four risk factors, and 1.89 (95 % CI: 1.69–2.11) for those with five risk factors. In Model 3, the HRs for individuals with one, two, three, four, and five risk factors were 2.24 (95 % CI: 1.68–2.99), 1.40 (95 % CI: 1.21–1.62), 1.26 (95 % CI: 1.14–1.38), 1.17 (95 % CI: 1.07–1.28), and 1.49 (95 % CI: 1.33–1.66), respectively, all significantly associated with all-cause mortality (Table 3).

3.4. Association between the combination of cardiometabolic risk factors for MASLD and CVD-associated and all-cause mortalities

Fig. 2A and B displays forest plots of the Cox proportional HRs and 95 % CIs for CVD-associated and all-cause mortalities, respectively, based on various combinations of cardiometabolic risk factors for MASLD in Model 3. The combination of overweight or obesity, high BP, and high glucose significantly increased the risk of CVD-associated mortality (HR 1.57; 95 % CI: 1.03–2.39; $p = 0.034$). Similarly, the combination of overweight or obesity, high BP, and a low HDL-C concentration was significantly increased the risk of all-cause mortality (HR 2.16; 95 % CI: 1.07–4.34; $p = 0.031$). Furthermore, the combination of overweight or obesity, high BP, and high glucose significantly increased the risk of all-cause mortality (HR 2.08; 95 % CI: 1.38–3.13; $p < 0.001$). Notably, the combination of hypertriglyceridemia, a low HDL-C, and high glucose was associated with a significantly increased risk of both incident CVD-associated (HR 3.64; 95 % CI: 1.44–9.22; $p = 0.006$) and all-cause (HR 4.57; 95 % CI: 1.74–12.05; $p = 0.002$) mortalities.

Table 1
Baseline characteristics according to the presence of MASLD and number of cardiometabolic risk factors.

Variables	Overall	Non-MASLD group	MASLD group					
			Number of cardiometabolic risk factors					
			1	2	3	4	5 (All)	P-value
N (%)	146191	129935 (88.9 %)	392 (0.3 %)	2072 (1.4 %)	5043 (3.4 %)	6028 (4.1 %)	2721 (1.9 %)	
Age (years)	53.7 ± 8.7	53.7 ± 8.7	51.7 ± 8	52.3 ± 8.4	53.1 ± 8.7	54.4 ± 8.6	56.1 ± 8.3	<0.001
Sex								<0.001
Male, n (%)	53004 (36 %)	41647 (32 %)	283 (72 %)	1599 (77 %)	3784 (75 %)	4226 (70 %)	1465 (54 %)	
Female, n (%)	93187 (64 %)	88288 (68 %)	109 (28 %)	473 (23 %)	1259 (25 %)	1802 (30 %)	1256 (46 %)	
BMI (kg/m^2)	24 ± 3	23.5 ± 2.6	27.4 ± 3.6	27.6 ± 3.3	27.8 ± 3	27.8 ± 2.7	28.3 ± 2.8	<0.001
Waist circumference (cm)	81.4 ± 8.8	79.9 ± 7.8	93.1 ± 7.5	93.1 ± 7.2	93.3 ± 6.8	93.2 ± 6.4	93.8 ± 6.6	<0.001
SBP (mmHg)	122.7 ± 15.6	121.7 ± 15.4	118.7 ± 8.4	123.7 ± 13.5	128.8 ± 15.3	132.7 ± 15.4	135.7 ± 14.3	<0.001
DBP (mmHg)	76.4 ± 10.2	75.7 ± 10	74.8 ± 6.3	78.2 ± 9.2	81.2 ± 10.2	83.2 ± 10.1	84.4 ± 9.8	<0.001
Total cholesterol (mg/dL)	197.1 ± 35.7	195.9 ± 35	204.5 ± 35	208.5 ± 37.9	208.7 ± 38.7	207.3 ± 40.9	201.5 ± 40.5	<0.001
HDL-C (mg/dL)	52.2 ± 13	53.2 ± 13	53.8 ± 10.7	50.9 ± 10.6	47.6 ± 10.5	43.5 ± 9.7	37 ± 5.5	<0.001
LDL-C (mg/dL)	119.2 ± 32.4	119.7 ± 31.7	123.5 ± 33	120.9 ± 36.3	117.8 ± 36.8	112.7 ± 38.4	106.8 ± 38.9	<0.001
Triglycerides (mg/dL)	131.5 ± 91.9	115.7 ± 63.8	145.9 ± 106.8	193.6 ± 124.1	232 ± 141.1	280.2 ± 159.6	317.4 ± 189.2	<0.001
FPG (mg/dL)	95.2 ± 21.4	93.8 ± 19.6	90.2 ± 12.7	94.2 ± 18.5	101.1 ± 26.4	110.8 ± 31.5	118.1 ± 34.4	<0.001
HbA1c (%)	5.7 ± 0.8	5.7 ± 0.7	5.4 ± 0.7	5.6 ± 0.7	5.9 ± 0.9	6.3 ± 1.1	6.5 ± 1.1	<0.001
Insulin (μU/mL)	7 ± 7.5	6.4 ± 5.5	7.9 ± 4.8	10.1 ± 36.1	10.1 ± 8.5	11.1 ± 10.4	12.9 ± 10.8	<0.001
AST (mg/dL)	24.4 ± 19.1	23.3 ± 17	38.1 ± 34	33.9 ± 30	32.8 ± 30.2	32.6 ± 33.8	31.4 ± 17.6	<0.001
ALT (mg/dL)	23 ± 22.4	21.1 ± 18.6	44.5 ± 46.1	40.2 ± 50.3	38.8 ± 46.3	38 ± 30.5	37.1 ± 23.5	<0.001
γGTP (mg/dL)	31.4 ± 47.3	24.8 ± 23.8	133.4 ± 156.4	108.1 ± 165.9	87.2 ± 98.5	81 ± 108.4	61.2 ± 65.5	<0.001
Alcohol consumption, n (%)	67109 (46 %)	56293 (43 %)	291 (74 %)	1543 (74 %)	3585 (71 %)	3995 (66 %)	1402 (52 %)	<0.001
Smoking status, n (%)	95489 (65 %)	84388 (65 %)	266 (68 %)	1441 (70 %)	3490 (69 %)	4109 (68 %)	1795 (66 %)	<0.001
Hypertension, n (%)	45096 (31 %)	36383 (28 %)	18 (4.6 %)	505 (24 %)	2299 (46 %)	3765 (62 %)	2126 (78 %)	<0.001
Diabetes mellitus, n (%)	15037 (10 %)	11223 (8.6 %)	12 (3.1 %)	162 (7.8 %)	787 (16 %)	1690 (28 %)	1163 (43 %)	<0.001
Dyslipidemia, n (%)	74654 (51 %)	61619 (47 %)	103 (26 %)	1143 (55 %)	3634 (72 %)	5434 (90 %)	2721 (100 %)	<0.001
Fatty liver index	26.7 ± 22.6	20.7 ± 15.6	69.0 ± 7.4	71.5 ± 8.5	73.4 ± 9.4	75.5 ± 10.0	76.2 ± 10.2	<0.001
All-cause mortality, n (%)	9183 (6.3 %)	7658 (5.9 %)	47 (12 %)	179 (8.6 %)	435 (8.6 %)	531 (8.8 %)	333 (12 %)	<0.001
CVD-related mortality, n (%)	1716 (1.2 %)	1423 (1.1 %)	4 (1.0 %)	27 (1.3 %)	83 (1.6 %)	106 (1.8 %)	73 (2.7 %)	<0.001
Cardiometabolic risk factor ①[a], n (%)	15827 (10.8 %)	0 (0 %)	325 (82.9 %)	1913 (92.3 %)	4887 (96.9 %)	5981 (99.2 %)	2721 (100 %)	
Cardiometabolic risk factor ②[b], n (%)	11272 (7.7 %)	0 (0 %)	11 (2.8 %)	681 (32.9 %)	2991 (59.3 %)	4868 (80.8 %)	2721 (100 %)	
Cardiometabolic risk factor ③[c], n (%)	13083 (8.9 %)	0 (0 %)	43 (11.0 %)	994 (48.0 %)	3661 (72.6 %)	5664 (94.0 %)	2721 (100 %)	
Cardiometabolic risk factor ④[d], n (%)	7302 (5.0 %)	0 (0 %)	2 (0.5 %)	166 (8.0 %)	1347 (26.7 %)	3066 (50.9 %)	2721 (100 %)	
Cardiometabolic risk factor ⑤[e], n (%)	9898 (6.8 %)	0 (0 %)	11 (2.8 %)	390 (18.8 %)	2243 (44.5 %)	4533 (75.2 %)	2721 (100 %)	

Data are expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables.
Abbreviations: MASLD, Metabolic dysfunction–associated steatotic liver disease; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, Fasting plasma glucose; HbA1c, Glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; AST, Aspartate transaminase; ALT, Alanine transaminase; γGTP, Gamma-glutamyl transpeptidase; CVD, Cardiovascular disease.
[a] Overweight or obesity: BMI ≥23 kg/m^2 or waist circumference ≥90 cm in men and ≥80 cm in women.
[b] High BP: SBP ≥130 mmHg, DBP ≥85 mmHg, or drug treatment.
[c] Hypertriglyceridemia: triglycerides ≥150 mg/dL or drug treatment.
[d] Low HDL-C: <40 mg/dL in men and <50 mg/dL in women.
[e] High glucose: FPG ≥100 mg/dL, 2-h post load glucose levels ≥140 mg/dL, HbA1c ≥ 5.7 %, or drug treatment.

Table 2
Cox proportional hazard regression analysis for CVD-related mortality by MASLD status and number of cardiometabolic risk factors.

Model	Non-MASLD group		MASLD group									
			Number of cardiometabolic risk factors									
			1		2		3		4		5 (All)	
	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value
Model 1[a]	1	Ref	0.87 (0.33–2.32)	0.778	1.14 (0.78–1.67)	0.489	1.43 (1.15–1.79)	0.001	1.51 (1.24–1.83)	<0.001	2.14 (1.69–2.71)	<0.001
Model 2[b]	1	Ref	1.05 (0.39–2.82)	0.916	1.27 (0.86–1.86)	0.224	1.42 (1.14–1.78)	0.002	1.35 (1.11–1.65)	0.003	1.72 (1.36–2.18)	<0.001
Model 3[c]	1	Ref	1.06 (0.40–2.83)	0.910	1.28 (0.87–1.87)	0.213	1.43 (1.14–1.79)	0.002	1.36 (1.11–1.66)	<0.001	1.72 (1.36–2.18)	<0.001

Abbreviations: MASLD, Metabolic dysfunction–associated steatotic liver disease; HR, Hazard ratio; CI, Confidence interval.
[a] Unadjusted model.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, alcohol consumption, and smoking status.

Table 3
Cox proportional hazard regression analysis for all-cause mortality by MASLD status and number of cardiometabolic risk factors.

Model	Non-MASLD group		MASLD group									
			Number of cardiometabolic risk factors									
			1		2		3		4		5 (All)	
	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value	HR (95 % CI)	P-value
Model 1[a]	1	Ref	1.99 (1.50–2.65)	<0.001	1.43 (1.23–1.66)	<0.001	1.42 (1.29–1.56)	<0.001	1.43 (1.31–1.56)	<0.001	1.89 (1.69–2.11)	<0.001
Model 2[b]	1	Ref	2.21 (1.66–2.95)	<0.001	1.37 (1.18–1.59)	<0.001	1.24 (1.13–1.37)	<0.001	1.15 (1.06–1.26)	0.002	1.49 (1.33–1.66)	<0.001
Model 3[c]	1	Ref	2.24 (1.68–2.99)	<0.001	1.40 (1.21–1.62)	<0.001	1.26 (1.14–1.38)	<0.001	1.17 (1.07–1.28)	<0.001	1.49 (1.33–1.66)	<0.001

Abbreviations: MASLD, Metabolic dysfunction–associated steatotic liver disease; HR, Hazard ratio; CI, Confidence interval.
[a] Unadjusted model.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, alcohol consumption, and smoking status.

3.5. Cox proportional hazard spline curves of CVD-associated and all-cause mortalities based on the number of cardiometabolic risk factors for MASLD

A linear relationship was observed between the number of cardiometabolic risk factors for MASLD and the risk of CVD-associated (Fig. 3A) and all-cause mortalities (Fig. 3B), with increasing HRs as the number of risk factors increased.

4. Discussion

The definition of MASLD has evolved to include hepatic steatosis and at least one cardiometabolic risk factor. In line with this updated definition, in this study, we categorized individuals with a FLI <60 or a FLI ≥60 without accompanying cardiometabolic risk factors into the non-MASLD group and compared this group with the MASLD group. Our results align with this redefined classification, revealing that individuals with MASLD had a significantly higher all-cause mortality rate than did those in the non-MASLD group, with a particularly elevated CVD-associated mortality rate in individuals presenting with three or more cardiometabolic risk factors. Notably, the combination of hypertriglyceridemia, a low HDL-C, and high glucose significantly increased the risk of both CVD-associated and all-cause mortalities within the MASLD cohort.

The new name and definition of MASLD provide a more concise and lesser stigmatizing term compared to NAFLD, allowing for better identification of high-risk patients by accurately linking liver disease to cardiometabolic risk factors [1]. Individuals with MASLD and cardiometabolic risk factors exhibited more severe disease and higher mortality rates compared to those without such risk factors [10]. Several studies have suggested a close association between hepatic steatosis and cardiometabolic risk factors, as well as mutual promotion in the pathogenic processes [17–20]. This may explain the higher incidence of CVD-associated mortality observed in individuals with multiple cardiometabolic risk factors for MASLD. Previous studies have shown increased all-cause mortality in patients with NAFLD and cardiometabolic risk factors [21–23]. Our findings align with those of earlier studies that reported an increase in fibrosis severity [24–26] and all-cause mortality rate [21–23] as the number of cardiometabolic risk factors increased. The American Association for the Study of Liver Diseases, American Heart Association, European Association for the Study of the Liver, and European Society of Cardiology strongly recommend CVD risk assessment for patients with MASLD [1,13,27]. However, to the best of our knowledge, no precise investigation regarding the combinations of specific cardiometabolic risk factors has been undertaken. Our study addressed this gap by evaluating CVD-associated and all-cause mortalities in relation to the number and combination of cardiometabolic risk factors associated with MASLD. It is important to acknowledge that the association between MASLD and increased mortality risk is largely driven by the presence of metabolic syndrome components. Since MASLD and metabolic syndrome share common cardiometabolic risk factors, the increased mortality risk in patients with MASLD may be attributed to the severity of the underlying metabolic syndrome rather than MASLD per se. Our results support this notion, as individuals with three or more cardiometabolic risk factors—who likely meet the criteria for metabolic syndrome [28]—had a significantly higher risk of CVD mortality. We will emphasize this distinction by recognizing that metabolic syndrome plays a crucial role in driving these outcomes.

Several potential mechanisms link MASLD to the development of CVD, including disturbances in lipid and lipoprotein metabolism, insulin resistance, oxidative stress, systemic inflammation, endothelial dysfunction, and coagulopathy [29]. Among these, dyslipidemia and insulin resistance are the primary therapeutic targets for managing CVD risk. MASLD is associated with atherogenic lipid profiles characterized by elevated concentrations of very low-density lipoprotein (VLDL), LDL-C, and TGs, and a reduced concentration of HDL-C [30]. This dyslipidemia pattern is consistent with the findings of our study on cardiometabolic risk factor combinations. The underlying pathophysiology of MASLD involves disruptions in lipid, lipoprotein, and glucose metabolism, contributing to insulin resistance and promoting atherogenesis [31]. In insulin-resistant adipose tissue, impaired insulin-mediated suppression of lipase activity increases lipolysis. Additionally, defective esterification and re-esterification processes lead to an enhanced release of free fatty acids, which results in a greater influx of fatty acids to the liver [32]. This exacerbates hepatic insulin resistance and impairs insulin signaling in the hepatocytes [33]. As insulin resistance progresses, hyperglycemia further promotes VLDL secretion, which leads to increased LDL-C and decreased HDL-C concentrations, both of which play key roles in atherosclerosis development [34]. Moreover, hepatic insulin resistance elevates glucose production and fosters systemic inflammation, accelerating the formation of atherosclerotic plaques. These metabolic alterations are central to the increased CVD risk in patients with MASLD, highlighting the importance of targeting dyslipidemia and insulin resistance to mitigate CVD risk [35].

While prior research has not clearly identified the most critical combination of cardiometabolic risk factors driving CVD-associated and all-cause mortalities in patients with MASLD, our study revealed that the combination of hypertriglyceridemia, low HDL-C, and high glucose is strongly associated with an increased risk. This finding highlights the need for targeted screening and management of these specific risk factors in this patient population. Interestingly, our results diverged from those of a global CVD risk consortium study that identified hypertension as the most important factor contributing to the development of CVD [36].

Our study further emphasizes that the management of MASLD should

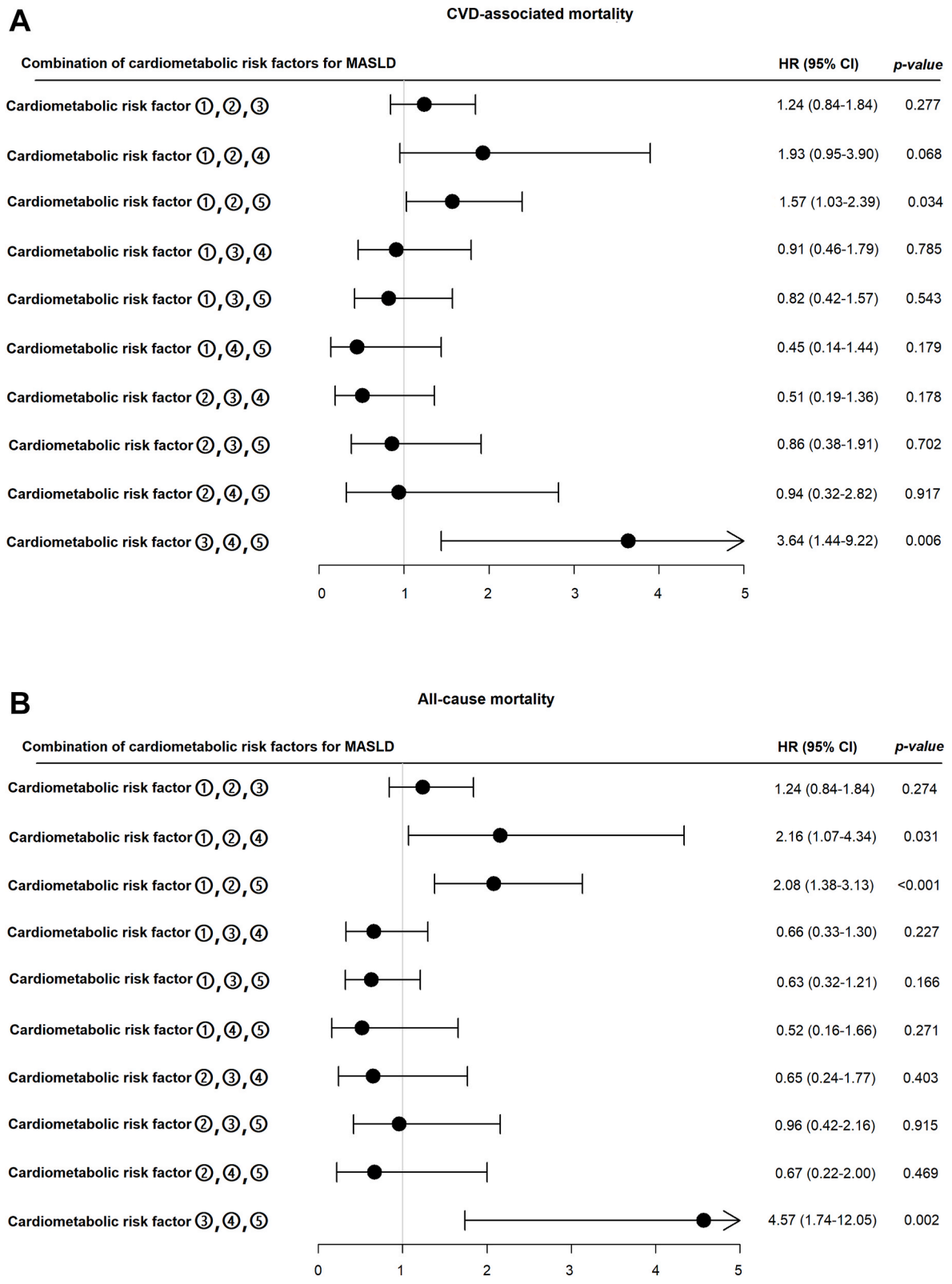

Fig. 2. Forest plot of Cox proportional HRs and 95 % CIs for (A) CVD-associated mortality and (B) all-cause mortality based on the combination of cardiometabolic risk factors for MASLD
CVD, Cardiovascular disease; MASLD, Metabolic dysfunction–associated steatotic liver disease
Cardiometabolic risk factor ①: Overweight or obesity
Cardiometabolic risk factor ②: High BP
Cardiometabolic risk factor ③: Hypertriglyceridemia
Cardiometabolic risk factor ④: Low HDL-C
Cardiometabolic risk factor ⑤: High glucose.

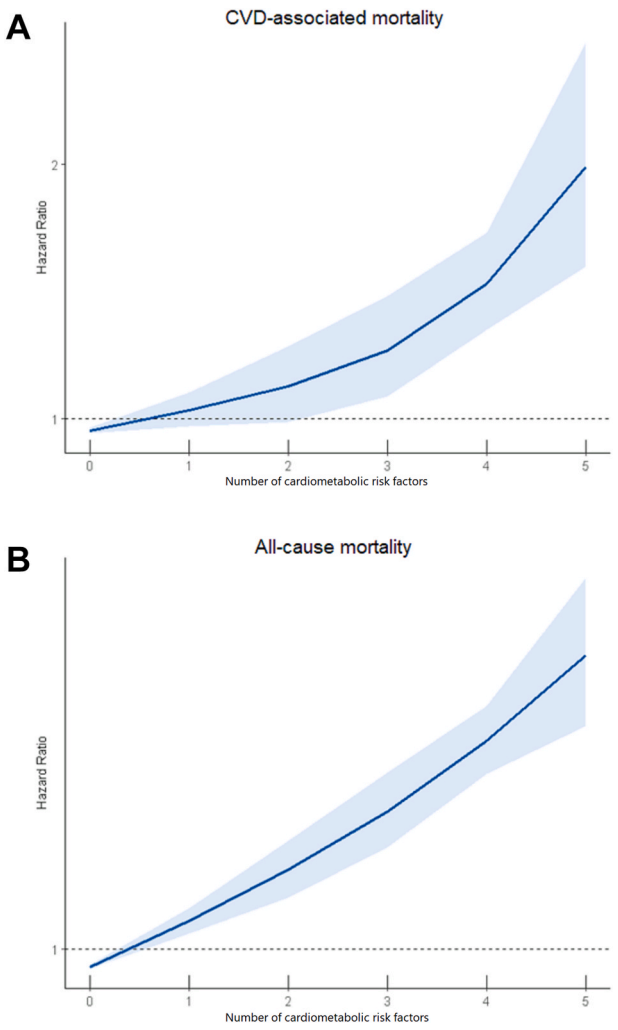

Fig. 3. Cox proportional hazard spline curves of (A) CVD-associated mortality and (B) all-cause mortality based on the number of cardiometabolic risk factors for MASLD
CVD, Cardiovascular disease; MASLD, Metabolic dysfunction–associated steatotic liver disease.

align closely with the management of metabolic syndrome. While MASLD is defined by hepatic steatosis and cardiometabolic risk factors, its impact on mortality appears to be largely attributed to the clustering of these risk factors. Therefore, targeting metabolic syndrome as a whole—including obesity, hypertension, dyslipidemia, and glucose dysregulation—should be prioritized in reducing CVD risk in MASLD patients. This approach aligns with current recommendations for CVD risk reduction in metabolic syndrome, reinforcing the importance of comprehensive risk factor management rather than focusing solely on MASLD as an independent entity.

This study has several limitations. First, since the study population was limited to Koreans, the results may not apply to other racial groups with different genetic traits and lifestyles. Second, owing to the use of baseline cardiometabolic risk factors and anthropometric measurements, changes during the follow-up period could not be accounted for. Third, we used the FLI to diagnose MASLD, which may not be as accurate as histological confirmation or other advanced imaging methods. However, using the FLI is useful in large population-based epidemiological studies, and its accuracy has been previously demonstrated [28].

Despite these weaknesses, the strength of this large, population-based cohort study with a long follow-up period lies in the assessment of the number and combination of cardiometabolic risk factors for MASLD in relation to CVD-associated and all-cause mortalities, as well as the identification of excellent prognostic value in predicting CVD-associated and all-cause mortality risk.

5. Conclusion

In conclusion, our study demonstrates that cardiometabolic risk factors in patients with MASLD are significantly associated with an increased risk of both CVD-associated and all-cause mortalities. In particular, the combination of hypertriglyceridemia, a low HDL-cholesterol, and high glucose significantly increased the incidence of these outcomes. These findings highlight the importance of targeted clinical management for patients with MASLD, especially those in high-risk groups. Future research should focus on developing tailored interventions that consider the long-term effects of the number and combination of cardiometabolic risk factors in patients with MASLD.

Author contributions

JHK, YJK, and JWL contributed to conceptualization. YL and CMN contributed to methodology. YL contributed to software. JHK and YL contributed to validation. YL and CMN contributed to formal analysis. JHK and YL contributed to investigation. YJK contributed to resources and data curation. JHK contributed to writing—original draft preparation. YJK and JWL contributed to writing—review and editing. YL contributed to visualization. YJK and JWL contributed to supervision. YJK contributed to project administration. JWL contributed to funding acquisition.

Data availability statement

The dataset used in this study (Ansan and Ansung cohort) is available from the Korea Centers for Disease Control and Prevention (http://www.cdc.go.kr/CDC/eng/main.jsp upon request.

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Declaration of competing interest

The authors declare that they have no competing interests.

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Abbreviations

γGTP	gamma-glutamyl transpeptidase
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
BP	blood pressure
CI	confidence interval
CVD	cardiovascular disease
FLI	fatty liver index

FPG	fasting plasma glucose
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
ICD	International Classification of Diseases
KoGES	Korean Genome and Epidemiology Study
LDL-C	low-density lipoprotein cholesterol
MASLD	metabolic dysfunction–associated steatotic liver disease
NAFLD	nonalcoholic fatty liver disease
TG	triglyceride
WC	waist circumference

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