

Mortality and Cardiovascular Outcomes in Patients with MAFLD Compared with Patients with MASLD: A Systematic Review and Meta-Analysis

Jiwon Yang¹, Ye Rim Kim¹, Seong Kyun Na², Seonok Kim³, Jihyun An⁴, Ju Hyun Shim¹

¹Department of Gastroenterology, Liver Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea;

²Department of Gastroenterology, Inje University Sanggye Paik Hospital, Seoul, Korea; ³Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; ⁴Department of Gastroenterology and Hepatology, Hanyang University College of Medicine, Guri, Korea

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Corresponding Author

Ju Hyun Shim

ORCID <https://orcid.org/0000-0002-7336-1371>

E-mail s5854@amc.seoul.kr

Jihyun An

ORCID <https://orcid.org/0000-0002-0110-0965>

E-mail starlit1@hanyang.ac.kr

Jiwon Yang and Ye Rim Kim contributed equally to this work as first authors.

Background/Aims: Although metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) represent the updated nomenclature and diagnostic criteria for nonalcoholic fatty liver disease, studies comparing the prognostic implications of these conditions remain limited. This meta-analysis aimed to quantify the associations among MAFLD, MASLD, and long-term clinical outcomes.

Methods: A comprehensive literature search was performed to identify cohort studies that assessed the association of MASLD and MAFLD with all-cause mortality, cause-specific (cardiovascular and cancer-related) mortality, and the incidence of cardiovascular disease in the PubMed, Embase, Web of Science, CINAHL, and CENTRAL databases from inception through October 31, 2024. Pooled hazard ratios (HRs) were calculated for relevant outcomes.

Results: We identified 18 cohort studies, comprising 10,653,666 patients with MAFLD from 13 studies and 3,202,447 patients with MASLD from nine studies. MAFLD was significantly associated with an increased risk of overall mortality (pooled HR [95% confidence interval], 1.30 [1.16 to 1.47]) and cardiovascular mortality (1.31 [1.08 to 1.60]; both $p < 0.01$), but not with cancer-related mortality (1.10 [0.97 to 1.24]; $p = 0.130$). Conversely, MASLD was associated with a higher risk for all mortality outcomes: overall mortality (1.34 [1.12 to 1.61]), cardiovascular mortality (1.17 [1.07 to 1.27]), and cancer-related mortality (1.24 [1.19 to 1.29]; all $p < 0.01$). The risk of cardiovascular disease was increased in patients with both MAFLD (1.48 [1.31 to 1.66]) and MASLD (1.33 [1.21 to 1.46]; both $p < 0.001$).

Conclusions: MAFLD and MASLD were both associated with increased risks of mortality and cardiovascular outcomes. Notably, a significant association with cancer-related mortality was observed for MASLD, but not for MAFLD. (*Gut Liver*, 2026;20:137-152)

Key Words: Metabolic dysfunction-associated steatotic liver disease; Metabolic dysfunction-associated fatty liver disease; Mortality; Cardiovascular diseases

INTRODUCTION

Metabolic dysfunction-associated fatty liver disease (MAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD) represent updated nomenclature and diagnostic frameworks that have been proposed to replace the term nonalcoholic fatty liver disease (NAFLD).¹⁻³ These terms were developed to eliminate the potential stigma-

tization associated with the words “fatty” and “alcoholic” in NAFLD, while also reflecting the diverse etiologies of steatotic liver diseases (SLDs).⁴ However, they have distinct diagnostic criteria. MAFLD is diagnosed based on the presence of hepatic steatosis along with at least one of the following metabolic risk factors: overweight/obesity, type 2 diabetes mellitus (T2DM), or metabolic dysfunction.^{2,5} Importantly, MAFLD allows for coexistence with other liver

diseases including viral hepatitis and alcohol-related liver disease. In contrast, MASLD is defined as part of a broader classification under SLD and emphasizes cardiometabolic dysfunction. It also requires the presence of hepatic steatosis but maintains the historical exclusion of significant alcohol consumption (>140 g/week for women and 210 g/week for men) and other chronic liver diseases.^{1,3} In other words, MAFLD permits overlap with other liver diseases based on metabolic criteria, while MASLD adheres to stricter exclusions, preserving NAFLD's traditional definition.

In addition to an elevated risk of liver-related events and hepatocellular carcinoma,^{6,7} individuals with NAFLD have been shown to exhibit higher risks of all-cause mortality, extrahepatic malignancies, and cardiovascular diseases (CVDs) compared to those without NAFLD or general populations.⁸⁻¹² In line with findings from NAFLD studies, several investigations have demonstrated that MAFLD and MASLD are significantly associated with increased risks of mortality and cardiovascular (CV) outcomes.¹³⁻³⁰ These findings underscore the importance of carefully assessing mortality and CV risk in individuals with MAFLD or MASLD and support the development of surveillance strategies targeting high-risk populations. Nonetheless, the associations between these disease entities and prognostic outcomes vary across studies, likely due to differences in covariate adjustment, study design, and geographic region.^{13,23,27,31-34} For instance, a large population-based study using data from the United Kingdom Biobank reported that both MASLD and MAFLD were significantly associated with increased risks of all-cause and CV mortality, even after adjusting for potential confounders.²⁷ However, data from the United States Third National Health and Nutrition Examination Survey, which included 13,856 adults with available ultrasonographic data, showed that CV mortality was significantly increased in MAFLD but not in MASLD, and neither condition was associated with cancer-related mortality.³⁵

Therefore, it is essential to clarify the association between MAFLD or MASLD and prognostic outcomes to improve surveillance and prevention strategies. This meta-analysis aims to evaluate and quantify the risk of mortality and CVDs in MASLD and MAFLD, respectively, and to determine which definition more accurately predicts the long-term hard outcomes through a systematic review of pertinent clinical studies.

MATERIALS AND METHODS

1. Search strategy and selection criteria

This meta-analysis was performed and reported in accordance with the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) guidelines. The protocol has been registered in the International Prospective Register of Systematic Reviews database (PROSPERO registration number: CRD42024548216). The Institutional Review Board of Asan Medical Center approved this meta-analysis and waived the requirement for informed consent from individual patients (approval number: 2024-0681).

We conducted a search for human cohort studies published from inception to October 31, 2024, using scholarly databases such as PubMed, Embase, Web of Science, CINAHL, and the CENTRAL. The detailed search strategy is presented in Supplementary Table 1. Two authors (Y.R.K. and J.A.) independently reviewed the titles and abstracts of the studies identified through the search to exclude those that did not address the research question of interest. Subsequently, the full texts of the remaining articles, along with their references, were thoroughly examined to confirm the inclusion of relevant information. In cases of discrepancies, consensus was achieved through discussion with another author (J.H.S.).

To be eligible, studies had to meet the following criteria: (1) include patients diagnosed with MAFLD or MASLD; (2) report the incidence of overall mortality, CV mortality, cancer-related mortality, and incident CVD; (3) use a longitudinal design; (4) follow-up duration of more than 1 year; (5) include a control arm, such as non-MASLD, non-MAFLD, or non-SLD for comparison; and (6) provide data on hazard ratio (HR) with 95% confidence interval (CI). Given that the terminology for MASLD was introduced recently, we did not impose restrictions on the types of articles included. Thus, abstracts and letters were included in the literature search and screening process. When we found multiple publications based on the same study population, we included only the most recent and informative one. Studies were excluded if they met any of the following criteria: (1) published in a non-English language; (2) focused on pediatric populations (aged <19 years); and (3) classified as preclinical studies, case reports, case series, case-control studies, systematic reviews, or meta-analyses. The flow diagram summarizing the study identification and selection process is presented in Fig. 1.

2. Definition of MAFLD and MASLD

MAFLD was defined as the presence of hepatic steatosis with metabolic dysfunction, which includes being overweight or obese, having T2DM, or exhibiting a combination of at least two of the seven metabolic risk factors.² MASLD was defined as the presence of hepatic steatosis along with at least one of the five cardiometabolic criteria in adults.¹ The detailed criteria for MAFLD and MASLD are presented in Supplementary Table 2.

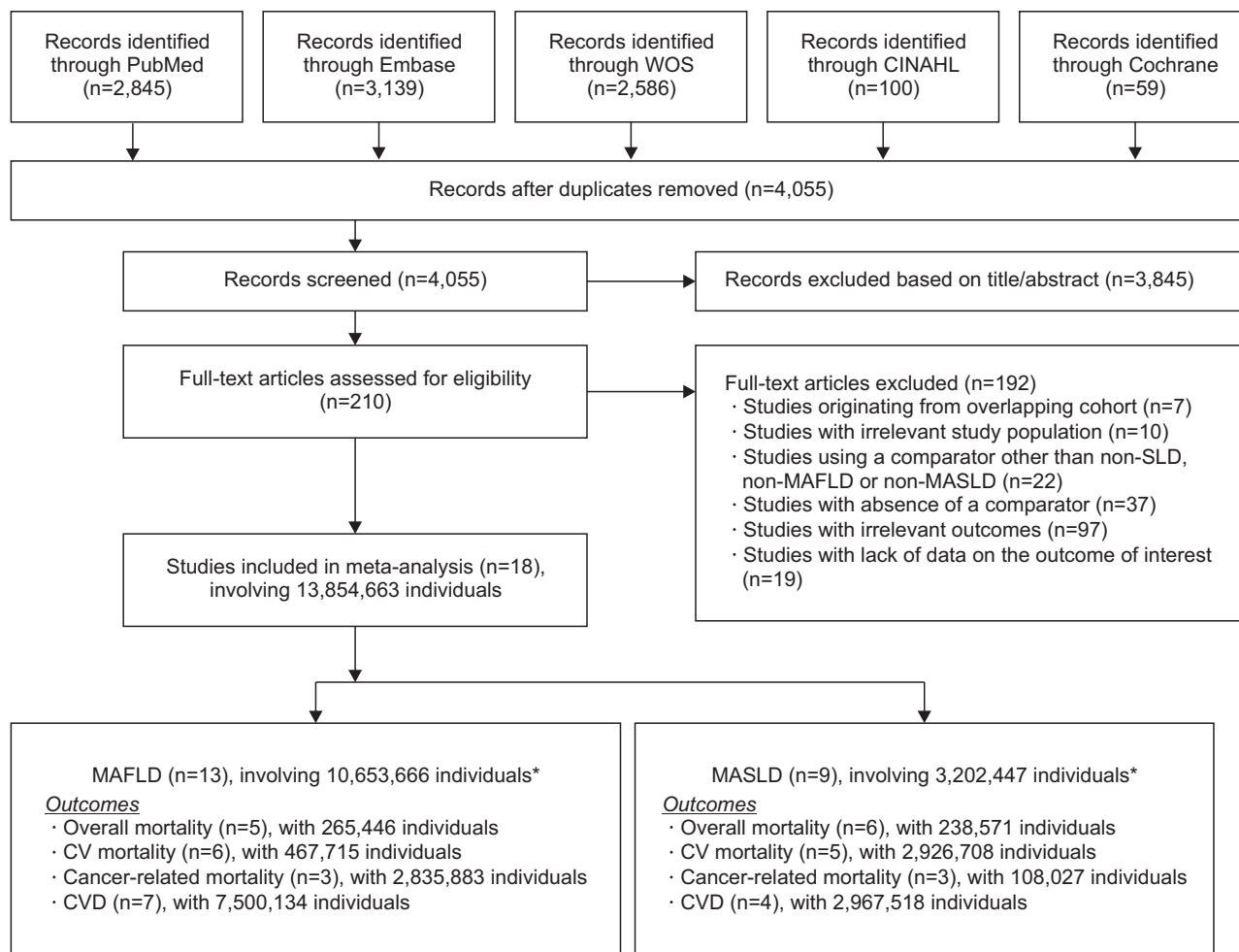


Fig. 1. PRISMA checklist. WOS, Web of Science; CINAHL, Cumulative Index to Nursing and Allied Health Literature; SLD, steatotic liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; CV, cardiovascular; CVD, cardiovascular disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. *Four studies^{13,18,22,27} assessed both MASLD and MAFLD outcomes.

3. Data extraction

Data were independently extracted by two reviewers (Y.R.K. and J.A.) using a pre-established form. In addition to the standard bibliometric variables, information on the following variables was also collected: category of hepatic steatosis (MAFLD or MASLD); study design; year of publication; median follow-up duration; study region; methods of steatosis assessment (fatty liver index [FLI], abdominal ultrasound [US], or liver biopsy); age; sex; prevalence of T2DM; total number of participants; cases of overall mortality, cancer-related mortality, CV mortality, or CVD; HR and 95% CI; and adjusted covariates. Any discrepancies in data extraction were resolved by consensus, with reference to the original articles for clarification.

4. Outcomes of interest

The primary outcome was the overall mortality of indi-

viduals classified according to the definitions of MASLD and MAFLD (Supplementary Table 2). The secondary outcomes included CV mortality, cancer-related mortality, and incident CVD. The definitions of CV mortality, cancer-related mortality, and CVD were derived from the original studies included in this meta-analysis (Supplementary Table 3). The comparison groups included those without SLD or those who did not meet the diagnostic criteria for the respective conditions (i.e., non-SLD, non-MASLD, or non-MAFLD).

5. Quality assessment and publication bias

The methodological quality of the cohort studies was independently assessed by two authors (J.Y. and J.A.) using the Newcastle-Ottawa Scale.³⁶ Within this scale, studies were evaluated across three categories: selection of study groups (four items), comparability of study groups (two items), and

ascertainment of the outcome of interest (three items). Each item was assigned a score of one point, except in the comparability category, where additional points were awarded for controlling for age and/or sex, allowing for a maximum of 2 points in this category. Publication bias was assessed quantitatively using Egger's rank correlation regression test and qualitatively through the visualization of funnel plots depicting the logarithmic HRs against their standard errors.³⁷

6. Statistical analysis

A random-effects meta-analysis model was employed to calculate pooled HR and 95% CI. Heterogeneity among study-specific estimates was assessed using two complementary methods. First, Cochran's Q statistic was calculated to determine whether the observed variations in study results exceeded what would be expected by chance. This was accomplished by summing the weighted squared deviations of each study's estimate from the overall weighted mean effect size. Second, to quantify the proportion of total variation attributable to heterogeneity rather than chance, the I^2 statistic was computed. In this analysis, an I^2 value greater than 50% indicated significant heterogeneity.³⁸ Specifically, I^2 values of approximately 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively, while a p-value greater than 0.10 was considered to indicate homogeneity.³⁹

To mitigate the impact of heterogeneity across included studies on outcomes assessment, we performed subgroup analyses stratified by the following parameters: diagnostic modality for steatosis (US vs FLI), geographical region (Eastern populations vs Western populations), study methodology (prospective design vs retrospective design), mean or median age of participants (≥ 50 years vs < 50 years vs not reported), sex distribution ($\geq 60\%$ male participants vs $< 60\%$ male participants vs not reported), T2DM prevalence at baseline ($\geq 15\%$ vs $< 15\%$ vs not reported), comparator group (non-MAFLD vs non-MASLD vs non-SLD), and median follow-up duration (≥ 10 years vs < 10 years). Threshold values for stratification were determined based on previously established criteria by Ha *et al.*⁴⁰ Additionally, we employed random-effects meta-regression models to evaluate the impact of these baseline covariates on the observed heterogeneity.

All statistical analyses were conducted using the "meta" packages in R software (Version 4.4.2, R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

RESULTS

1. Summary of the literature search

As shown in the PRISMA flow diagram, our literature search yielded 4,055 articles after the removal of duplicates. We screened 4,055 potentially relevant articles and subsequently reviewed the full text of 210 articles. Of these, 192 articles were excluded for the following reasons: (1) studies originating from overlapping cohorts ($n=7$); (2) irrelevant study population ($n=10$); (3) use of a comparator other than non-MAFLD, non-MASLD or non-SLD ($n=22$); (4) absence of a comparator ($n=37$); (5) irrelevant outcomes ($n=97$); and (6) insufficient data on the outcome of interest ($n=19$). Ultimately, 18 studies were included in this meta-analysis, comprising 16 peer-reviewed original articles^{13-26,29,30} and two conference abstracts (Fig. 1).^{27,28} Among these, nine studies exclusively focused on MAFLD,^{16,17,20,21,23,25,26,28,29} five studies on MASLD,^{14,15,19,24,30} and four studies examined both MAFLD and MASLD in the same population.^{13,18,22,27} Overall, data from 13 studies comprising 10,653,666 patients classified as having MAFLD^{13,16-18,20-23,25-29} and from nine studies comprising 3,202,447 patients diagnosed with MASLD^{13-15,18,19,22,24,27,30} were analyzed.

The baseline characteristics of the included studies are summarized in Table 1. Among the studies, eight articles (44.4%) assessed steatosis using abdominal US,^{13,17,19,20,26,28-30} while 10 articles utilized the FLI;^{14-16,18,21-25,27} one study diagnosed steatosis using abdominal US, liver biopsy or controlled attenuated parameter.¹⁹ The study population primarily consisted of Asian patients, accounting for 14 articles (77.8%).^{15-18,20-26,28-30} Excluding one study that lacked data on sex,²⁸ the proportion of male patients exceeded 60% in most studies (10 articles).^{14,16,19-26} The mean or median age of the study populations across all included studies ranged between 41.9 and 61.6 years, except for two studies that did not report age data.^{28,30} Of the included studies, eight reported a prevalence of T2DM greater than 15%,^{13,15,18,19,21,23,25,29} while two studies did not provide data on T2DM status.^{27,28} The median follow-up duration ranged from 3.99 to 26.9 years. The detailed definitions of comparison groups used in the included studies are presented in Supplementary Table 4.

2. Risk of mortality outcomes and CVDs in patients with MAFLD

Among the 13 articles focusing on patients with MAFLD, five studies examined the overall mortality as an outcome, involving a total of 265,446 MAFLD patients (Supplementary Table 5).^{13,18,20,23,27} In the pooled analysis, MAFLD was significantly associated with an increased risk of overall mortality compared to its comparators (pooled

Table 1. Baseline Characteristics of the Included Studies

Diagnosis	First author (year, country)	Study design	Comparators	Median follow-up, yr	Steatosis assessment	Study population				Outcomes	Adjustment
						No. of participants	Age, yr*	Male sex (%)	Prevalence of T2DM (%)		
MAFLD	Moon [2022, South Korea] ²³	Prospective	Non-MAFLD	15.7	FLI ≥60	1,509	52.4	67.5	24.9	Overall mortality, CV mortality, cancer-related mortality, CVD	Age, sex, BMI, chronic kidney disease, smoking status, hypertension, dyslipidemia, diabetes, high-sensitivity C-reactive protein, viral hepatitis, excessive alcohol consumption
	Kim [2023, South Korea] ²⁰	Prospective	Non-MAFLD	5.7	US	98,649	41.95 [†]	75.15 [†]	10.59 [†]	Overall mortality, CV mortality	NR
	Han [2024, South Korea] ¹⁸	Retrospective	Non-MAFLD	9.2	FLI ≥30	9,120	52.5	49.2	19.8	Overall mortality	Age, sex, alcohol drink, smoking, low socioeconomic status, regular exercise, BMI, hypertension, diabetes, viral hepatitis, dyslipidemia, chronic kidney disease, prior history of CVD and, malignancy
	Song [2024, USA] ¹³	Retrospective	Non-MAFLD	26.9	US	1,450	48.0	60.0	17.0	Overall mortality, CV mortality, cancer-related mortality	Sex, age, race/ethnicity, marital status, education, sedentary lifestyle, smoking status, BMI, waist circumference
	Zhang [2024, UK] ²⁷	Prospective	Non-MAFLD	13.3	FLI ≥60	154,718	56.6 [‡]	46.2 [‡]	NR	Overall mortality, CV mortality, CVD	Age, sex, ethnicity, education, Townsend Deprivation Index, income levels, smoking status, alcohol intake, physical activity, LDL-C, eGFR
	Cheng [2023, Taiwan] ²⁸	Retrospective	Non-SLD	8.1	US	33,658	NR	NR	NR	CV mortality	Socioeconomic status, alcohol drinking, smoking, exercise habit, viral hepatitis, chronic kidney disease
	Yoo [2023, South Korea] ²⁶	Retrospective	Non-MAFLD	8.77	US	177,731	42.7	76.7	11.8	CV mortality	Age, sex, education, smoking, regular exercise [3 times/wk], plasma LDL-C
	Chung [2023, South Korea] ¹⁶	Retrospective	Non-MAFLD	8.3	FLI ≥30	2,832,924	49.6	72.1	14.7	Cancer-related mortality	Age, sex, income, smoking, exercise, eGFR, CCI score, waist circumference, glucose, total cholesterol, systolic blood pressure
	Yoneda [2021, Japan] ²⁵	Retrospective	Non-MAFLD	3.99	FLI ≥60	237,242	46.0	84.5	20.6	CVD	Age, sex, smoking habit, LDL-C, statin use
	Lee [2021, South Korea] ²¹	Retrospective	Non-MAFLD	10.1	FLI ≥30	3,573,644	51.0	71.6	15.8	CVD	Age, sex, household income quartile, residential area, CCI, tobacco use, exercise frequency, eGFR
	Guo [2022, China] ¹⁷	Prospective	Non-MAFLD	4.7	US	1,681	42.9	52.3	10.9	CVD	Age, sex, systolic blood pressure, diastolic blood pressure, HDL-C, eGFR, T2DM, smoking
	Liang [2022, China] ²⁹	Retrospective	Non-SLD	4.6	US	3,212	61.6 [‡]	42.4 [‡]	29.6	CVD	Age, sex, educational background, smoking status, leisure-time exercise at baseline
	Lee [2024, South Korea] ²²	Retrospective	Non-MAFLD	12.3	FLI ≥30	3,528,128	49	75.6	9.4 [§]	CVD	Age, sex, household income quartile, residential area, CCI, tobacco use, physical activity, eGFR

Table 1. Continued

Diagnosis	First author (year, country)	Study design	Comparators	Median follow-up, yr	Steatosis assessment	Study population				Outcomes	Adjustment
						No. of participants	Age, yr*	Male sex (%)	Prevalence of T2DM (%)		
MASLD	Bao [2024, UK] ¹⁴	Prospective	Non-MASLD	13.7	FLI ≥60	102,821	57.1	60.7	12.9	Overall mortality, cancer-related mortality	Age, sex, ethnicity, education, Townsend Deprivation Index, income levels, smoking status, alcohol intake, activity group by the International Physical Activity Questionnaire, eGFR, CVD
	Chen [2024, Taiwan] ³⁰	Retrospective	Non-SLD	16	US	123,280	NR	58.2	11.7	Overall mortality, CV mortality	Age, sex, smoking and drinking status, any comorbidity, work strength
	Choe [2024, South Korea] ¹⁵	Prospective	Non-SLD	17.5	FLI ≥30	3,642	53.7	51.4	18.2	Overall mortality, CV mortality, cancer-related mortality	CVD was adjusted for age, sex, diabetes, hypertension, dyslipidemia, chronic kidney disease, smoking status, alcohol intake
	Han [2024, South Korea] ¹⁸	Retrospective	Non-SLD	9.2	FLI ≥30	7,111	53.9	42.9	21.3	Overall mortality	Age, sex, alcohol drink, smoking, low socioeconomic status, regular exercise, BMI, hypertension, diabetes, viral hepatitis, dyslipidemia, chronic kidney disease, prior history of CVDs, malignancy
	Israelsen [2024, Denmark] ¹⁹	Prospective	Non-SLD	5.8	US ¹¹	153	57.0	80.0	82.0 [†]	Overall mortality	Age, sex, liver stiffness
	Song [2024, USA] ¹³	Retrospective	Non-MASLD	26.9	US	1,564	47.0	58.0	15.0	Overall mortality, CV mortality, cancer-related mortality	Sex, age, race/ethnicity, marital status, education, sedentary lifestyle, smoking status, BMI, waist circumference
	Lee [2024, South Korea] ²²	Retrospective	Non-MASLD	12.3	FLI ≥30	2,686,615	49.0	71.3	9.1 [§]	CV mortality, CVD	Age, sex, household income quartile, residential area, CCI, tobacco use, physical activity, eGFR
	Zhang [2024, UK] ²⁷	Prospective	Non-MASLD	13.3	FLI ≥60	111,607	56.6 [‡]	46.2 [‡]	NR	CV mortality, CVD	Age, sex, ethnicity, education, Townsend Deprivation Index, income levels, smoking status, alcohol intake, physical activity, LDL-C, eGFR
	Moon [2023, South Korea] ²⁴	Retrospective	Non-SLD	9.0	FLI ≥60	165,654	56.9	67.3	14.6	CVD	Age, sex, BMI, household income, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, moderate-to-vigorous physical activity, CCI, aspirin, non-steroidal anti-inflammatory drugs

T2DM, type 2 diabetes mellitus; MASLD, metabolic dysfunction-associated fatty liver disease; FLI, fatty liver index; CV, cardiovascular; CVD, cardiovascular disease; BMI, body mass index; US, ultrasound; NR, not reported; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; SLD, steatotic liver disease; CCI, Charlson Comorbidity Index; HDL-C, high-density lipoprotein cholesterol; MASLD, metabolic dysfunction-associated steatotic liver disease.

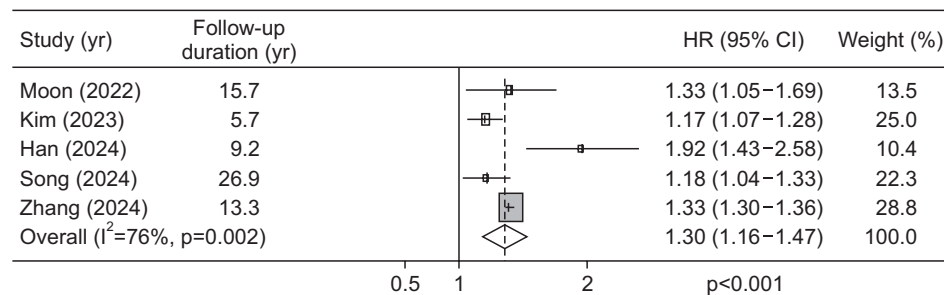
*Data are presented as the mean or median; [†]Data were derived from the group with MAFLD combined with nonalcoholic fatty liver disease; [‡]Data were derived from the general population; [§]T2DM was defined as the use of glucose-lowering drugs; ^{||}The steatosis assessment method included biopsy, US, or controlled attenuated parameters; [¶]T2DM was defined as a fasting glucose level ≥5.6 mmol/L, a glycated hemoglobin level ≥39 mmol/mol, a diagnosis of T2DM, or the use of anti-diabetic treatment.

HR, 1.30; 95% CI, 1.16 to 1.47; $p < 0.001$ with $I^2 = 76\%$) (Fig. 2A). Assessment of CV mortality from six studies including 467,715 MAFLD patients demonstrated similarly elevated risk (HR, 1.31; 95% CI, 1.08 to 1.60; $p = 0.006$ with $I^2 = 85\%$) (Fig. 2B, Supplementary Table 6).^{13,20,23,26-28}

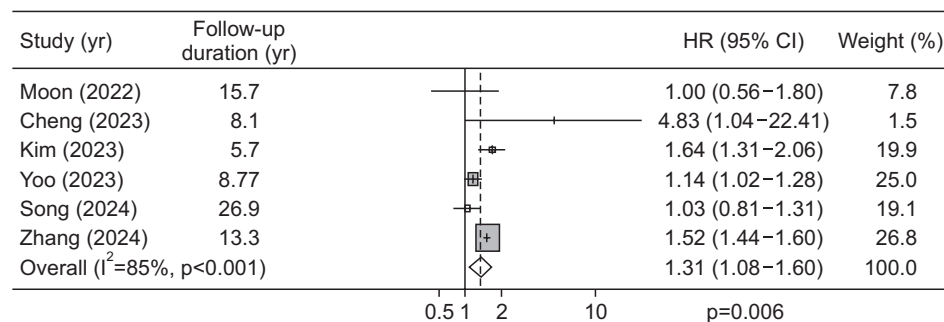
Three studies investigated the association between MAFLD and cancer-related mortality in 2,835,883 MAFLD

patients (Supplementary Table 7).^{13,16,23} Notably, the risk of cancer-related mortality showed no significant difference between MAFLD patients and comparators, despite exhibiting low-to-moderate heterogeneity (HR, 1.10; 95% CI, 0.97 to 1.24; $p = 0.130$ with $I^2 = 27\%$) (Fig. 2C). Evaluation of incident CVD from seven studies with 7,500,134 MAFLD revealed substantially higher risk in MAFLD patients ver-

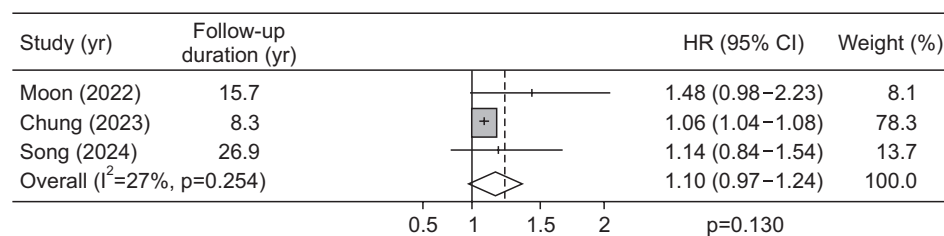
A Overall mortality



B CV mortality



C Cancer-related mortality



D Incident CVD

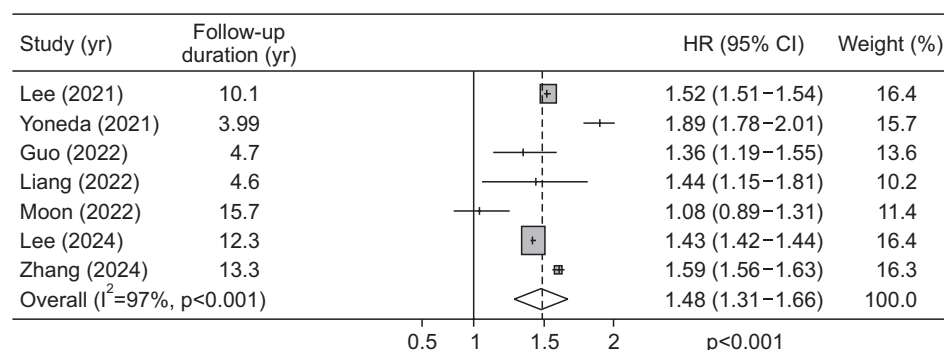


Fig. 2. Forest plot and pooled estimates of the clinical effect of MAFLD on mortality and CVD. (A) Overall mortality, (B) CV mortality, (C) cancer-related mortality, and (D) incident CVD. MAFLD, metabolic dysfunction-associated fatty liver disease; CVD, cardiovascular disease; CV, cardiovascular; HR, hazard ratio; CI, confidence interval.

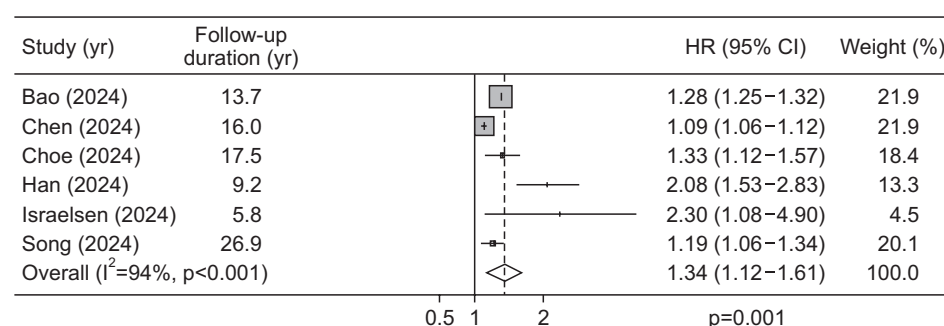
sus those without SLD or MAFLD (HR, 1.48; 95% CI, 1.31 to 1.66; $p<0.001$; $I^2=97\%$) (Fig. 2D, Supplementary Table 8).^{17,21-23,25,27,29}

3. Risk of mortality and CVDs in patients with MASLD

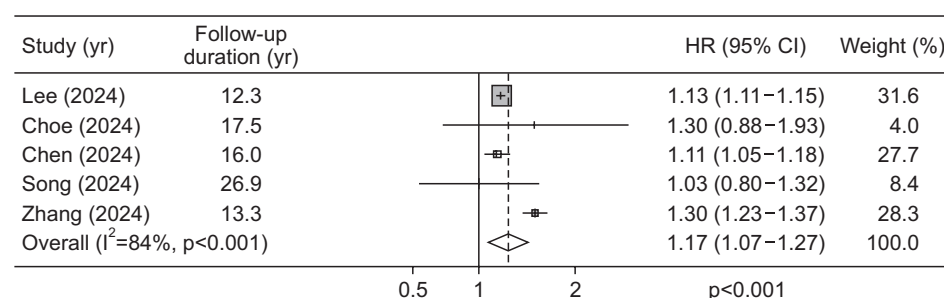
Among all the articles on patients with MASLD, six studies investigated the association between MASLD and overall mortality in 238,571 MASLD patients (Supplementary Table 5).^{13-15,18,19,30} In the pooled analysis, patients

with MASLD showed a significantly higher risk of overall mortality compared to those without SLD or MASLD (HR, 1.34; 95% CI, 1.12 to 1.61; $p=0.001$ with $I^2=94\%$) (Fig. 3A). CV mortality was assessed in five studies encompassing 2,926,708 MASLD patients (Supplementary Table 6).^{13,15,22,27,30} Results demonstrated a significant increase in CV mortality risk among MASLD patients versus comparators (HR, 1.17; 95% CI, 1.07 to 1.27; $p<0.001$; $I^2=84\%$) (Fig. 3B). For cancer-related mortality, pooled data from

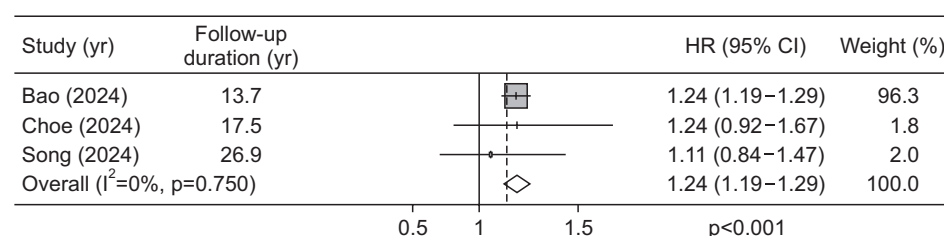
A Overall mortality



B CV mortality



C Cancer-related mortality



D Incident CVD

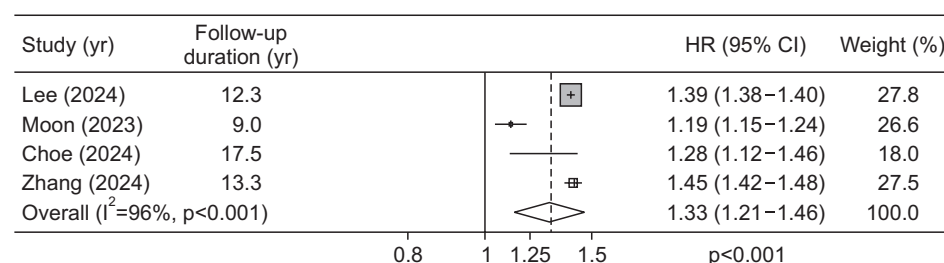


Fig. 3. Forest plot and pooled estimates of the clinical effect of MASLD on mortality and CVD. (A) Overall mortality, (B) CV mortality, (C) cancer-related mortality, and (D) incident CVD. MASLD, metabolic dysfunction-associated steatotic liver disease; CVD, cardiovascular disease; CV, cardiovascular; HR, hazard ratio; CI, confidence interval.

three studies with 108,027 MASLD patients indicated a significantly heightened risk with remarkable consistency across studies (HR, 1.24; 95% CI, 1.19 to 1.29; $p<0.001$; $I^2=0\%$) (Fig. 3C, Supplementary Table 7).¹³⁻¹⁵

Four studies evaluated the risk of incident CVD in 2,967,518 patients with MASLD (Supplementary Table 8).^{15,22,24,27} The incidence risk of CVD was significantly higher in patients with MASLD compared to non-SLD or non-MASLD controls (HR, 1.33; 95% CI, 1.21 to 1.46; $p<0.001$ with $I^2=96\%$) (Fig. 3D).

4. Subgroup analyses of mortality and CV events in MAFLD and MASLD

Subgroup analyses were performed to assess effect mod-

ification across study characteristics and explore sources of heterogeneity for the outcomes of overall mortality, CV mortality, and incident CVD, as shown in Supplementary Figs 1 and 2. Subgroup analysis for cancer-related mortality was not conducted due to low heterogeneity observed in the overall meta-analysis for both MAFLD and MASLD individuals.

For MAFLD, subgroup findings were largely consistent with the main results, although significant effect size differences were observed based on methods of steatosis assessment for overall mortality and T2DM prevalence for both overall mortality and incident CVD (all p for group difference <0.05) (Table 2, Supplementary Fig. 1). Study design demonstrated a significant effect on the association

Table 2. Subgroup Analyses of Mortality and Cardiovascular Diseases in Patients with MAFLD and MASLD

Variable	MAFLD				MASLD			
	No. of studies	HR (95% CI)	I^2 [%]	p for group differences	No. of studies	HR (95% CI)	I^2 [%]	p for group differences
Overall mortality								
All	5	1.30 (1.16–1.47)	76		6	1.34 (1.12–1.61)	94	
Steatosis assessment				<0.001				0.028
FLI ≥ 30	1	1.92 (1.43–2.58)	NA		2	1.63 (1.05–2.52)	84	
FLI ≥ 60	2	1.33 (1.30–1.36)	0		1	1.28 (1.25–1.32)	NA	
Ultrasound*	2	1.17 (1.09–1.26)	0		3	1.13 (1.03–1.25)	65	
Study region				0.530				0.580
Eastern countries	3	1.40 (1.06–1.85)	80		3	1.41 (0.98–2.01)	91	
Western countries	2	1.27 (1.14–1.43)	72		3	1.27 (1.22–1.33)	47	
Study design				0.543				0.771
Prospective	3	1.27 (1.15–1.40)	73		3	1.28 (1.25–1.32)	20	
Retrospective	2	1.48 (0.92–2.37)	89		3	1.35 (0.94–1.96)	89	
Age				0.052				0.024
≥ 50 yr	3	1.45 (1.19–1.77)	66		4	1.54 (1.18–2.00)	75	
< 50 yr	2	1.17 (1.09–1.26)	0		2	1.12 (1.03–1.21)	51	
Male sex				0.147				0.667
$\geq 60\%$	3	1.19 (1.11–1.27)	0		2	1.51 (0.90–2.54)	57	
$< 60\%$	2	1.55 (1.09–2.21)	83		4	1.33 (1.04–1.71)	87	
Prevalence of T2DM				0.022				0.146
$\geq 15\%$	3	1.41 (1.07–1.85)	78		3	1.45 (1.06–1.97)	82	
$< 15\%$	1	1.17 (1.07–1.28)	NA		2	1.18 (1.01–1.38)	98	
Not reported	1	1.33 (1.30–1.36)	NA		1	2.30 (1.08–4.90)	NA	
Median follow-up				0.600				<0.001
≥ 10 yr	3	1.29 (1.18–1.40)	43		4	1.21 (1.10–1.32)	96	
< 10 yr	2	1.47 (0.90–2.38)	90		2	2.11 (1.59–2.81)	0	
Type of comparators				NA				0.334
Non-MAFLD	5	1.30 (1.16–1.47)	76		NA			
Non-MASLD	NA				2	1.26 (1.20–1.33)	29	
Non-SLD	0	-	-		4	1.50 (1.07–2.10)	88	
Cardiovascular mortality								
All	6	1.31 (1.08–1.60)	85		5	1.17 (1.07–1.27)	84	
Steatosis assessment				0.793				<0.001
FLI ≥ 30	0	-	-		2	1.13 (1.11–1.15)	0	
FLI ≥ 60	2	1.37 (0.96–1.95)	48		1	1.30 (1.23–1.37)	NA	
Ultrasound	4	1.29 (0.98–1.70)	76		2	1.11 (1.04–1.17)	0	
Study region				0.843				0.602
Eastern countries	4	1.34 (1.00–1.80)	74		3	1.13 (1.11–1.15)	0	
Western countries	2	1.28 (0.87–1.86)	89		2	1.20 (0.96–1.49)	68	

Table 2. Continued

Variable	MAFLD				MASLD			
	No. of studies	HR (95% CI)	I ² (%)	p for group differences	No. of studies	HR (95% CI)	I ² (%)	p for group differences
Study design				<0.001				<0.001
Prospective	3	1.52 [1.45–1.60]	16		2	1.30 [1.23–1.37]	0	
Retrospective	3	1.13 [1.02–1.25]	50		3	1.13 [1.11–1.15]	0	
Age				0.222				<0.001
≥50 yr	2	1.37 [0.96–1.95]	48		2	1.30 [1.23–1.37]	0	
<50 yr	3	1.24 [0.95–1.61]	79		3	1.13 [1.11–1.15]	0	
Not reported	1	4.83 [1.04–22.41]	NA		0	-	-	
Male sex				0.053				0.461
≥60%	4	1.21 [0.96–1.52]	70		1	1.13 [1.11–1.15]	NA	
<60%	1	1.52 [1.44–1.60]	NA		4	1.18 [1.05–1.33]	82	
Not reported	1	4.83 [1.04–22.41]	NA		0	-	-	
Prevalence of T2DM				0.216				<0.001
≥15%	2	1.03 [0.82–1.28]	0		2	1.10 [0.89–1.36]	0	
<15%	2	1.35 [0.95–1.92]	87		2	1.13 [1.11–1.15]	0	
Not reported	2	2.08 [0.76–5.69]	54		1	1.30 [1.23–1.37]	NA	
Median follow-up				0.500				NA
≥10 yr	3	1.23 [0.90–1.67]	82		5	1.17 [1.07–1.27]	84	
<10 yr	3	1.46 [0.98–2.18]	82		0	-	-	
Type of comparators				0.094				0.402
Non-MAFLD	5	1.29 [1.06–1.56]	87		NA			
Non-MASLD	NA				3	1.18 [1.05–1.33]	92	
Non-SLD	1	4.83 [1.04–22.41]	NA		2	1.11 [1.05–1.18]	0	
Cardiovascular disease								
All	7	1.48 [1.31–1.66]	97		4	1.33 [1.21–1.46]	96	
Steatosis assessment				0.593				0.694
FLI ≥30	2	1.47 [1.39–1.57]	99		2	1.37 [1.29–1.46]	36	
FLI ≥60	3	1.50 [1.10–2.05]	95		2	1.31 [1.08–1.60]	99	
Ultrasound	2	1.38 [1.23–1.55]	0		0	-	-	
Study region				0.219				0.024
Eastern countries	6	1.45 [1.26–1.67]	97		3	1.29 [1.16–1.42]	97	
Western countries	1	1.59 [1.56–1.63]	NA		1	1.45 [1.42–1.48]	NA	
Study design				0.241				0.455
Prospective	3	1.35 [1.09–1.67]	90		2	1.39 [1.23–1.56]	71	
Retrospective	4	1.57 [1.37–1.80]	98		2	1.29 [1.11–1.50]	98	
Age				0.506				0.326
≥50 yr	4	1.42 [1.21–1.66]	89		3	1.31 [1.15–1.48]	98	
<50 yr	3	1.55 [1.27–1.89]	98		1	1.39 [1.38–1.40]	NA	
Male sex				0.909				0.455
≥60%	4	1.47 [1.19–1.82]	98		2	1.29 [1.11–1.50]	98	
<60%	3	1.49 [1.33–1.67]	66		2	1.39 [1.23–1.56]	71	
Prevalence of T2DM				<0.001				0.059
≥15%	4	1.47 [1.18–1.85]	95		1	1.28 [1.12–1.46]	NA	
<15%	2	1.43 [1.42–1.44]	0		2	1.29 [1.11–1.50]	98	
Not reported	1	1.59 [1.56–1.63]	NA		1	1.45 [1.42–1.48]	NA	
Median follow-up				0.465				<0.001
≥10 yr	4	1.42 [1.24–1.63]	98		3	1.40 [1.34–1.47]	88	
<10 yr	3	1.57 [1.26–1.94]	91		1	1.19 [1.15–1.24]	NA	
Type of comparators				0.841				<0.001
Non-MAFLD	6	1.48 [1.29–1.69]	98		NA			
Non-MASLD	NA				2	1.42 [1.36–1.48]	93	
Non-SLD	1	1.44 [1.15–1.81]	NA		2	1.20 [1.15–1.26]	11	

MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; HR, hazard ratio; CI, confidence interval; FLI, fatty liver index; T2DM, type 2 diabetes mellitus; SLD, steatotic liver disease; NA, not applicable.

*One study (Israelsen 2024)¹⁹ that included patients diagnosed with steatosis using biopsy, ultrasound, or controlled attenuation parameters was categorized as the ultrasound group.

Table 3. Meta-Regression Analysis of the Effects of Covariates on Overall Mortality in Patients with MAFLD and MASLD

Variable	MAFLD		MASLD	
	Effect estimate (95% CI)	p-value	Effect estimate (95% CI)	p-value
Steatosis assessment		<0.001		0.460
Ultrasound	Reference		Reference	
Fatty liver index ≥ 30	0.492 [0.187 to 0.798]		0.273 [-0.168 to 0.174]	
Fatty liver index ≥ 60	0.125 [0.049 to 0.201]		0.043 [-0.460 to 0.545]	
Study design		0.511		0.823
Retrospective	Reference		Reference	
Prospective	-0.111 [-0.441 to 0.219]		0.05 [-0.387 to 0.486]	
Study region		0.571		0.858
Western	Reference		Reference	
Eastern	0.093 [-0.230 to 0.417]		0.04 [-0.393 to 0.472]	
Age, yr	0.013 [-0.009 to 0.036]	0.247	0.029 [-0.015 to 0.073]	0.192
Male sex, %	-0.007 [-0.018 to 0.004]	0.212	-0.007 [-0.030 to 0.015]	0.508
T2DM, %	0.016 [-0.025 to 0.058]	0.447	0.045 [0.012 to 0.077]	0.007
Median follow-up, yr	-0.006 [-0.027 to 0.016]	0.595	-0.024 [-0.053 to 0.005]	0.102

MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; CI, confidence interval; T2DM, type 2 diabetes mellitus.

between MAFLD and CV mortality, with prospective studies revealing a higher risk compared to retrospective designs (HR, 1.52; 95% CI, 1.45 to 1.60 vs HR, 1.13; 95% CI, 1.02 to 1.25; p for group difference <0.001), accompanied by reduced heterogeneity (overall: $I^2=85\%$ vs prospective design: $I^2=16\%$; retrospective design: $I^2=50\%$).

For MASLD, the elevated risks of overall mortality and CV mortality remained consistent across most subgroups (Table 2, Supplementary Fig. 2). Notably, MASLD patients aged ≥ 50 years (HR, 1.54; 95% CI, 1.18 to 2.00) and those with a median follow-up duration <10 years (HR, 2.11; 95% CI, 1.59 to 2.81) demonstrated significantly higher overall mortality risk compared to their counterparts (p for group difference=0.024 and <0.001, respectively), with substantially reduced heterogeneity (overall: $I^2=94\%$ vs age ≥ 50 years: $I^2=75\%$; follow-up <10 years: $I^2=0\%$). The method of steatosis assessment and study design exhibited significant modification effects on the association between MASLD and CV mortality (all p for group difference <0.001), resulting in improved heterogeneity (overall: $I^2=84\%$ vs both FLI ≥ 30 and US: $I^2=0\%$; both study designs: $I^2=0\%$). For CVD incidence, the estimated effect size for MASLD varied by comparator type. When non-MASLD individuals were used as the reference group, MASLD was associated with CVD (HR, 1.42; 95% CI, 1.36 to 1.48), whereas the HR was 1.20 (95% CI, 1.15 to 1.26) when non-SLD comparators were used. The test for subgroup differences was statistically significant ($p<0.001$), indicating that comparator type influences the magnitude of the observed association.

5. Meta-regression analysis for overall mortality in MAFLD and MASLD

We performed meta-regression to identify associations between study-level characteristics and overall mortality, as shown in Table 3. In brief, age, the proportion of male, study region, and the length of follow-up did not have significant effects on all-cause mortality in MAFLD and MASLD patients. Only steatosis assessment using FLI was associated with increased risk of overall mortality in MAFLD, whereas this significance was not observed in MASLD. In terms of MASLD, a significant positive association between the proportion of patients with pre-existing T2DM and increased overall mortality was observed (Supplementary Fig. 3).

6. Quality assessment

The quality assessment of the included articles and PRISMA checklist are provided in Supplementary Tables 9 and 10, respectively. All included studies demonstrated good methodological quality, with Newcastle-Ottawa Scale scores ranging from 7 to 9 points.

7. Publication bias

Despite the limited number of studies included for each outcome, neither the rank correlation test nor Egger's test showed statistically significant evidence of publication bias for overall mortality ($p=0.805$), CV mortality ($p=0.564$), cancer-related mortality ($p=0.312$), and CVD ($p=0.480$) in studies with MAFLD (Supplementary Fig. 4). Similarly, for the MASLD, no significant publication bias was observed for these same outcomes: overall mortality ($p=0.458$), CV mortality ($p=0.631$), cancer-related mortality ($p=0.509$),

and CVD ($p=0.589$) (Supplementary Fig. 5).

DISCUSSION

With the introduction of MAFLD and MASLD as alternative nomenclatures for NAFLD, the differences in their diagnostic criteria have sparked ongoing debate regarding whether they accurately reflect prognostic outcomes consistent with existing NAFLD-related data. In this meta-analysis, both MAFLD and MASLD demonstrated a strong association with an increased risk of overall mortality, CV mortality, and CVD. Notably, MASLD was significantly associated with a poor prognosis for cancer-related mortality, whereas MAFLD did not exhibit a significant association. To the best of our knowledge, our study is the first meta-analysis to comprehensively evaluate prognostic outcomes in MAFLD and MASLD employing rigorous subgroup and meta-regression methodologies to address inter-study heterogeneity. By integrating data from large cohort studies across both Asian and Western populations, our analysis provides valuable insights into mortality and CV outcomes associated with these evolving diagnostic frameworks.

Compared to MASLD, MAFLD exhibited higher HRs for CV mortality (HR: 1.31 vs 1.17) and CVD (HR: 1.48 vs 1.33). This discrepancy may be attributed to the broader inclusion criteria of MAFLD, which encompasses significant alcohol consumption and various etiologies of liver disease. Although our meta-analysis did not directly compare MAFLD and MASLD due to the limited number of original studies, a recent large-scale prospective study on CV mortality between the two classifications demonstrated that MAFLD had a significantly higher risk of CV mortality than MASLD.²⁷ However, the variables adjusted for CV mortality in MAFLD varied across studies (Supplementary Table 6); in the study by Song *et al.*,¹³ statistical significance was lost after multiple adjustments. In our meta-analysis, we observed high heterogeneity among studies examining CV mortality. Subgroup analysis revealed that study design significantly influenced CV mortality outcomes, reducing heterogeneity in both MASLD and MAFLD. Notably, prospective studies showed a higher risk of CV mortality but demonstrated lower heterogeneity compared to retrospective studies. This finding may be explained by the potential for missing outcomes and inaccuracies in self-reported data inherent in retrospective study designs. Regarding MASLD specifically, participants aged ≥ 50 years demonstrated a higher HR (1.30; 95% CI, 1.23 to 1.37) compared to those under 50 years (1.13; 95% CI, 1.11 to 1.15), with minimal heterogeneity observed in both age groups. These findings reinforce the well-established association between

advancing age, increased cardiometabolic burden, and adverse CV outcomes in MASLD,⁴¹ highlighting the critical need for age-specific risk stratification in clinical practice. Additionally, while diagnostic methods for hepatic steatosis assessment contributed to heterogeneity in the overall analysis, both FLI and US consistently demonstrated increased CV mortality risk in MASLD patients.

Interestingly, MASLD was significantly associated with increased cancer-related mortality, whereas MAFLD was not. This discrepancy may be partly explained by their differing diagnostic frameworks and the resulting population characteristics. MAFLD includes individuals with coexisting liver diseases, potentially introducing competing causes of death that attenuate the observed association with cancer-related mortality. Additionally, MAFLD's broader diagnostic criteria may result in a more heterogeneous population with variable metabolic risk profiles, potentially diluting the cancer-specific mortality signal. In contrast, MASLD excludes individuals with coexisting chronic liver diseases, resulting in a more homogeneous study population with a consistent burden of metabolic dysfunction. MASLD specifically requires the presence of cardiometabolic risk factors such as obesity, T2DM, hypertension, and dyslipidemia—conditions that are well established to increase cancer risk. This more uniform metabolic burden likely strengthens the observed association with cancer-related mortality. A recently published nationwide Swedish cohort study (2002 to 2020) found that both hepatocellular carcinoma-related mortality (HR, 35.0; 95% CI, 17.0 to 72.1) and non-hepatocellular carcinoma cancer mortality (HR, 1.47; 95% CI, 1.32 to 1.63) were significantly increased in MASLD patients compared to controls.⁴² These findings from an independent large-scale cohort further support our meta-analysis results, reinforcing that MASLD identifies a population at elevated cancer risk due to its distinct metabolic and etiologic characteristics. The excessive cancer-related mortality in MASLD suggests that early multidisciplinary care should be prioritized, involving primary care physicians, hepatologists, endocrinologists, and oncologists for comprehensive risk stratification and management.⁴³ Additionally, lifestyle modifications including weight reduction, healthy diet, and regular physical activity should be reinforced as important measures to treat underlying liver disease and potentially reduce cancer risk.⁴⁴ These efforts should be supported by public health initiatives that recognize MASLD as a major global health challenge.

In the present meta-analysis, both MASLD and MAFLD were significantly associated with increased overall mortality. Despite overall consistency in the direction of effect estimates, substantial heterogeneity was observed across studies. Subgroup analyses revealed that certain study-level

characteristics contributed to this heterogeneity in overall mortality estimates, particularly in the MASLD population. Stratification by steatosis assessment methods, study region, participant age characteristics, and median follow-up duration notably reduced heterogeneity while maintaining a consistent significant association between MASLD and overall mortality. Furthermore, meta-regression analysis demonstrated that the prevalence of T2DM significantly influenced mortality outcomes in MASLD patients, suggesting that MASLD patients with concurrent diabetes may require more intensive therapeutic interventions to reduce mortality risk.

Our study has some limitations. First, given that the design of the included studies was an observational cohort study, establishing a definitive causal link between clinical outcomes and either MAFLD or MASLD remains challenging. Second, due to the limited number of studies with shared control groups, direct comparisons or network meta-analyses between MAFLD and MASLD were not feasible. As a result, the current comparisons are based on indirect evidence rather than head-to-head analyses within the same populations. This limitation introduces the possibility that observed differences reflect variations in study design, patient characteristics, comparator groups, or covariate adjustments, rather than true differences in prognostic value. To investigate potential sources of heterogeneity, we performed subgroup and meta-regression analyses where feasible; however, given the indirect nature of the comparisons, effect size estimates should be interpreted with caution. Third, patient numbers were unevenly distributed across studies, with a few large-scale studies disproportionately influencing the pooled estimates, particularly for cancer-related mortality. Additionally, most included studies failed to adequately account for competing risks, especially CV mortality, which represents a leading cause of death in these populations. This methodological limitation may have resulted in underestimation of cancer-related mortality, particularly in MAFLD populations where higher rates of early CV death could mask cancer outcomes. Future studies employing balanced sample sizes and appropriate competing risk analyses are warranted to validate these findings. Fourth, hepatic steatosis was assessed using either US or FLI, which differs in diagnostic performance and population applicability. FLI demonstrates moderate accuracy (area under the receiver operating characteristic curve, 0.84) for detecting hepatic steatosis (FLI <30: 87% sensitivity; FLI ≥60: 86% specificity),⁴⁵ but may underestimate steatosis in lean Asian individuals due to their typically lower BMI distribution, potentially leading to misclassification.⁴⁶ In contrast, US demonstrates higher accuracy (area under the receiver operating characteristic curve, 0.93; sensitivity, 84.8%; specificity, 93.6%)

for detecting moderate-to-severe hepatic steatosis, but it is operator-dependent.⁴⁷ Despite these differences in diagnostic modalities, stratified analyses by assessment method of hepatic steatosis consistently demonstrated significant associations between both MAFLD and MASLD and mortality outcomes. Fifth, we were unable to evaluate the degree of fibrosis—an important factor associated with outcomes in both MASLD and MAFLD—because the original studies did not report these values. Additionally, we could not analyze liver-related mortality and events for either condition, as only one study in each diagnostic group reported these relevant outcomes,^{14,23} preventing meaningful comparative analysis.

In conclusion, our meta-analysis demonstrated that both MAFLD and MASLD were significantly associated with increased risks of overall mortality, CV mortality, and CVD. Distinctively, MASLD showed an additional significant association with cancer-related mortality that was not observed with MAFLD. Given the rising prevalence of SLD in conjunction with metabolic dysfunction-related conditions, our findings may provide valuable insights into determining the most clinically relevant nomenclature for classifying individuals with SLD, potentially improving prevention strategies for mortality and CV risk. These results could inform the development of more refined and targeted surveillance approaches. However, as our analysis was based on indirect comparisons across heterogeneous studies, the observed differences between MAFLD and MASLD should be interpreted with caution. Prospective, head-to-head studies are warranted to validate and further elucidate these associations.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study concept and design; Data acquisition; Data analysis and interpretation: all authors. Drafting of the manuscript: all authors. Critical revision of the manuscript for important intellectual content: J.Y., Y.R.K., S.K.N., J.A., J.H.S. Statistical analysis: all authors. Obtained funding: J.H.S. Study supervision: J.A., J.H.S. Approval of final manuscript: all authors.

ORCID

Jiwon Yang	https://orcid.org/0009-0002-1577-1759
Ye Rim Kim	https://orcid.org/0009-0001-8925-4298
Seong Kyun Na	https://orcid.org/0000-0002-1767-0233
Seonok Kim	https://orcid.org/0000-0001-9010-5460
Jihyun An	https://orcid.org/0000-0002-0110-0965
Ju Hyun Shim	https://orcid.org/0000-0002-7336-1371

SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at <https://doi.org/10.5009/gnl250275>.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data were created or analyzed in this study. All articles referenced in this manuscript are publicly accessible through PubMed, Embase, CINAHL, the Cochrane Library, and Web of Science.

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