

Individual Cardiometabolic Risk Factors and Long-Term Cardiovascular Outcomes in Metabolic Dysfunction-Associated Steatotic Liver Disease

Naoki Shibata

masa5ne0088@yahoo.co.jp

Ogaki Municipal Hospital: Ogaki Shimin Byoin <https://orcid.org/0000-0001-6748-1505>

Yasuhiro Morita

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Takanori Ito

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Yasunori Kanzaki

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Naoki Watanabe

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Naoki Yoshioka

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Yoshihito Arao

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Hiroyuki Miyazawa

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Satoshi Yasuda

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Hidenori Toyoda

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Itsuro Morishima

Ogaki Municipal Hospital: Ogaki Shimin Byoin

Research Article

Keywords: metabolic dysfunction-associated steatotic liver disease, cardiometabolic risk factors, diabetes mellitus, high-density lipoprotein cholesterol, cardiovascular outcomes

Posted Date: October 22nd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11164764/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Abstract

Background:

Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined by hepatic steatosis and at least one of five cardiometabolic risk factors (CMRFs); however, whether individual CMRFs carry equivalent prognostic information for cardiovascular outcomes remains unclear.

Methods:

We retrospectively analyzed 2,962 patients with MASLD who underwent abdominal ultrasonography between 2006 and 2015. Patients were randomly assigned to derivation ($n = 2,073$) and validation ($n = 889$) cohorts. Associations of five MASLD-qualifying CMRFs with major adverse cardiac and cerebrovascular events (MACCE) were evaluated using multivariable Cox regression. Patients were subsequently classified according to CMRFs independently associated with MACCE.

Results:

During follow-up of up to 10 years, 183 MACCE occurred in the derivation cohort. After adjustment for age, sex, and all five CMRFs, diabetes mellitus (DM) (hazard ratio [HR], 1.42; 95% confidence interval [CI], 1.06–1.90) and low high-density lipoprotein cholesterol (HDL-C) (HR, 1.43; 95% CI, 1.05–1.95) were independently associated with MACCE, whereas body mass index ≥ 23 kg/m², hypertension, and hypertriglyceridemia were not. Patients were classified as having neither factor, DM alone, low HDL-C alone, or both factors. MACCE risk differed significantly among the four groups in both the derivation and validation cohorts (log-rank $P < 0.001$ and $P = 0.019$, respectively). In the validation cohort, the 5-year time-dependent area under the curve was 0.757 for age and sex, 0.763 after incorporating CMRF count, and 0.777 after incorporating the DM/low HDL-C classification.

Conclusions:

Among patients with MASLD, individual CMRFs were not equally associated with cardiovascular and cerebrovascular outcomes. The type and combination of CMRFs, particularly DM and low HDL-C, may provide useful prognostic information beyond CMRF count alone.

Retrospectively registered: The study was approved by the ethics committee of Ogaki Municipal Hospital (approval number: 20230928-11).

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as a systemic cardiometabolic disorder rather than an isolated liver disease[1–4]. Cardiovascular disease represents a major determinant of long-term prognosis in patients with MASLD, with affected individuals experiencing an increased risk of cardiovascular events and mortality[3, 5, 6]. Accordingly, identification

of patients with MASLD who are at increased risk of major adverse cardiac and cerebrovascular events (MACCE) is clinically important. Although hepatic fibrosis and disease severity have been associated with cardiovascular outcomes, cardiovascular risk in MASLD is also closely linked to the accompanying cardiometabolic abnormalities[5–7].

MASLD is defined by the presence of hepatic steatosis together with at least one of five cardiometabolic risk factors (CMRFs) : overweight or obesity, impaired glucose regulation or diabetes mellitus (DM), hypertension, hypertriglyceridemia, and low high-density lipoprotein cholesterol (HDL-C).[1] Although these CMRFs are treated equivalently for the diagnosis of MASLD, they represent distinct metabolic abnormalities and may not contribute equally to subsequent cardiovascular risk. In our previous study of patients with MASLD, the accumulation of CMRFs, together with age, enabled stratification of the risk of major adverse cardiac events, suggesting that the cardiometabolic burden is relevant to cardiovascular prognosis[8]. This finding highlighted the importance of overall cardiometabolic burden; however, a simple count of CMRFs does not account for differences in the prognostic significance of individual components. Indeed, emerging studies suggest that cardiovascular and mortality risks may differ according to the type and combination of CMRFs[9–11]. Whether specific CMRFs carry greater prognostic information than others among patients with MASLD therefore remains incompletely understood.

Therefore, the present study aimed to investigate the associations of each of the five MASLD-qualifying CMRFs with long-term cardiovascular and cerebrovascular outcomes. Using derivation and validation cohorts, we further evaluated whether classification based on CMRFs independently associated with MACCE could stratify subsequent risk and compared its prognostic discrimination with that based on the number of CMRFs.

2. Materials and methods

2.1. Study population, data collection, and definitions

We retrospectively identified 13,368 consecutive patients with ultrasonographic hepatic steatosis who underwent abdominal ultrasonography between January 2006 and December 2015 (Fig. 1).

Ultrasonography was performed either as part of routine health examinations or for the evaluation of clinical symptoms. All ultrasonographic images were independently reviewed by at least two experienced physicians who were blinded to the patients' clinical information. Hepatic steatosis was assessed using a previously reported ultrasonographic fatty liver scoring system (Supplementary Table 1).

Demographic characteristics, medical history, and laboratory data obtained within 3 months of the ultrasonographic examination were extracted from the electronic medical records. Clinical follow-up was performed using hospital medical records and, when necessary, systematic telephone interviews. Follow-up was censored at the date of the last hospital visit or the last confirmed telephone contact.

This retrospective observational study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ogaki Municipal Hospital (approval No. 20230928-11). The requirement for written informed consent was waived, and an opt-out approach was adopted through the hospital website.

2.2. Definition of MASLD

MASLD was defined according to the international multi-society consensus statement as the presence of hepatic steatosis together with at least one cardiometabolic risk factor (CMRF)[1]. The following five CMRFs were evaluated: body mass index (BMI) ≥ 23 kg/m², diabetes mellitus (DM), hypertension, hypertriglyceridemia, and low high-density lipoprotein cholesterol (HDL-C). BMI ≥ 23 kg/m² was used according to the consensus criteria for Asian populations. Impaired glucose regulation or DM was defined as fasting plasma glucose ≥ 100 mg/dL, HbA1c $\geq 5.7\%$, a previous diagnosis of DM, or the use of antidiabetic medication. Hypertension was defined as systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg, or the use of antihypertensive medication. Hypertriglyceridemia was defined as triglycerides ≥ 150 mg/dL or lipid-lowering therapy. Low HDL-C was defined as < 40 mg/dL in men and < 50 mg/dL in women or lipid-lowering therapy. MASLD was diagnosed in patients with hepatic steatosis and at least one of these five CMRFs.

2.3. Outcomes and study endpoint

The primary outcome was major adverse cardiac and cerebrovascular events (MACCE), defined as a composite of cardiac death, nonfatal myocardial infarction, coronary revascularization, neurological death, and stroke. Clinical outcomes were identified through review of hospital medical records and systematic follow-up. Time-to-event analyses were censored at 10 years; patients without an event were censored at the date of the last confirmed follow-up or at 10 years, whichever occurred first. Patients without an event were censored at the date of the last confirmed follow-up.

2.4. Statistical analysis

Patients were randomly assigned to a derivation cohort (70%) and a validation cohort (30%) using simple random sampling[12, 13]. Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range), as appropriate, and categorical variables as number (percentage). Group comparisons were performed using the Student's t test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. In the derivation cohort, multivariable Cox proportional hazards regression analysis was performed to evaluate the independent associations between the five cardiometabolic risk factors defining MASLD and the primary outcome after adjustment for age and sex. Based on the results of the multivariable analysis, a simplified risk classification was developed using the independently associated factors. Kaplan–Meier analysis with the log-rank test was used to compare cumulative event rates among the risk groups in both the derivation and validation cohorts. The 5-year time-dependent area under the curve (AUC) was calculated for models incorporating age and sex, the number of MASLD-qualifying CMRFs, and the derived risk classification.[14] A two-sided P value < 0.05 was considered statistically significant. All

statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Study population and baseline characteristics

A total of 2,962 patients with MASLD were included in the present study and randomly assigned to the derivation (n = 2,073) and validation (n = 889) cohorts (Fig. 1). Baseline characteristics were generally comparable between the two cohorts (Supplementary Table S2). During follow-up, MACCE occurred in 183 patients in the derivation cohort. Baseline characteristics according to the occurrence of MACCE are shown in Table 1. Patients who experienced MACCE were older, more frequently male, and had a higher prevalence of DM and low HDL-C than those without MACCE. In contrast, the prevalence of BMI ≥ 23 kg/m², hypertension, and hypertriglyceridemia did not differ significantly between the groups. The distribution of the number of MASLD-qualifying CMRFs also differed significantly according to the occurrence of MACCE (P = 0.001).

Table 1

Baseline characteristics according to the occurrence of major adverse cardiac and cerebrovascular events in the derivation cohort

Characteristics	MACCE (-) (n = 1,890)	MACCE (+) (n = 183)	P value
Demographics and history			
Age, years	61.0 (52.0–69.0)	67.0 (61.0–74.0)	< 0.001
Male sex	976 (51.6%)	125 (68.3%)	< 0.001
Body mass index, kg/m ²	25.2 (23.4–27.6)	24.9 (23.3–27.1)	0.36
Systolic blood pressure, mmHg	147.0 (133.0–163.0)	160.0 (145.0–178.0)	< 0.001
Diastolic blood pressure, mmHg	78.0 (68.0–87.0)	75.0 (66.0–84.0)	0.009
Hypertension	1,572 (83.2%)	160 (87.4%)	0.27
Diabetes mellitus	673 (35.6%)	91 (49.7%)	< 0.001
Current smoking	485 (26.6%)	56 (30.9%)	0.28
Laboratory findings			
Aspartate aminotransferase, U/L	24.0 (19.0–34.0)	23.0 (18.0–33.0)	0.24
Alanine aminotransferase, U/L	27.0 (18.0–46.0)	24.0 (17.0–36.0)	0.004
γ-glutamyl transferase, U/L	34.0 (22.0–56.0)	32.0 (21.0–50.0)	0.37
Platelet count	24.5 (20.8–29.5)	22.7 (18.9–28.4)	0.002
Albumin, g/dL	4.4 (4.2–4.6)	4.3 (4.1–4.5)	< 0.001
Estimated glomerular filtration rate, mL/min/1.73 m ²	79.4 (68.3–92.8)	72.6 (60.3–84.2)	< 0.001
Hemoglobin A1c, %	5.7 (5.2–7.1)	6.1 (5.5–7.8)	< 0.001
Triglycerides, mg/dL	133.0 (95.0–191.0)	144.0 (102.0–193.0)	0.24
HDL cholesterol, mg/dL	47.0 (40.0–56.0)	42.0 (35.0–51.0)	< 0.001
LDL cholesterol, mg/dL	125.0 (104.0–148.0)	110.0 (89.0–140.0)	< 0.001
Data are presented as median (interquartile range) or number (percentage).			
HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACCE, major adverse cardiac and cerebrovascular events; MASLD, metabolic dysfunction-associated steatotic liver disease.			

Characteristics	MACCE (-) (n = 1,890)	MACCE (+) (n = 183)	P value
Demographics and history			
MASLD qualifying cardiometabolic risk factors			
BMI $\geq$ 23 kg/m ²	1,510 (79.9%)	144 (78.7%)	0.80
Triglycerides $\geq$ 150 mg/dL	798 (42.2%)	87 (47.5%)	0.21
Low HDL cholesterol	796 (42.1%)	95 (51.9%)	0.013
Number of MASLD qualifying factors			0.001
1	214 (11.3%)	13 (7.1%)	
2	543 (28.7%)	37 (20.2%)	
3	628 (33.2%)	60 (32.8%)	
4	360 (19.0%)	55 (30.1%)	
5	145 (7.7%)	18 (9.8%)	
Data are presented as median (interquartile range) or number (percentage).			
HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACCE, major adverse cardiac and cerebrovascular events; MASLD, metabolic dysfunction-associated steatotic liver disease.			

Association of individual cardiometabolic risk factors with MACCE

In the multivariable Cox proportional hazards analysis including age, sex, and all five MASLD-qualifying CMRFs, DM and low HDL-C were independently associated with MACCE in the derivation cohort (Table 2). The adjusted HRs were 1.42 (95% CI, 1.06–1.90; P = 0.019) for DM and 1.43 (95% CI, 1.05–1.95; P = 0.022) for low HDL-C. In contrast, BMI $\geq$ 23 kg/m², hypertension, and hypertriglyceridemia were not independently associated with MACCE. Older age and male sex were also independently associated with MACCE.

Table 2

Multivariable Cox proportional hazards analysis for MACCE in the derivation and validation cohorts

Variable	Derivation HR (95% CI)	P value	Validation HR (95% CI)	P value
Age, per 1-year increase	1.05 (1.03–1.06)	< 0.001	1.06 (1.03–1.08)	< 0.001
Male sex	2.28 (1.66–3.13)	< 0.001	4.18 (2.51–6.97)	< 0.001
Diabetes mellitus	1.42 (1.06–1.90)	0.018	1.35 (0.89–2.05)	0.16
Low HDL cholesterol	1.43 (1.05–1.95)	0.02	1.68 (1.09–2.59)	0.02
Hypertension	1.26 (0.81–1.95)	0.31	1.96 (0.98–3.91)	0.056
Hypertriglyceridemia	1.10 (0.81–1.49)	0.56	0.91 (0.59–1.40)	0.66
Body mass index ≥ 23 kg/m ²	1.10 (0.77–1.56)	0.62	0.85 (0.53–1.38)	0.52
Hazard ratios were estimated using a multivariable Cox proportional hazards model including age, sex, diabetes mellitus, low HDL cholesterol, hypertension, hypertriglyceridemia, and body mass index ≥ 23 kg/m ² .				
BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events.				

Based on these findings, patients were classified into four groups according to the presence or absence of DM and low HDL-C: neither factor, DM alone, low HDL-C alone, and both factors. Kaplan–Meier analysis demonstrated significant differences in event-free survival among the four groups in both the derivation and validation cohorts (log-rank $P < 0.001$ and $P = 0.019$, respectively; Fig. 2A and B). In the derivation cohort, compared with patients with neither factor, the age- and sex-adjusted HRs for MACCE were 1.42 (95% CI, 0.93–2.16; $P = 0.100$) for DM alone, 1.47 (95% CI, 0.98–2.22; $P = 0.063$) for low HDL-C alone, and 2.12 (95% CI, 1.42–3.16; $P < 0.001$) for both factors (Table 3).

Table 3

Association of the diabetes mellitus and low HDL cholesterol classification with MACCE in the derivation and validation cohorts

Group	Derivation HR (95% CI)	P value	Validation HR (95% CI)	P value
Neither DM nor low HDL	Reference		Reference	
DM only	1.42 (0.93–2.16)	0.10	2.02 (1.09–3.73)	0.025
Low HDL only	1.47 (0.98–2.22)	0.063	2.34 (1.29–4.23)	0.005
Both DM and low HDL	2.12 (1.42–3.16)	< 0.001	2.19 (1.19–4.03)	0.012
Hazard ratios were adjusted for age and sex. The reference group comprised patients with neither diabetes mellitus nor low HDL cholesterol.				
CI, confidence interval; DM, diabetes mellitus; HDL, high-density lipoprotein; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events.				

Similar findings were observed in the validation cohort. Compared with patients with neither factor, the adjusted HRs for MACCE were 2.02 (95% CI, 1.09–3.73; $P = 0.025$) for DM alone, 2.34 (95% CI, 1.29–4.23; $P = 0.005$) for low HDL-C alone, and 2.19 (95% CI, 1.19–4.03; $P = 0.012$) for both factors (Table 3).

Predictive performance

Model discrimination for 5-year MACCE was assessed in the validation cohort (Supplementary Table S4). The 5-year time-dependent AUC was 0.757 for the model including age and sex, 0.763 for the model including age, sex, and the number of MASLD-qualifying CMRFs, and 0.777 for the model including age, sex, and the DM/low HDL-C classification.

4. Discussion

In the present study, we investigated the prognostic significance of individual CMRFs used to define MASLD for long-term cardiovascular and cerebrovascular outcomes. The main findings were as follows. First, among the five MASLD-qualifying CMRFs, DM and low HDL-C were independently associated with MACCE after adjustment for age, sex, and the other CMRFs, whereas BMI ≥ 23 kg/m², hypertension, and hypertriglyceridemia were not. Second, a simple classification based on the presence or absence of DM and low HDL-C stratified the risk of MACCE in the derivation cohort, with similar findings observed in the validation cohort. Finally, model discrimination in the validation cohort showed modest numerical improvement when the DM/low HDL-C classification was added to age and sex, compared with the addition of the number of MASLD-qualifying CMRFs. These findings suggest that the individual components used to define MASLD may not carry equivalent prognostic information for cardiovascular and cerebrovascular outcomes and that the type and combination of CMRFs, rather than their number alone, may be relevant for risk stratification.

Previous studies have also suggested that the prognostic implications of individual CMRFs may differ among patients with MASLD. Dukewich et al. reported that high blood pressure, glucose intolerance, and low HDL-C were independently associated with all-cause mortality, whereas other CMRFs were not, suggesting heterogeneity in the prognostic significance of individual metabolic abnormalities[9]. Similarly, another study evaluating both the type and number of CMRFs identified elevated glucose and hypertension as independent predictors of cardiac-specific mortality[15]. Although the specific CMRFs associated with outcomes have differed across studies, these observations support the concept that the composition of cardiometabolic abnormalities, rather than their mere presence or number, may be relevant to risk stratification in MASLD. In the present study, DM and low HDL-C were independently associated with MACCE. DM is a well-established cardiovascular risk factor and may represent a more advanced stage of metabolic dysfunction characterized by insulin resistance and chronic hyperglycemia[16]. These abnormalities promote oxidative stress, systemic inflammation, and endothelial dysfunction, thereby accelerating atherosclerosis and increasing cardiovascular risk.[15, 17, 18] Low HDL-C may similarly identify an adverse metabolic phenotype rather than merely representing an isolated lipid abnormality[19]. In the setting of insulin resistance, low HDL-C commonly clusters with hypertriglyceridemia, triglyceride-rich lipoproteins, and small dense LDL particles, constituting an atherogenic dyslipidemic phenotype.[6, 20, 21] Because insulin resistance is a central metabolic feature of MASLD, DM and low HDL-C may therefore identify patients with a greater burden of systemic metabolic dysfunction and a more atherogenic cardiovascular risk profile.

In contrast, BMI ≥ 23 kg/m², hypertension, and hypertriglyceridemia were not independently associated with MACCE in the present study. Several factors may explain these findings. First, BMI may not adequately capture metabolically adverse adiposity, particularly in Asian populations. Asian individuals tend to accumulate visceral and ectopic fat and develop insulin resistance and other metabolic abnormalities at lower BMI levels than Western populations, and lean MASLD is relatively common in Japan[22, 23]. Furthermore, a recent meta-analysis showed that lean MASLD was associated with cardiovascular outcomes despite a more favorable conventional cardiometabolic profile, including lower prevalences of hypertension and dyslipidemia, suggesting that BMI alone may not fully reflect cardiovascular risk in MASLD[24]. Thus, dichotomizing BMI at 23 kg/m² may have limited its ability to discriminate cardiovascular risk in our Japanese cohort. Second, hypertension was not independently associated with MACCE in our cohort, although previous studies have reported significant associations between hypertension and cardiovascular outcomes in patients with MASLD or NAFLD[15, 25]. The discrepancy may reflect differences in study populations, cardiovascular endpoints, and definitions of hypertension. Notably, in the present study, systolic blood pressure was significantly higher among patients who developed MACCE, whereas the prevalence of hypertension did not differ significantly between those with and without MACCE. This finding suggests that categorizing hypertension simply as present or absent may not fully capture the continuous cardiovascular risk associated with blood pressure levels, severity, duration, and treatment status. Finally, hypertriglyceridemia and low HDL-C frequently coexist as manifestations of insulin resistance and atherogenic dyslipidemia[6]. Because hypertriglyceridemia and low HDL-C share underlying metabolic pathways [19, 26], their prognostic

information may partly overlap when considered simultaneously. This potential overlap may have attenuated the independent association of hypertriglyceridemia in our multivariable model. Nevertheless, hypertriglyceridemia has been associated with cardiac-specific mortality in other MASLD populations[15], and elevated triglycerides remain an established marker of cardiometabolic and cardiovascular risk[27]. Therefore, the lack of independent associations for BMI, hypertension, and hypertriglyceridemia in the present study should not be interpreted as evidence that these factors are clinically unimportant, but rather as suggesting that their prognostic contributions may vary according to population, phenotype, and the other cardiometabolic abnormalities considered simultaneously.

Limitations

Several limitations should be acknowledged. First, this was a retrospective, single-center observational study, and therefore selection bias, unmeasured confounding, and residual confounding cannot be excluded. Second, the study population was enrolled between 2006 and 2015. During and after this period, the management of cardiometabolic risk factors, particularly diabetes and dyslipidemia, as well as the treatment of coronary artery disease, including PCI, has substantially evolved. These temporal changes may have influenced subsequent cardiovascular outcomes, and therefore, the associations observed in this cohort may not fully reflect those in contemporary practice. Third, the five CMRFs were assessed at baseline, and changes in metabolic status and medical treatment during follow-up were not considered. Thus, our findings reflect the prognostic significance of the cardiometabolic phenotype at baseline rather than the effects of persistent or time-varying metabolic abnormalities. Fourth, waist circumference was not available in our database. Therefore, the overweight/obesity criterion for MASLD was assessed using BMI alone, which may have resulted in misclassification of some patients with central adiposity who did not meet the BMI threshold. Fifth, CMRFs were analyzed according to the dichotomous thresholds used to define MASLD. Such categorization may not fully capture the severity or continuous risk associated with individual factors, as illustrated by the higher systolic blood pressure among patients who developed MACCE despite the absence of an independent association with hypertension as a categorical variable. Sixth, hepatic steatosis was diagnosed by ultrasonography rather than histological or more quantitative imaging assessment, and the severity of hepatic fibrosis was not the primary focus of the present analysis. Finally, although the findings were reproduced in an independent validation subset, both the derivation and validation cohorts were derived from the same single-center population. External validation in contemporary, geographically and ethnically diverse MASLD populations is therefore warranted.

Conclusion

Among patients with MASLD, the five CMRFs used to define MASLD were not equally associated with long-term cardiovascular and cerebrovascular outcomes. DM and low HDL-C were independently associated with MACCE, and their presence identified patients at higher risk in both the derivation and validation cohorts. These findings suggest that the type and combination of CMRFs, in addition to their number, may provide useful information for cardiovascular risk stratification in patients with MASLD.

Declarations

Competing Interests: The authors have no conflicts of interest to disclose.

References

1. M.E. Rinella, J.V. Lazarus, V. Ratziu, S.M. Francque, A.J. Sanyal, F. Kanwal, D. Romero, M.F. Abdelmalek, Q.M. Anstee, J.P. Arab, M. Arrese, R. Bataller, U. Beuers, J. Boursier, E. Bugianesi, C.D. Byrne, G.E. Castro Narro, A. Chowdhury, H. Cortez-Pinto, D.R. Cryer, K. Cusi, M. El-Kassas, S. Klein, W. Eskridge, J. Fan, S. Gawrieh, C.D. Guy, S.A. Harrison, S.U. Kim, B.G. Koot, M. Korenjak, K.V. Kowdley, F. Lacaille, R. Loomba, R. Mitchell-Thain, T.R. Morgan, E.E. Powell, M. Roden, M. Romero-Gómez, M. Silva, S.P. Singh, S.C. Sookoian, C.W. Spearman, D. Tiniakos, L. Valenti, M.B. Vos, V.W.-S. Wong, S. Xanthakos, Y. Yilmaz, Z. Younossi, A. Hobbs, M. Villota-Rivas, P.N. Newsome, NAFLD Nomenclature consensus group, A multisociety Delphi consensus statement on new fatty liver disease nomenclature, *Hepatology* 78 (2023) 1966–1986.
2. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity, EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary, *Diabetologia* 67 (2024) 2375–2392.
3. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO), EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD), *J. Hepatol.* 81 (2024) 492–542.
4. N. Akuta, T. Kogiso, K. Ikejima, M. Otsuka, T. Kawaguchi, M. Kawanaka, H. Takahashi, N. Tamaki, H. Nakagawa, H. Hikita, H. Fujii, K. Yamaguchi, M. Yoneda, K. Kon, A. Uchiyama, Y. Seko, S. Sakane, R. Shigefuku, N. Fujiwara, M. Iwaki, T. Kobayashi, T. Adachi, Y. Takeuchi, T. Tsutsumi, D. Nakano, K. Shibayama, N. Urata, H. Miyaaki, H. Kuroda, M. Koseki, H. Sone, Y. Matsubayashi, K. Kakisaka, A. Takai, K. Notsumata, M. Seike, Y. Takei, Y. Takeyama, S. Eguchi, S. Watanabe, H. Isomoto, H. Yotsuyanagi, T. Itoi, T. Takehara, S. Mochida, Evidence-based clinical practice guidelines for metabolic dysfunction-associated steatotic liver disease (MASLD) 2026, *J. Gastroenterol.* 61 (2026) 693–710.
5. B. Ismail, P. Nabilou, L.L. Gluud, S. Møller, Cardiovascular implications of MASLD: overview of the evidence, *Scand. J. Gastroenterol.* 60 (2025) 910–918.
6. A. Mellemkjær, M.B. Kjær, D. Haldrup, H. Grønbaek, K.L. Thomsen, Management of cardiovascular risk in patients with metabolic dysfunction-associated steatotic liver disease, *Eur. J. Intern. Med.* 122 (2024) 28–34.
7. N. Shibata, T. Ito, H. Toyoda, A. Tanaka, Y. Morita, Y. Kanzaki, N. Watanabe, N. Yoshioka, S. Yasuda, I. Morishima, Predictability of noninvasive liver fibrosis score for cardiac events in patients with nonalcoholic fatty liver disease, *Nutr. Metab. Cardiovasc. Dis.* 34 (2024) 2115–2123.

8. N. Shibata, Y. Morita, T. Ito, Y. Kanzaki, N. Watanabe, N. Yoshioka, Y. Arao, S. Yasuda, Y. Koshiyama, H. Toyoda, I. Morishima, A machine learning algorithm for stratification of risk of cardiovascular disease in metabolic dysfunction-associated steatotic liver disease, *Eur. J. Intern. Med.* 129 (2024) 62–70.
9. M. Dukewich, J.L. Dodge, L. Yuan, N.A. Terrault, Differential effects of cardiometabolic risk factors on all-cause mortality in United States adults with metabolic dysfunction-associated steatotic liver disease (MASLD), *Clin. Gastroenterol. Hepatol.* 24 (2026) 1344–1353.
10. J.-H. Kim, Y. Lee, C.-M. Nam, Y.-J. Kwon, J.-W. Lee, Impact of cardiometabolic risk factors for metabolic dysfunction-associated steatotic liver disease on mortality, *Nutr. Metab. Cardiovasc. Dis.* 35 (2025) 103965.
11. N. Tamaki, T. Kimura, S.-I. Wakabayashi, T. Umemura, N. Izumi, R. Loomba, M. Kurosaki, Cardiometabolic criteria as predictors and treatment targets of liver-related events and cardiovascular events in metabolic dysfunction-associated steatotic liver disease, *Aliment. Pharmacol. Ther.* 60 (2024) 1033–1041.
12. N. Shibata, Y. Morita, Y. Kanzaki, N. Watanabe, I. Morishima, Intravascular ultrasound-guided balloon spacer technique for unstable device passage during LAD PCI, *JACC Case Rep.* (2026) 109648.
13. S. Komeyama, T. Kondo, T. Okumura, N. Shibata, T. Imaizumi, K. Dohi, H. Izawa, N. Ohte, T. Amano, T. Murohara, Clinical impact of cardiac arrest in patients with fulminant myocarditis requiring veno-arterial extracorporeal membrane oxygenation: Insights from the CHANGE PUMP 2 study, *Int. Heart J.* 67 (2026) 228–237.
14. A.N. Kamarudin, T. Cox, R. Kolamunnage-Dona, Time-dependent ROC curve analysis in medical research: current methods and applications, *BMC Med. Res. Methodol.* 17 (2017) 53.
15. Y. Zhang, Y. Wang, Y. Xu, X. Liu, Y. Qu, T. Li, Risk stratification for patients with MASLD based on cardiometabolic risk factors, *BMC Public Health* 26 (2026). <https://doi.org/10.1186/s12889-026-26961-w>.
16. A.W. Khan, K.A.M. Jandeleit-Dahm, Atherosclerosis in diabetes mellitus: novel mechanisms and mechanism-based therapeutic approaches, *Nat. Rev. Cardiol.* 22 (2025) 482–496.
17. N.W.S. Chew, X.H. Pan, B. Chong, C. Chandramouli, M. Muthiah, C.S.P. Lam, Type 2 diabetes mellitus and cardiometabolic outcomes in metabolic dysfunction-associated steatotic liver disease population, *Diabetes Res. Clin. Pract.* 211 (2024) 111652.
18. G.A. Mensah, N. Arnold, S.D. Prabhu, P.M. Ridker, F.K. Welty, Inflammation and cardiovascular disease: 2025 ACC scientific statement: A report of the American college of cardiology, *J. Am. Coll. Cardiol.* 87 (2026) 1381–1404.
19. L. Luciani, M. Pedrelli, P. Parini, Modification of lipoprotein metabolism and function driving atherogenesis in diabetes, *Atherosclerosis* 394 (2024) 117545.
20. J.I. Mechanick, M.E. Farkouh, J.D. Newman, W.T. Garvey, Cardiometabolic-based chronic disease, adiposity and dysglycemia drivers: JACC State-of-the-Art Review, *J. Am. Coll. Cardiol.* 75 (2020) 525–538.

21. C. Hashem, S.E. Altin, J.R. Guyton, W.E. Boden, Nonlinearity of the inverse relationship between high-density lipoprotein (HDL) cholesterol and incident cardiovascular risk: Is it time to revisit the “HDL hypothesis”?, *J. Clin. Lipidol.* 19 (2025) 238–246.
22. Y. Seko, K. Yamaguchi, Management of MASLD/MASH: challenges, innovations, and the future of patient-centered care in Japan, *J. Gastroenterol.* 61 (2026) 880–908.
23. T. Ito, M. Ishigami, B. Zou, T. Tanaka, H. Takahashi, M. Kurosaki, M. Maeda, K.N. Thin, K. Tanaka, Y. Takahashi, Y. Itoh, K. Oniki, Y. Seko, J. Saruwatari, M. Kawanaka, M. Atsukawa, H. Hyogo, M. Ono, E. Ogawa, S.D. Barnett, C.D. Stave, R.C. Cheung, M. Fujishiro, Y. Eguchi, H. Toyoda, M.H. Nguyen, The epidemiology of NAFLD and lean NAFLD in Japan: a meta-analysis with individual and forecasting analysis, 1995-2040, *Hepatol. Int.* 15 (2021) 366–379.
24. N. Nso, D. Mergen, M. Ikram, V. Macrinici, K. Hussain, K. Lee, D. Ugwendum, M. Trimingham, S. Balasubramanian, R. Sam, B. Njei, Cardiovascular morbidity and mortality in lean vs. non-lean MASLD: A comprehensive meta-analysis, *Curr. Probl. Cardiol.* 49 (2024) 102569.
25. M. Li, W. Chen, Y. Deng, W. Xie, Impacts of cardiometabolic risk factors and alcohol consumption on all-cause mortality among MASLD and its subgroups, *Nutr. Metab. Cardiovasc. Dis.* 34 (2024) 2085–2094.
26. H.E. Bays, C.F. Kirkpatrick, K.C. Maki, P.P. Toth, R.T. Morgan, J. Tondt, S.M. Christensen, D.L. Dixon, T.A. Jacobson, Obesity, dyslipidemia, and cardiovascular disease: A joint expert review from the Obesity Medicine Association and the National Lipid Association 2024, *J. Clin. Lipidol.* 18 (2024) e320–e350.
27. R.S. Blumenthal, P.B. Morris, M. Gaudino, H.M. Johnson, T.S. Anderson, V.A. Bittner, R. Blankstein, L.C. Brewer, L. Cho, S.D. de Ferranti, E. Gianos, T.J. Gluckman, K.F. Gradney, I. Isiadinso, D.M. Lloyd-Jones, J.C. Marrs, S.S. Martin, K.H. McLain, L.S. Mehta, S. Mora, W.M. Mulugeta, P. Natarajan, A.M. Navar, C.E. Orringer, T.S. Polonsky, H.R. Reynolds, J.J. Saseen, M.D. Shapiro, D.E. Soffer, S.A. Tynes, C.D. Villavaso, S.S. Virani, J.T. Wilkins, 2026
ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of Dyslipidemia: A report of the American college of cardiology/American heart association joint committee on clinical practice guidelines, *J. Am. Coll. Cardiol.* 87 (2026) 2624–2757.

Figures

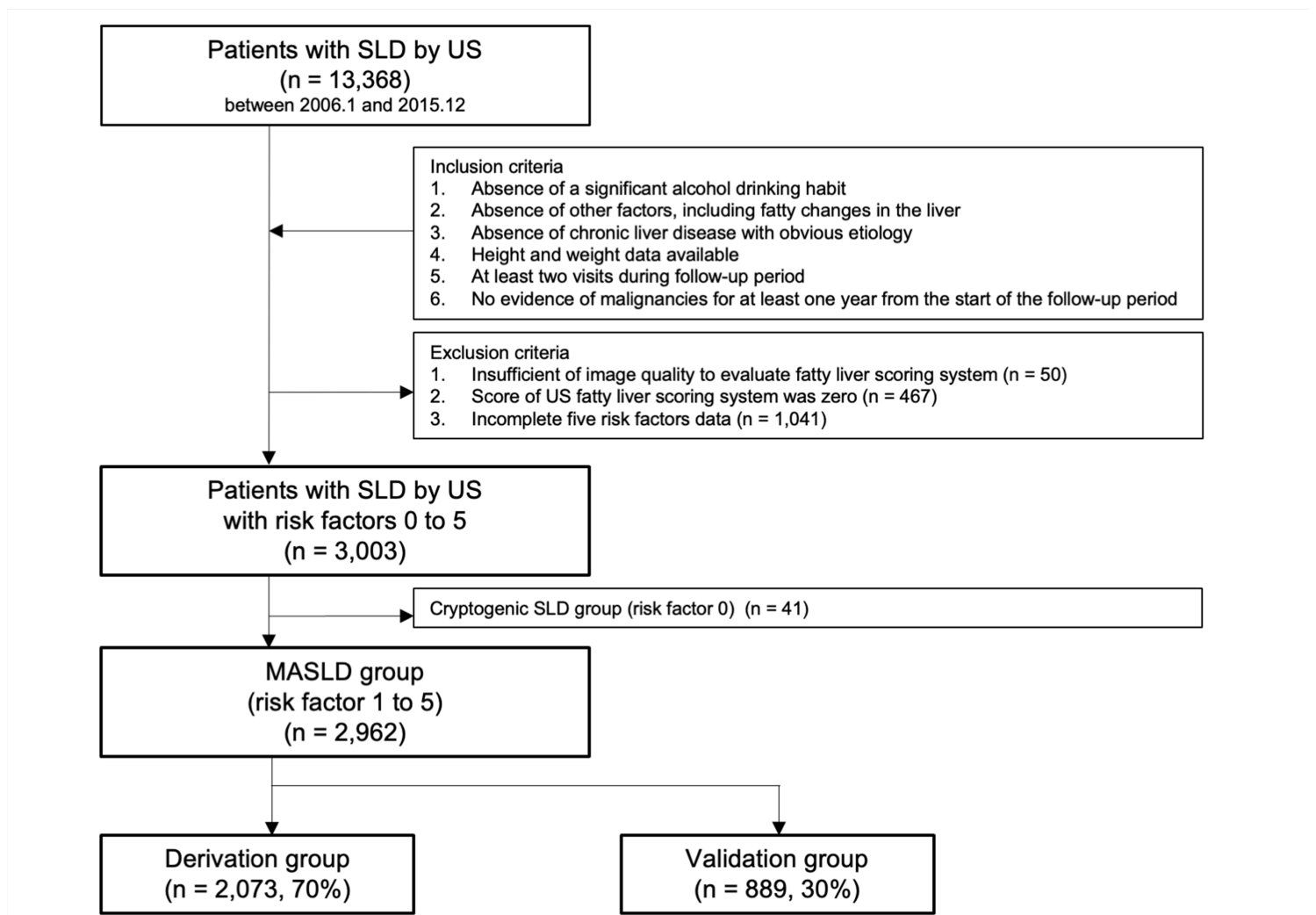


Figure 1

Flowchart of the patient selection process

MASLD, metabolic dysfunction-associated steatotic liver disease; SLD, Steatotic liver disease; US, ultrasonography

A. Derivation cohort

B. Validation cohort

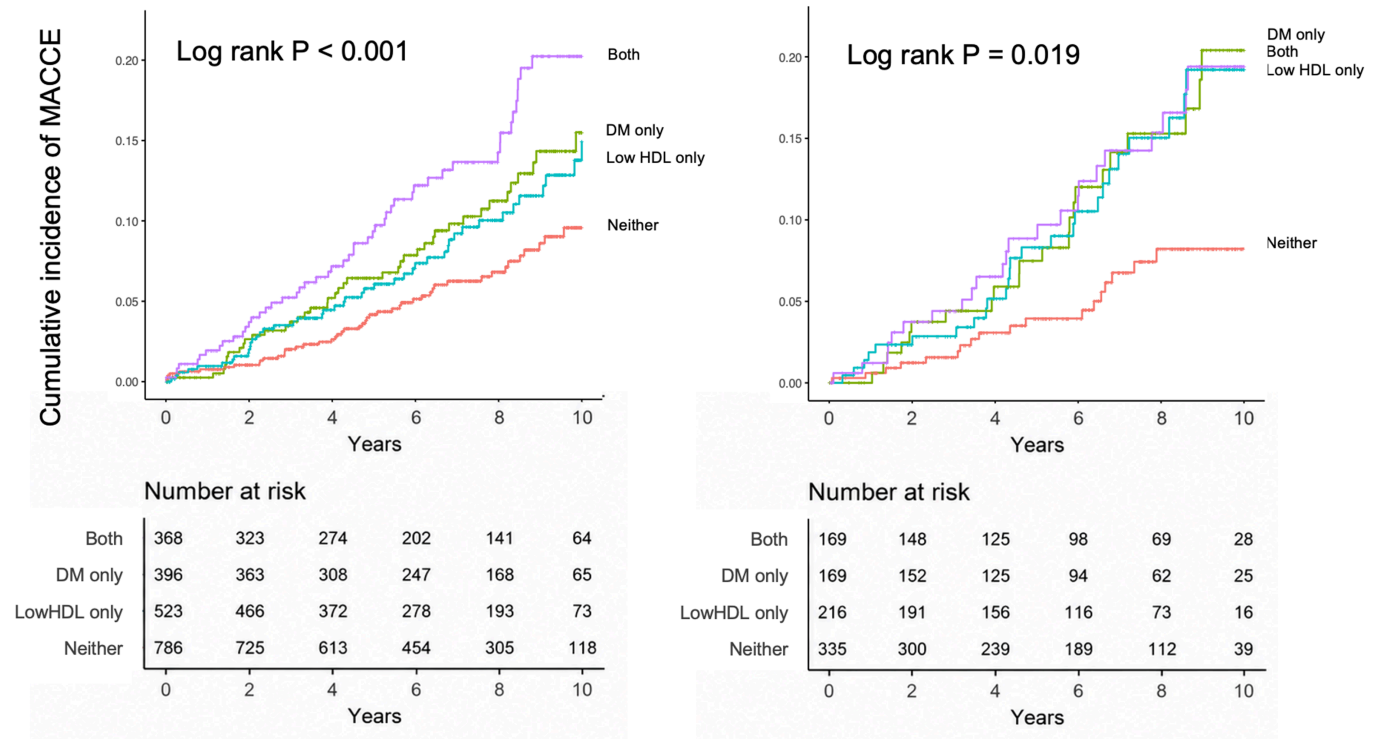


Figure 2

Cumulative incidence of major adverse cardiac and cerebrovascular events according to diabetes mellitus and low high-density lipoprotein cholesterol.

Kaplan–Meier curves showing the cumulative incidence of major adverse cardiac and cerebrovascular events according to the presence or absence of diabetes mellitus and low high-density lipoprotein cholesterol in the derivation cohort (A) and validation cohort (B).

DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; MACCE, major adverse cardiac and cerebrovascular events.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementarytableS1.docx](#)
- [SupplementarytableS2.docx](#)

- [SupplementarytableS3.docx](#)
- [SupplementarytableS4.docx](#)