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Association of metabolic dysfunction-associated steatotic liver disease and steatosis-associated fibrosis estimator with subclinical coronary atherosclerosis: observation cohort study

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Previous population-based studies have demonstrated differences in cardiovascular events according to the new classification of steatotic liver disease (SLD). However, detailed data on coronary artery status have not been presented. We aimed to investigate the association between subtypes of SLD and coronary artery status using findings from coronary computed tomography angiography (CCTA). We analyzed 8622 asymptomatic individuals without coronary artery disease (CAD) who underwent both abdominal ultrasonography and CCTA. Study participants were divided into four groups: 934 in the no SLD without cardiometabolic (CM) criteria group, 4811 in the no SLD with CM criteria group, 2494 in the metabolic dysfunction-associated steatotic liver disease (MASLD) group, and 252 in the MASLD with increased alcohol intake (Met-ALD) group. Obstructive CAD was defined as coronary arterial stenosis ≥ 50%. Compared with the no SLD without CM group, the no SLD with CM, MASLD, and Met-ALD groups were significantly associated with any coronary plaque (multivariable-adjusted OR 2.05 [95% CI 1.67–2.52], 2.71 [2.18–3.35], and 2.36 [1.69–3.31], respectively); calcified plaques (1.97 [1.59–2.43], 2.54 [2.04–3.16], and 2.10 [1.49–2.96], respectively); non-calcified plaques (2.04 [1.28–3.25], 2.42 [1.51–3.89], and 3.26 [1.73–6.13], respectively); and obstructive CAD (2.57 [1.53–4.32], 3.64 [2.15–6.16], and 3.51 [1.73–7.10], respectively) (*p* for all < 0.05). In addition, the inverse probability of treatment weighting (IPTW) analyses showed similar ORs for coronary plaques and obstructive CAD. Additionally, higher steatosis-associated fibrosis estimator (SAFE) was strongly associated with all atherosclerotic plaques and obstructive CAD. This association remained significant after multivariable adjustment and IPTW analyses. Subtypes of SLD had significant, yet different strengths of associations with subclinical coronary atherosclerosis. SAFE score classification effectively stratified the distinct associations with subclinical atherosclerosis in subjects with MASLD.

Keywords Metabolic dysfunction-associated steatotic liver disease, Met-ALD, Computed tomography angiography, Steatosis-associated fibrosis estimator (SAFE) score, Atherosclerosis

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Abbreviations

BMI	Body mass index
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CM	Cardio-metabolic
IPTW	Inverse probability of treatment weighting
MASLD	Metabolic dysfunction-associated steatotic liver disease
Met-ALD	Metabolic dysfunction and alcohol-associated liver disease
NAFLD	Non-alcoholic fatty liver disease
NFS NAFLD	Fibrosis score
OR	Odds ratio
SAFE	Steatosis-associated fibrosis estimator
SLD	Steatotic liver disease
ALD	Alcoholic liver disease

The global rise in obesity and metabolic syndrome, driven by sedentary lifestyles and changes in environmental and dietary factors, has become a widespread concern and burden, affecting populations worldwide, including Asians[1–3]. Non-alcoholic fatty liver disease (NAFLD) is recognized globally, with a prevalence of approximately 30%, and is the most common hepatic disorder[4]. However, criticisms have emerged regarding the suitability of the terms 'non-alcoholic' and 'fatty' in accurately understanding the etiology of the disease and its potentially stigmatizing nature[5]. Additionally, stringent alcohol-related criteria have occasionally led to inaccurate classification of some patients or their exclusion from clinical trials[6]. In response to these concerns and demands, the multinational, multi-society Delphi consensus recently redefined fatty liver disease as steatotic liver disease (SLD) and categorized it into five distinct types. Furthermore, to replace NAFLD, it introduced a new nomenclature for fatty liver diseases: metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction and alcohol-associated liver disease (Met-ALD)[7].

Hepatic steatosis is considered important not only as a condition of the liver but also in terms of inter-organ crosstalk[8,9]. Cardiovascular disease has been identified as the primary cause of mortality in patients with NAFLD[10], which is considered as an independent risk factor for adverse cardiovascular outcomes[11]. Additionally, fibrosis burden is recognized as a significant prognostic factor in individuals with NAFLD[12]. However, data on the association of MASLD and Met-ALD with subclinical atherosclerosis, as well as the association between MASLD and fibrosis stage, are limited. Recent advancements in coronary computed tomography angiography (CCTA) have made this imaging technique a pivotal diagnostic modality for the non-invasive evaluation of coronary artery disease (CAD), facilitating the detection of coronary atherosclerotic plaques and stenosis[13]. The present study aimed to investigate the association between MASLD and subclinical coronary atherosclerosis and explore the relationship between the newly proposed fibrosis index, steatosis-associated fibrosis estimator (SAFE) score[14], and subclinical coronary atherosclerosis.

Materials and methods

Study population

This retrospective, single-center cohort study was conducted at Ulsan University Hospital, South Korea. A total of 10,135 subjects aged ≥ 20 years who opted for both CCTA and abdominal ultrasonography as part of a general health examination from January 2009 to March 2020 at the Health Screening and Promotion Center of Ulsan University Hospital were enrolled in the study. Figure 1 illustrates the participant selection process in detail. The exclusion criteria included: (1) previous history of angina, myocardial infarction, and/or percutaneous coronary intervention; (2) abnormal resting electrocardiographic results, that is, pathologic Q-waves, ischemic T-wave or ST segment changes, or left bundle-branch blocks; (3) renal insufficiency (serum creatinine > 1.5 mg/dL); (4) previous history of cerebrovascular disease; (5) structural heart disease; (6) previous history of open heart surgery; (7) previous cardiac procedures such as radiofrequency catheter ablation or patent foramen ovale device closure; and (8) insufficient medical records or poor image quality. After applying the exclusion criteria, 8622 study participants were included in the analysis. Although participants were initially classified into six groups (No SLD without CM criteria, No SLD with CM criteria, MASLD, Met-ALD, ALD, and Cryptogenic SLD), our primary analysis focused specifically on the four groups (No SLD without CM criteria, No SLD with CM criteria, MASLD, and Met-ALD), considering their clinical significance and sufficient sample sizes. Data for all six groups is provided separately in Supplementary Table 1.

Ethics statement

This study was approved by the Institutional Review Board of Ulsan University Hospital, Ulsan, South Korea. Given its retrospective design of this study, the requirement for informed consent was waived by the Institutional Review Board of the Ulsan University Hospital, Ulsan, South Korea (IRB No. UUH 2020-12-033). All methods were conducted in accordance with relevant guidelines and regulations.

Clinical and laboratory measurements

Comprehensive demographic and clinical data of the study participants were retrieved from the database of the Health Screening and Promotion Center of Ulsan University Hospital. During the general medical checkup, height, body weight, waist circumference, and blood pressure were measured according to standard procedures, as detailed in previous studies[15,16]. Prior to the general examination, all participants completed a self-report questionnaire detailing their medical, family, and social history, such as alcohol consumption, smoking status, monthly income, marital status, and levels of physical activity. Physical activity was assessed using the validated

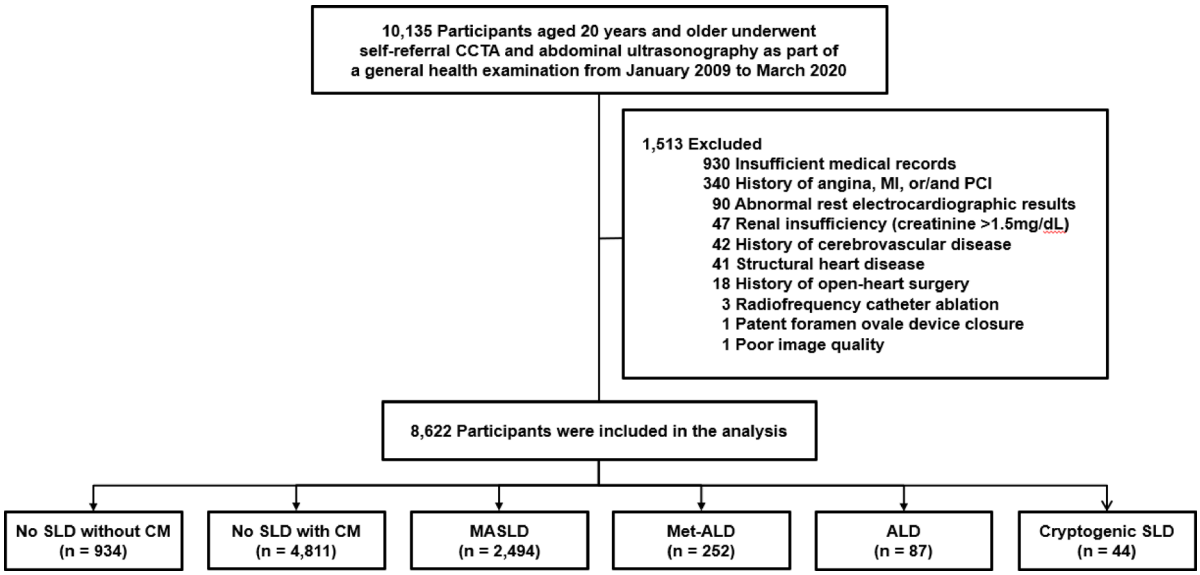

Fig. 1. Flow chart of study population.

Korean version of the self-administered International Physical Activity Questionnaire, which includes questions regarding physical activity over the past 7 days[17]. The average daily alcohol intake was calculated based on the surveyed quantity and frequency of alcohol intake. Alcohol consumption was categorized into no drinking, mild, moderate, and heavy drinking according to the criteria specified by diagnostic criteria for new SLD classification[7], based on the calculated average daily alcohol intake expressed in grams. Past medical history included diabetes mellitus, hypertension, dyslipidemia, angina, myocardial infarction, percutaneous coronary intervention, cerebrovascular disease, structural heart disease, open heart surgery, and previous cardiac procedures, such as radiofrequency catheter ablation or patent foramen ovale device closure. A family history of CAD was delineated as the reporting of a first-degree relative, irrespective of age, on the self-administered questionnaire[18]. Blood samples were extracted after overnight fasting to measure total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, fasting blood glucose, hemoglobin A1c, creatinine, aspartate aminotransferase, and alanine aminotransferase. Obesity was defined as a body mass index (BMI) of ≥ 25 kg/m^2[19], while cardio-metabolic (CM) criteria specified a BMI of ≥ 23 kg/m^2[7]. Diabetes mellitus was defined as fasting plasma glucose ≥ 126 mg/dL or hemoglobin A1c levels ≥ 6.5%, a self-reported history of diabetes mellitus, or current treatment for diabetes (either dietary or pharmacological), as indicated on the structured questionnaire[20]. Hypertension was defined as blood pressure ≥ 140/90 mmHg, a self-reported history of hypertension, or the use of antihypertensive agents. Dyslipidemia was defined as total cholesterol ≥ 240 mg/dL or the use of a lipid-lowering agents[21].

Definition of SLD, cardio-metabolic risk and subgroups in the study

SLD was identified by the presence of hepatic steatosis, characterized by diffuse increased hepatic parenchymal echogenicity as assessed through abdominal ultrasonography[22]. The measurement involves a qualitative visual examination of liver brightness using a Sequoia 512 scanner (Acuson, Mountain View, CA) equipped with a 4.0 MHz convex probe. This assessment includes comparing the echo intensity of the liver with that of the kidneys, evaluating the depth of echo penetration into the deeper regions of the liver, and assessing the visibility of vascular structures within the liver[23]. MASLD was characterized as the presence of SLD and one or more CM risk factors. CM risk was defined as follows: (1) BMI ≥ 23 kg/m^2 or waist circumference ≥ 90 cm (for men) or ≥ 80 cm (for women); (2) fasting blood glucose ≥ 100 mg/dL or hemoglobin A1c ≥ 5.7% or type 2 diabetes or use of glucose-lowering agents; (3) blood pressure ≥ 130/85 mmHg or use of antihypertensive agents; (4) triglyceride level ≥ 150 mg/dL or use of lipid-lowering drugs; or (5) HDL-C level < 40 mg/dL (for men) or < 50 mg/dL (for women) or use of lipid-lowering agents. For individuals with MASLD, alcohol intake is defined as alcohol consumption of less than 20 g per day for women and 30 g per day for men. Met-ALD was classified as MASLD with concomitant moderate alcohol consumption (30–60 g per day for men and 20–50 g per day for women). In addition, alcohol-related liver disease (ALD) was noted in cases of MASLD with concomitant excessive alcohol use (> 60 g/day for men and > 50 g/day for women). Lastly, cryptogenic SLD was identified as SLD in the absence of both CM risk and alcohol intake[7].

Non-invasive indices of hepatic fibrosis and hepatic steatosis

In the current study, non-invasive indices of hepatic fibrosis were assessed using the NAFLD fibrosis score (NFS) based on a published equation[24]. The cut-off values of advanced fibrosis NFS < − 1.455) were adopted as outlined in a previous study[25]. The newly proposed Steatosis-Associated Fibrosis Estimator (SAFE) score was introduced to evaluate the stage of hepatic fibrosis. The study participants were categorized into three groups, including

those with low (SAFE score < 0), intermediate (SAFE 0 to 100), and high probability of advanced hepatic fibrosis (SAFE > 100)[14].

CCTA image acquisition and analysis

CCTA was performed using either single-source 64-slice (LightSpeed VCT, GE, Milwaukee, WI, USA) or dual-source (Somatom Definition, Siemens, Erlangen, Germany) computed tomography. The CCTA protocol has been described previously[15,16]. CCTA images were interpreted by experienced cardiovascular radiologists and a cardiologist (WJK, SHC, and GMP, each with over 10 years of experience) using a dedicated workstation (Syngo. via, Siemens or Aquarius iNtuition, TeraRecon Inc., Durham, NC, USA). Coronary artery calcium scores were computed and categorized into five groups: 0, 1–10, 11–100, 101–400, and > 400. Plaques were categorized based on their composition: those with calcified tissue comprising > 50% of the plaque area (density > 130 Hounsfield units) were identified as calcified plaques; those with less than 50% calcium content were defined as mixed plaques; and plaques devoid of calcium were defined as non-calcified lesions. A stenosis diameter of 50% or greater was specified as obstructive CAD[26].

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as means and standard deviations. Between-group comparisons were conducted using the Chi-square test or Fisher's exact test for categorical variables and Student's t-tests or the Kruskal–Wallis test for continuous variables, as appropriate. Univariate and multivariate logistic regression analyses were used to assess the associations between no SLD with or without CM criteria, Met-ALD, MASLD, and adverse CCTA findings, adjusting for clinically significant cardiovascular risk factors, such as age, male sex, smoking status, and family history of CAD. Obesity, hypertension, and dyslipidemia were excluded from the analysis for adjustment purposes because they are part of the CM criteria. A weighted logistic regression model with inverse probability of treatment weighting (IPTW) was also employed to adjust for differences in the baseline characteristics of the subjects. Variables for IPTW included current marital status, physical activity, monthly income, and ALT levels above the upper normal limit, in addition to the recognized cardiovascular risk factors. The associations between NFS, SAFE score, and adverse CCTA findings in individuals with MASLD were also assessed using univariate, multivariate, and IPTW analyses. Age, BMI, alanine aminotransferase level above the upper normal limit, and diabetes mellitus were excluded from the variables for the adjusted and IPTW analyses, as these were factors in the equation for calculating fibrosis indices. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs), and a p value < 0.05 was considered statistically significant. Data processing and statistical analyses were conducted using R software (Version 4.2.2, R Foundation, Vienna, Austria). R packages of 'WeightIt' and 'cobalt' were used to conduct IPTW analysis and to determine covariate balance.

Results

Baseline characteristics of the study population

The baseline characteristics of the study participants are presented in Table 1 and Supplementary Table 1. A total of 8622 subjects were included in the analysis (Fig. 1). Four groups were included in the analysis: no SLD without CM criteria (n = 934), no SLD with CM criteria (n = 4811), MASLD (n = 2494), and Met-ALD (n = 252) groups. The mean ages of each group were 51.0 ± 8.1, 54.2 ± 8.1, 54.1 ± 7.9, and 51.9 ± 7.0 years, respectively ($p < 0.001$). Male sex was more prevalent in the MASLD and Met-ALD groups (73.2% and 86.5%, respectively) than in the no SLD without CM criteria and no SLD with CM criteria groups (46.0% and 60.9%, respectively). The MASLD and Met-ALD groups also showed higher BMI and waist circumference than the No SLD groups. Additionally, the proportions of diabetes, hypertension, and dyslipidemia were significantly higher in the MASLD and Met-ALD groups than in the no SLD groups.

Comparison of CCTA findings between groups

CCTA findings in the groups according to SLD presence, alcohol intake, and CM criteria are presented in Table 2 and Supplementary Table 2. The mean coronary artery calcium score was significantly different across the groups, with 16.8 ± 153.1 in the no SLD without CM group, 38.5 ± 154.3 in the no SLD with CM group, 47.9 ± 172.3 in the MASLD group, and 38.7 ± 118.3 in the Met-ALD group ($p < 0.001$). Coronary plaque and plaque characteristics were significantly different between the groups. Calcified plaques were commonly observed in the MASLD group (37.4%), followed by the Met-ALD group (32.1%), the no SLD with CM group (30.2%), and the no SLD without CM group (14.1%) ($p < 0.001$). Non-calcified plaques were present in 2.1% of the no SLD without CM group, 5.5% of the no SLD with CM group, 6.9% of the MASLD group, and 8.7% of the Met-ALD group, with the highest predominance ($p < 0.001$). Mixed plaques were found in 0.3% of the no SLD without CM group, 3.5% of the no SLD with CM group, 5.0% of the MASLD group, and 4.0% of the Met-ALD group ($p < 0.001$). In addition, obstructive CAD (≥ 50% diameter stenosis) was observed in 1.7% of the no SLD without CM group, 5.7% of the no SLD with CM group, 8.3% of the MASLD group, and 7.1% of the Met-ALD group ($p < 0.001$) (Table 2).

Association of MASLD and Met-ALD with subclinical coronary atherosclerosis

The association of no SLD with CM criteria, MASLD, and Met-ALD with subclinical coronary atherosclerosis on CCTA compared with no SLD without CM is shown in Table 3. The unadjusted analysis showed that the presence of SLD and CM criteria was strongly associated with coronary plagues and obstructive CAD (p for all < 0. 001). After adjustment for cardiovascular risk factors (age, male sex, smoking status, and family history of CAD), a strong association was detected between subclinical coronary atherosclerosis and obstructive CAD with SLD and CM criteria. Notably, in the multivariable and IPTW analyses, the ORs of subclinical coronary

	No SLD without CM criteria (n = 934)	No SLD with CM criteria (n = 4,811)	MASLD (n = 2494)	Met-ALD (n = 252)	*p* value
Age, years old, mean ± SD	51.0 ± 8.1	54.2 ± 8.1	54.1 ± 7.9	51.9 ± 7.0	< 0.001
Male sex, no. (%)	430 (46.0%)	2930 (60.9%)	1826 (73.2%)	218 (86.5%)	< 0.001
Body mass index, kg/m^2, mean ± SD	20.7 ± 1.5	23.8 ± 2.4	25.9 ± 2.8	25.7 ± 2.7	< 0.001
Waist circumference (cm), male	78.5 ± 4.6	85.7 ± 6.2	90.7 ± 6.8	90.1 ± 6.5	< 0.001
Waist circumference (cm), female	74.2 ± 4.0	82.7 ± 6.7	88.1 ± 7.6	88.4 ± 8.5	< 0.001
Systolic blood pressure, mmHg, mean ± SD	113.4 ± 10.1	125.0 ± 13.8	128.2 ± 13.1	126.8 ± 12.1	< 0.001
Diastolic blood pressure, mmHg, mean ± SD	71.7 ± 7.6	78.4 ± 9.4	80.3 ± 8.9	80.7 ± 8.9	< 0.001
Hypertension, no. (%)	0 (0%)	1621 (33.7%)	1064 (42.7%)	115 (45.6%)	< 0.001
Anti-hypertensive agent, no. (%)	0 (0%)	982 (21.4%)	659 (26.4%)	78 (31.0%)	< 0.001
Diabetes mellitus, no. (%)	0 (0%)	470 (9.8%)	531 (21.3%)	46 (18.3%)	< 0.001
Glucose lowering agent, no. (%)	0 (0%)	316 (6.6%)	315 (12.6%)	24 (9.5%)	< 0.001
Lipid-lowering agent use, no. (%)	0 (0%)	312 (6.5%)	216 (8.7%)	20 (7.9%)	< 0.001
Obesity[a], no. (%)	0 (0%)	1375 (28.6%)	1498 (60.1%)	141 (56.0%)	< 0.001
Family history of CAD[b], no. (%)	97 (10.4%)	428 (8.9%)	224 (9.0%)	18 (7.1%)	0.280
Alcohol intake[c], no. (%)					< 0.001
None	384 (41.1%)	1708 (35.5%)	925 (37.1%)	0 (0%)	
Mild	373 (39.9%)	2122 (44.1%)	1569 (62.9%)	0 (0%)	
Moderate	65 (7.0%)	336 (7.0%)	0 (0%)	252 (100%)	
Heavy	112 (12.0%)	645 (13.4%)	0 (0%)	0 (0%)	
Tobacco use, (n, %)					< 0.001
Never	587 (62.9%)	2435 (50.6%)	985 (39.5%)	62 (24.6%)	
Past	198 (21.2%)	1393 (28.95%)	885 (35.5%)	111 (44.1%)	
Current	149 (16.0%)	983 (20.4%)	624 (25.0%)	79 (31.4%)	
Physical activity[d]					
Moderate intensity (day)	1.5 ± 1.7	1.8 ± 1.8	1.4 ± 1.7	1.4 ± 1.5	< 0.001
High intensity (day)	1.2 ± 1.5	1.4 ± 1.7	1.1 ± 1.4	1.2 ± 1.3	< 0.001
Current marital status, yes, no. (%)	841 (90.0%)	4287 (89.1%)	2250 (90.2%)	231 (91.7%)	0.342
Monthly income (Korean won)					0.002
< 2 million	51 (5.5%)	378 (7.9%)	152 (6.1%)	12 (4.8%)	
2–4 million	166 (17.8%)	914 (19.0%)	448 (18.0%)	39 (15.5%)	
4–6 million	201 (21.5%)	997 (20.7%)	524 (21.0%)	71 (28.2%)	
≥ 6 million	457 (48.9%)	2187 (45.5%)	1217 (48.8%)	122 (48.4%)	
Unknown	59 (6.3%)	335 (7.0%)	153 (6.1%)	8 (3.2%)	
Fasting blood glucose, mg/dL, mean ± SD	83.7 ± 9.4	94.1 ± 18.9	103.3 ± 26.8	102.9 ± 24.0	< 0.001
Glycated hemoglobin, %, mean ± SD	5.3 ± 0.2	5.6 ± 0.6	6.0 ± 1.0	5.9 ± 0.9	< 0.001
Total cholesterol, mg/dL, mean ± SD	189.6 ± 34.6	188.6 ± 36.1	195.0 ± 37.7	199.0 ± 37.8	< 0.001
LDL-cholesterol, mg/dL, mean ± SD	121.6 ± 32.9	125.3 ± 33.4	132.4 ± 34.7	133.4 ± 36.3	< 0.001
HDL-cholesterol, mg/dL, mean ± SD	64.8 ± 14.9	54.3 ± 14.9	47.1 ± 12.1	47.4 ± 10.7	< 0.001
Triglyceride, mg/dL, mean ± SD	71.2 ± 27.1	103.4 ± 60.9	148.5 ± 95.3	158.6 ± 101.5	< 0.001
Creatinine, mg/dL, mean ± SD	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	< 0.001
AST, IU/L, mean ± SD	22.2 ± 10.9	23.4 ± 11.0	28.1 ± 15.6	29.6 ± 18.7	< 0.001
ALT, IU/L, mean ± SD	19.5 ± 15.4	23.3 ± 14.3	35.3 ± 23.3	36.9 ± 25.3	< 0.001
ALT > upper normal limit, no. (%)	420 (45.0%)	2004 (41.7%)	1053 (42.2%)	109 (43.3%)	0.266
NFS	− 2.4 ± 0.9	− 2.1 ± 1.0	− 2.2 ± 1.0	− 2.3 ± 1.0	< 0.001
NFS ≥ − 1.455, no. (%)	128 (13.7%)	1158 (24.1%)	564 (22.6%)	51 (20.24%)	< 0.001
Continued					

	No SLD without CM criteria (n = 934)	No SLD with CM criteria (n = 4,811)	MASLD (n = 2494)	Met-ALD (n = 252)	*p* value
NFS < − 1.455, no. (%)	806 (86.3%)	3653 (75.9%)	1930 (77.4%)	201 (79.8%)	
SAFE score, mean ± SD	37.9 ± 36.8	50.1 ± 41.8	53.9 ± 45.1	47.1 ± 43.6	< 0.001
SAFE score < 0, no. (%)	130 (13.9%)	461 (9.6%)	226 (9.1%)	30 (11.9%)	< 0.001
0 ≤ SAFE < 100, no. (%)	758 (81.2%)	3820 (79.4%)	1905 (76.4%)	190 (75.4%)	
SAFE score ≥ 100, no. (%)	46 (4.9%)	530 (11.0%)	363 (14.6%)	32 (12.7%)	

Table 1. Baseline characteristics in study population. Values are presented as mean ± standard deviation or number (%). *SLD* steatotic liver disease, *CM* cardiometabolic, *MASLD* metabolic dysfunction-associated steatotic liver disease, *Met-ALD* metabolic dysfunction-associated alcoholic liver disease, *SD* standard deviation, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *NFS* non-alcoholic fatty liver disease fibrosis score, *SAFE score* steatosis-associated fibrosis estimator score, *HSI* hepatic steatosis index. [a]Defined as a body mass index ≥ 25 kg/m^2. [b]Defined as family history of coronary artery disease in a first-degree relative of any age. [C]Alcohol intake was categorized according to the criteria specified by diagnostic criteria for new SLD classification, based on the calculated average daily intake expressed in grams. [d]Physical activity was assessed using the validated Korean version of the self-administered International Physical Activity Questionnaire, focusing on activities over the past 7 day.

	No SLD, without CM criteria (n = 934)	No SLD, with CM criteria (n = 4811)	MASLD (n = 2494)	Met-ALD (n = 252)	*p* value
CACS, mean ± SD	16.8 ± 153.1	38.5 ± 154.3	47.9 ± 172.3	38.7 ± 118.3	< 0.001
CACS, 0 (n, %)	802 (85.9%)	3331 (69.2%)	1530 (61.3%)	170 (67.5%)	< 0.001
CACS, 1–10 (n, %)	46 (4.9%)	401 (8.3%)	251 (10.1%)	28 (11.1%)	
CACS, 11–100 (n, %)	59 (6.3%)	646 (13.4%)	437 (17.5%)	28 (11.1%)	
CACS, 101–400 (n, %)	21 (2.2%)	321 (6.7%)	201 (8.1%)	16 (6.3%)	
CACS, > 400 (n, %)	6 (0.6%)	112 (2.3%)	75 (3.0%)	10 (4.0%)	
Any coronary plaque, (n, %)	140 (15.0%)	1563 (32.5%)	1007 (40.4%)	91 (36.1%)	< 0.001
Plaque characteristics					
Calcified plaque, (n, %)	132 (14.1%)	1454 (30.2%)	933 (37.4%)	81 (32.1%)	< 0.001
Non-calcified plaque, (n, %)	20 (2.1%)	265 (5.5%)	173 (6.9%)	22 (8.7%)	< 0.001
Mixed plaque, (n, %)	3 (0.3%)	169 (3.5%)	126 (5.0%)	10 (4.0%)	< 0.001
Obstructive CAD[a], (n, %)	16 (1.7%)	276 (5.7%)	207 (8.3%)	18 (7.1%)	< 0.001

Table 2. Comparison of coronary computed tomography angiographic findings according to status of steatotic liver disease. Values are shown as mean ± standard deviation or number (%). *SLD* steatotic liver disease, *CM* cardiometabolic, *MASLD* metabolic dysfunction-associated steatotic liver disease, *Met-ALD* metabolic dysfunction-associated alcoholic liver disease, *SD* standard deviation, *CACS* coronary artery calcium score, *CAD* coronary artery disease. [a]Obstructive coronary artery disease is defined as stenosis exceeding 50% at coronary computed tomography angiography.

atherosclerosis (excluding non-calcified plaques) were highest in the MASLD group, followed by Met-ALD, and no SLD with CM groups, when compared to the no SLD without CM group (Table 3, Fig. 2).

Association of hepatic fibrosis status and CCTA findings in individuals with MASLD

The association of NFS and SAFE score with subclinical coronary atherosclerosis in CCTA findings is presented in Table 4. NFS ≥ − 1.455 was significantly associated with all components of coronary plaques and obstructive CAD on CCTA in the unadjusted, adjusted (multivariable), and IPTW analyses (Table 4). The SAFE score, another newly suggested fibrosis index, indicated significant associations with all forms of subclinical coronary atherosclerosis on CCTA, except for mixed plaques, in individuals with a SAFE score between 0 and 100 in the unadjusted and adjusted (multivariable) analyses. However, in IPTW analysis, the association with mixed plaque in this group was found to be statistically significant. Particularly, SAFE score stratification showed a significant association with obstructive CAD. In both adjusted and IPTW analyses, a significant association was noted between a SAFE score of 0 ≤ SAFE score < 100 and obstructive CAD (OR 3.61, 95% CI 1.46–8.96, $p = 0.006$; OR 3.60, 95% CI 2.10–6.17, $p < 0.001$). Additionally, a strong association was demonstrated between a SAFE score of ≥ 100 and obstructive CAD (10.36, 95% CI 4.07–26.36, $p < 0.001$; OR 9.19, 95% CI 5.55–15.23, $p < 0.001$) (Table 4).

Discussion

In this large-scale, retrospective observational cohort study, 8622 subjects were categorized and compared based on hepatic steatosis, CM criteria, and alcohol intake. The main finding was that significant differences in subclinical coronary atherosclerosis findings, including coronary plaques and obstructive CAD, were noted

Variables	Unadjusted analysis		Adjusted analysis[a]		IPTW analysis[b]	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Any coronary plaque						
No SLD, without CM criteria	Reference		Reference		Reference	
No SLD, with CM criteria	2.73 (2.26–3.30)	< 0.001	2.05 (1.67–2.52)	< 0.001	1.48 (1.29–1.68)	< 0.001
MASLD	3.84 (3.16–4.68)	< 0.001	2.71 (2.18–3.35)	< 0.001	1.91 (1.68–2.18)	< 0.001
Met-ALD	3.21 (2.34–4.39)	< 0.001	2.36 (1.69–3.31)	< 0.001	1.63 (1.42–1.85)	< 0.001
Calcified plaque						
No SLD, without CM criteria	Reference		Reference		Reference	
No SLD, with CM criteria	2.63 (2.17–3.20)	< 0.001	1.97 (1.60–2.43)	< 0.001	1.41 (1.23–1.62)	< 0.001
MASLD	3.63 (2.97–4.44)	< 0.001	2.54 (2.04–3.16)	< 0.001	1.79 (1.57–2.05)	< 0.001
Met-ALD	2.88 (2.09–3.97)	< 0.001	2.10 (1.49–2.96)	< 0.001	1.41 (1.23–1.62)	< 0.001
Non-calcified plaque						
No SLD, without CM criteria	Reference		Reference		Reference	
No SLD, with CM criteria	2.66 (1.68–4.22)	< 0.001	2.04 (1.28–3.25)	0.003	1.40 (1.05–1.85)	0.020
MASLD	3.41 (2.13–5.45)	< 0.001	2.42 (1.51–3.89)	< 0.001	1.72 (1.31–2.26)	< 0.001
Met-ALD	4.37 (2.35–8.15)	< 0.001	3.26 (1.73–6.13)	< 0.001	2.07 (1.59–2.70)	< 0.001
Mixed plaque						
No SLD, without CM criteria	Reference		Reference		Reference	
No SLD, with CM criteria	11.30 (3.60–5.46)	< 0.001	8.37 (2.66–6.40)	< 0.001	4.37 (2.61–7.29)	< 0.001
MASLD	16.51(5.2452.02)	< 0.001	11.37 (3.59–5.97)	< 0.001	5.70 (3.45–9.42)	< 0.001
Met-ALD	12.82 (3.50–6.96)	< 0.001	9.44 (2.56–34.87)	0.001	4.72 (2.84–7.87)	< 0.001
Obstructive CAD						
No SLD, without CM criteria	Reference		Reference		Reference	
No SLD, with CM criteria	3.49 (2.10–5.81)	< 0.001	2.57 (1.53–4.32)	< 0.001	1.61 (1.21–2.15)	0.001
MASLD	5.19 (3.11–8.69)	< 0.001	3.64 (2.15–6.16)	< 0.001	2.24 (1.71–2.94)	< 0.001
Met-ALD	4.41 (2.22–8.79)	< 0.001	3.51 (1.73–7.10)	< 0.001	2.02 (1.53–2.66)	< 0.001

Table 3. Association between status of steatotic liver disease and coronary computed tomography angiographic findings. *CAD* coronary artery disease, *CI* confidence interval, *SLD* steatotic liver disease, *CM* cardiometabolic, *IPTW* inverse probability of treatment weighting, *MASLD* metabolic dysfunction-associated steatotic liver disease, *Met-ALD* metabolic dysfunction-associated alcoholic liver disease. [a]Covariates in the multivariable model include age, male sex, smoking status, and family history of coronary artery disease. [b]Covariates in the inverse probability of treatment weighting analysis include age, male sex, smoking status, family history of coronary artery disease, current marital status, physical activity, monthly income, and alanine aminotransferase > upper normal limit.

in the no SLD with CM criteria, MASLD, and Met-ALD groups compared to the no SLD without CM criteria group. These differences persisted even after adjustments for cardiovascular risk factors and confirmation in IPTW analyses. This evidence suggests that SLD, CM risk, and alcohol consumption are factors associated with subclinical coronary atherosclerosis. Notably, differences were observed in obstructive CAD and coronary plaques, except for non-calcified plaques, between MASLD and Met-ALD, with Met-ALD exhibiting lower adjusted ORs than MASLD. This finding aligns with those of a previous study that indicated a lower incidence of cardiovascular events in Met-ALD than in MASLD[27]. Moreover, the subclassification of NFS and the newly proposed SAFE score were associated with adverse subclinical coronary atherosclerosis findings, including obstructive CAD. Furthermore, we observed differences in coronary plaque characteristics among the No SLD with CM criteria group, MASLD, and Met-ALD groups. Individuals with MASLD and Met-ALD showed a higher prevalence of calcified, non-calcified, and mixed plaques compared to those without hepatic steatosis (No SLD with CM criteria). These findings may reflect differences in systemic inflammation, insulin resistance, and oxidative stress linked to hepatic steatosis, as supported by previous research evaluating NAFLD and overall cardiovascular risk[28,29]. Additionally, moderate alcohol consumption observed specifically in the Met-ALD group might potentially influence cardiovascular risk, although its specific effects on coronary plaque characteristics remain unclear and require further research.

New evidence has suggested that MASLD is not only a hepatic manifestation of metabolic syndrome but also an independent risk factor for other diseases and increased mortality[27–36]. MASLD or Met-ALD has been identified as a significant risk factor for fatal and non-fatal cardiovascular diseases[27,35]. Previous studies have shown that patients with NAFLD are more likely to have subclinical atherosclerosis, even in the absence of clinically apparent cardiovascular disease[36]. A combined analysis using multinational, large-scale data revealed a J-shaped correlation between the amount of alcohol consumption and the cumulative incidence of cardiovascular disease outcomes[37]. In this context, the novel SLD classification could be considered clinically more relevant for stratifying cardiovascular risk. However, there may be concerns that the criteria for categorizing alcohol

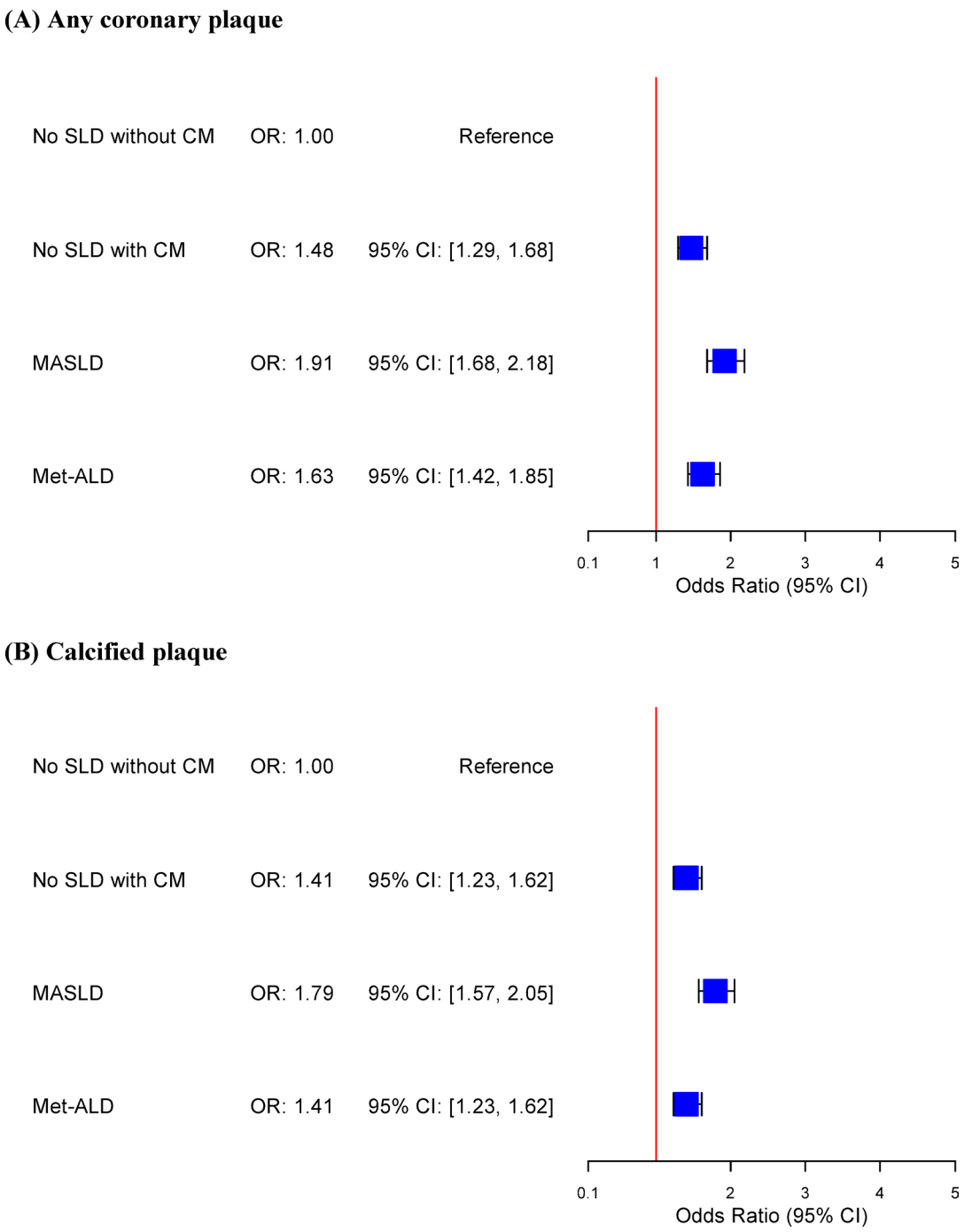

Fig. 2. Association between the status of steatotic liver disease and coronary computed tomography angiographic findings (IPTW analysis).

consumption are arbitrary, and the metabolic criteria could be perceived as more lenient than those for metabolic dysfunction-associated fatty liver disease. Therefore, it is crucial to conduct studies that demonstrate the differences in clinical outcomes or findings according to the new SLD classification.

The current study has several implications that are pertinent to clinical practice. First, we provided specific findings on coronary artery status, including coronary artery calcium score, subtypes of atherosclerotic plaques, and obstructive CAD on CCTA, according to the presence of SLD and CM risk between the groups of asymptomatic individuals. Moreover, in contrast to previous studies[27,34,35,38], in the present study, participants without SLD were divided into two groups based on the presence or absence of CM criteria, with the control group defined as individuals without SLD and CM criteria. The other groups were those without SLD but with CM criteria, MASLD, and Met-ALD. By demonstrating the differences in CCTA findings among asymptomatic subjects based on SLD, CM criteria, and alcohol intake, this study effectively categorized the subjects. This

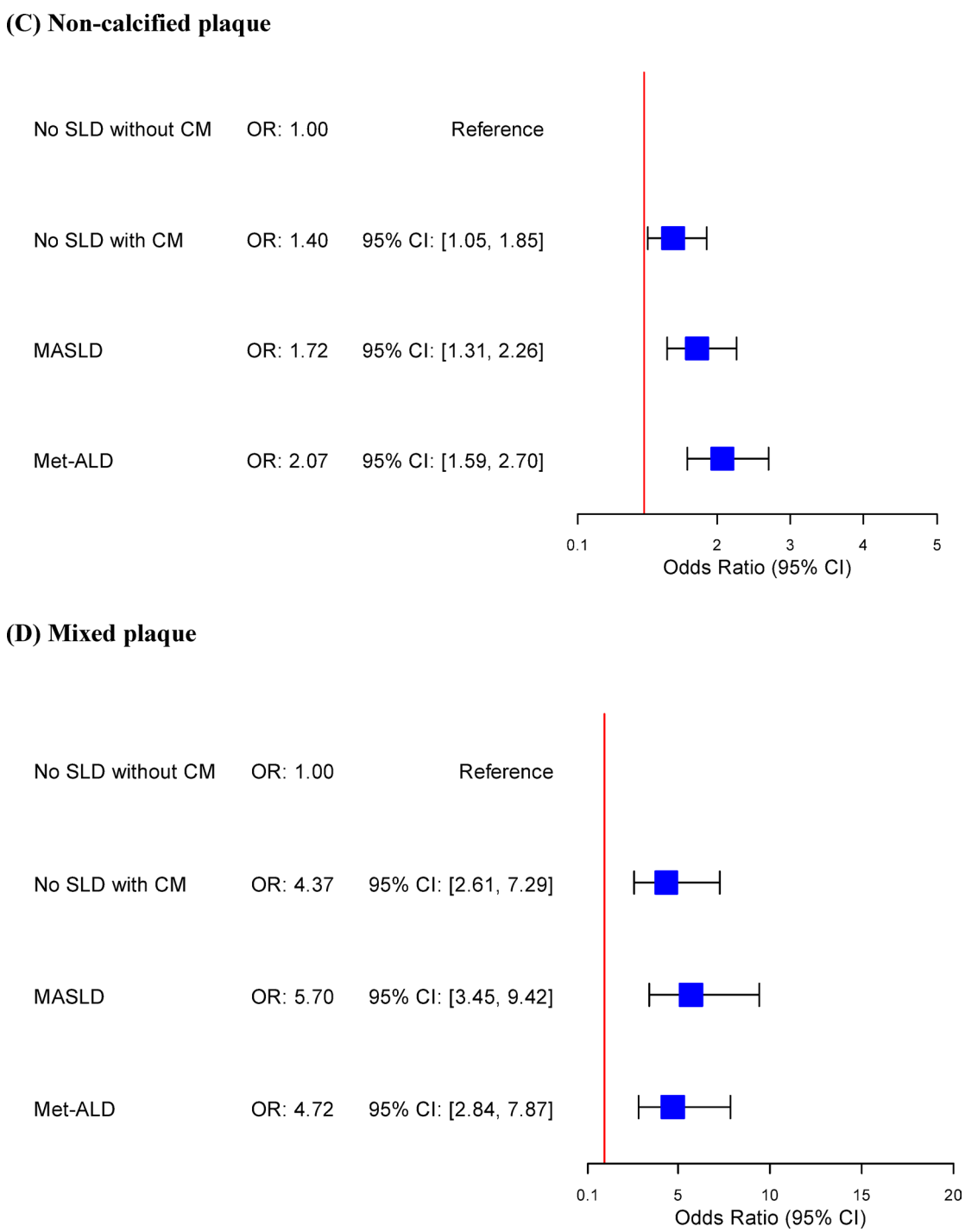

Fig. 2. (continued)

stratification could be clinically beneficial for identifying high-risk groups and implementing targeted prevention accordingly[26].

Second, recent studies reflecting the newly published SLD classification based on a nationwide health screening database and a community-dwelling cohort have demonstrated differences in cardiovascular events according to these new classifications[27,33]; however, the underlying mechanisms remain unexplained. Moreover, there is little evidence comparing the extent of subclinical coronary atherosclerosis among groups based on the new SLD classification. Given that atherosclerotic coronary plaque and obstructive CAD statuses can determine CAD prognosis, it is essential to understand these coronary artery statuses according to the new SLD classification. Therefore, this study indicates an association between specific CCTA findings and the SLD classification. The results were adjusted for known cardiovascular risk factors through multivariable analysis, and other potential confounding variables were controlled using IPTW analysis. A relatively strong association was observed even

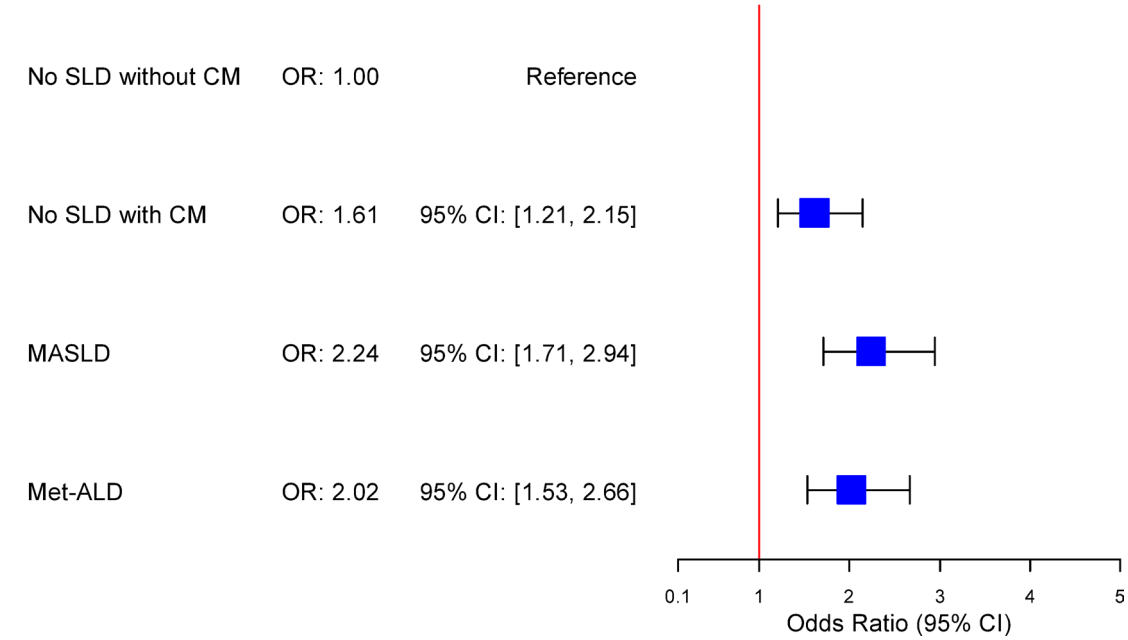

Fig. 2. (continued)

after adjusting for various confounding factors. Consequently, we believe that the present study offers insights into the mechanisms underlying the poorer cardiovascular outcomes observed in individuals with MASLD or Met-ALD.

Third, the distinction between Met-ALD and MASLD appears to be arbitrary. However, this study found different associations with subclinical coronary atherosclerosis in both groups, even after adjusting for various factors, including cardiovascular risk. Considering the inter-organ crosstalk in SLD, this finding suggests that there may be differences in the associations with other comorbidities between the two groups, warranting further clinical research.

Fourth, although previous studies have indicated that fibrosis burden is a key determinant of prognosis in NAFLD[12,39], a prospective study found no significant association between advanced hepatic fibrosis and the incidence of cardiovascular diseases[38]. Additionally, fibrosis indices, such as fibrosis index-4 or NFS, are likely to have low accuracy for screening hepatic fibrosis[40]. In this context, our study provides novel findings demonstrating that higher SAFE scores, indicative of increased hepatic fibrosis severity, are significantly associated with coronary plaque formation and obstructive coronary artery disease, particularly in the MASLD group. This is an important extension beyond previous study that mainly focused on coronary artery calcium scores alone[41,42]. These associations may be explained by potential mechanisms including systemic inflammation, endothelial dysfunction, and oxidative stress, which are commonly observed in advanced hepatic fibrosis and known to contribute to coronary atherosclerosis[10].

To the best of our knowledge, this is the first study to present the specific CCTA findings according to the new SLD classification and to demonstrate the association between subclinical coronary atherosclerosis and the SLD classification. The current study showed that stratification of the newly developed SAFE score is also relevant for identifying the association of subclinical coronary atherosclerosis in patients with MASLD. The strength of the present study is the analysis of a large retrospective observational cohort using various statistical methods. However, this study has several limitations. First, this was a retrospective observational study conducted at a single hospital; therefore, we could not determine causality between SLD classification and subclinical coronary atherosclerosis. Second, the participants voluntarily visited the hospital for a general health check-up. Therefore, there may have been a selection bias. Third, since this study was a cross-sectional analysis without clinical follow-up data, it was insufficient to evaluate the association between the SLD classification or subclinical coronary atherosclerosis and cardiac events. Further prospective studies with larger populations and long-term clinical follow-up are required to validate our findings. Fourth, since SLD was diagnosed by abdominal ultrasonography, not by liver biopsy, the study participants may have been misclassified. Fifth, the data from the self-reported questionnaires, such as those on alcohol intake and cigarette smoking, may have been affected by recall bias. Lastly, since all subjects were Korean, caution is needed when generalizing these findings to people from other regions, races, and ethnicities.

In this observational study, by categorizing subjects based on the presence of hepatic steatosis, CM criteria, and the amount of alcohol consumption, different strengths of association with subclinical coronary atherosclerosis were identified across the SLD groups. Notably, it was observed that moderate amount of alcohol intake had an impact on subclinical coronary atherosclerosis after adjustments for cardiovascular risk factors, consistent with

Variables	Unadjusted analysis		Adjusted analysis[a]		IPTW analysis[b]	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Any coronary plaque						
NFS < − 1.455 (reference)	Reference		Reference		Reference	
NFS ≥ − 1.455	2.02 (1.67–2.44)	< 0.001	2.09 (1.71–2.55)	< 0.001	1.90 (1.58–2.30)	< 0.001
SAFE < 0 (reference)	Reference		Reference		Reference	
0 ≤ SAFE < 100	3.30 (2.29–4.74)	< 0.001	3.59 (2.47–5.22)	< 0.001	3.44 (2.73–4.34)	< 0.001
SAFE ≥ 100	8.14 (5.40–2.27)	< 0.001	8.78 (5.74–13.43)	< 0.001	7.42 (5.88–9.35)	< 0.001
Calcified plaque						
NFS < − 1.455 (reference)	Reference		Reference		Reference	
NFS ≥ − 1.455	1.98 (1.64–2.40)	< 0.001	2.03 (1.66–2.47)	< 0.001	1.84 (1.52–2.22)	< 0.001
SAFE < 0 (reference)	Reference		Reference		Reference	
0 ≤ SAFE < 100	3.47 (2.36–5.11)	< 0.001	3.72 (2.51–5.51)	< 0.001	3.64 (2.86–4.64)	< 0.001
SAFE ≥ 100	8.04 (5.24–12.34)	< 0.001	8.44 (5.43–13.13)	< 0.001	7.30 (5.75–9.29)	< 0.001
Non-calcified plaque						
NFS < − 1.455 (reference)	Reference		Reference		Reference	
NFS ≥ − 1.455	1.52 (1.08–2.13)	0.016	1.57 (1.11–2.21)	0.011	1.52 (1.09–2.13)	0.015
SAFE < 0 (reference)	Reference		Reference		Reference	
0 ≤ SAFE < 100	2.44 (1.06–5.61)	0.035	2.64 (1.14–6.09)	0.023	2.50 (1.50–4.16)	< 0.001
SAFE ≥ 100	5.59 (2.35–13.28)	< 0.001	6.00 (2.50–14.39)	< 0.001	5.80 (3.62–9.27)	< 0.001
Mixed plaque						
NFS < − 1.455 (reference)	Reference		Reference		Reference	
NFS ≥ − 1.455	2.83 (1.96–4.08)	< 0.001	3.05 (2.10–4.45)	< 0.001	2.92 (2.04–4.18)	< 0.001
SAFE < 0 (reference)	Reference		Reference		Reference	
0 ≤ SAFE < 100	1.86 (0.75–4.65)	0.183	2.18 (0.87–5.49)	0.097	2.04 (1.14–3.65)	0.016
SAFE ≥ 100	6.10 (2.38–15.62)	< 0.001	6.99 (2.69–18.13)	< 0.001	6.43 (3.84–10.77)	< 0.001
Obstructive CAD						
NFS < − 1.455 (reference)	Reference		Reference		Reference	
NFS ≥ − 1.455	2.57 (1.91–3.45)	< 0.001	2.66 (1.97–3.61)	< 0.001	2.46 (1.83–3.31)	< 0.001
SAFE < 0 (reference)	Reference		Reference		Reference	
0 ≤ SAFE < 100	3.37 (1.37–8.32)	0.008	3.61 (1.46–8.96)	0.006	3.60 (2.10–6.17)	< 0.001
SAFE ≥ 100	10.01 (3.97–25.24)	< 0.001	10.36 (4.07–26.36)	< 0.001	9.19 (5.55–15.23)	< 0.001

Table 4. Association of hepatic-fibrosis status and coronary computed tomography angiographic findings in individuals with MASLD (n = 2,494). *MASLD* metabolic dysfunction-associated steatotic liver disease, *IPTW* inverse probability of treatment weighting, *NFS* non-alcoholic fatty liver disease fibrosis score, *SAFE* steatosis-associated fibrosis estimator, *CAD* coronary artery disease. [a]Covariates in the multivariable model include male sex, smoking status, family history of coronary artery disease, hypertension and dyslipidemia. [b]Covariates in the inverse probability of treatment weighting analysis include male sex, smoking status, family history of coronary artery disease, hypertension, dyslipidemia, current marital status, physical activity, and monthly income.

the findings of previous epidemiologic studies[27]. The newly proposed SAFE score classification demonstrated associations with subclinical coronary atherosclerosis and obstructive CAD in Koreans with MASLD, with each association depending on the respective subclassification. The results of the current study need to be validated in future prospective studies.

Data availability

Questions regarding data availability should be directed to the corresponding author, Professor K-M Park, at gmpark@uuh.ulsan.kr.

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Author contributions

Study conception, coordination and design, data analysis, manuscript writing and approval of the final version: J Jeong. Study coordination and design, data collection, data analysis, manuscript writing, and critical review of the manuscript and approval of the final version: S Park, YJ Jeon, S Lim, WJ Kwon, SH Choi, and NH Park. Data collection and critical review of the manuscript and approval of the final version: Seungbong Han. Data analysis, manuscript writing, critical review of the manuscript, and approval of the final version: GM Park. All authors reviewed the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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