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ORIGINAL ARTICLE

Coronary atherosclerosis across stages of metabolic dysfunction–associated steatotic liver disease: a VCTE–CCTA study

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Abstract

Background Metabolic dysfunction–associated steatotic liver disease (MASLD) and coronary artery disease (CAD) share common pathophysiologic pathways. However, the relationship between different stages of MASLD and distinct coronary atherosclerosis phenotypes remains unclear. We evaluated the association of hepatic steatosis and fibrosis with coronary artery disease outcomes using paired vibration-controlled transient elastography (VCTE) and coronary computed tomography angiography (CCTA).

Methods 425 adults who underwent both VCTE and CCTA within a three-month interval were included. MASLD was defined as controlled attenuation parameter (CAP) ≥248 dB/m, and significant fibrosis was defined as Liver Stiffness Measurement (LSM) ≥8 kPa. Coronary outcomes were assessed according to Coronary Artery Disease Reporting and Data System guidance. The primary outcome was plaque presence; secondary outcomes included obstructive stenosis, calcified plaque, high segment involvement, and CAD severity. Multivariable logistic regression models were progressively adjusted for demographic, lifestyle, and cardiometabolic factors.

Results MASLD was present in 47.3% of participants. Individuals with MASLD had a higher prevalence of overall plaque than those without (81.6% vs 60.7%, p<0.001), whereas obstructive stenosis did not differ between groups. MASLD was independently associated with higher odds of overall plaque presence after full adjustment (OR 2.22, 95% CI 1.04–4.73; p=0.038). In exploratory analyses, MASLD did not increase the odds of obstructive stenosis, calcified plaque, or CAD severity. In contrast, 1 kPa increase in LSM was associated with higher odds of obstructive stenosis (OR 1.14, 95% CI 1.00–1.30) and calcified plaque (OR 1.18, 95% CI 1.04–1.34), but not CAD presence and severity.

Conclusion MASLD was independently associated with the presence of coronary atherosclerotic plaque. Exploratory analyses further suggested that greater liver stiffness may be associated with obstructive stenosis and calcified plaque, raising the possibility that more advanced liver disease relates to specific features of advanced coronary artery disease. Confirmation in larger prospective studies is warranted.

Keywords MASLD · Coronary artery disease · Atherosclerosis · Fatty liver · CCTA · VCTE · NAFLD

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Introduction

Cardiovascular disease is the principal cause of mortality among individuals with metabolic dysfunction–associated steatotic liver disease (MASLD) [1]. While cardiovascular disease encompasses a broad range of conditions, coronary heart disease is the most common manifestation. It exists along a continuum, initially characterized by subclinical coronary atherosclerosis and progressively advancing to overt coronary artery disease (CAD), marked by plaque progression, luminal obstruction, and their associated clinical consequences in later stages [2].

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MASLD and CAD share key pathophysiological mechanisms, including insulin resistance, systemic inflammation, atherogenic dyslipidemia, and endothelial dysfunction, which may contribute to overlapping molecular pathways linking the two conditions [1]. Beyond shared risk factors, MASLD itself has increasingly been recognized as a potential contributor to CAD [3]. Multiple epidemiological studies have reported an independent association between steatotic liver disease and both subclinical and clinical manifestations of atherosclerosis [4]. However, important limitations remain in the existing literature. Most studies have characterized atherosclerosis using surrogate markers such as coronary artery calcium scores, carotid intima–media thickness, or arterial stiffness indices including brachial–ankle pulse wave velocity. These approaches do not provide information on plaque morphology, composition, or the presence of obstructive coronary stenosis, potentially overlooking clinically relevant aspects of the MASLD-CAD association. In contrast, coronary computed tomography angiography (CCTA) is recommended as a preferred non-invasive modality for assessing both coronary plaque characteristics and obstructive disease [5]. Furthermore, part of the prior evidence was generated in the era of nonalcoholic fatty liver disease (NAFLD), without incorporating the cardiometabolic framework underpinning the recently redefined MASLD construct [6–8]. This may limit the ability to disentangle whether observed associations are driven by hepatic steatosis itself or by accompanying metabolic dysfunction. Finally, hepatic steatosis in earlier studies has largely been assessed by ultrasonography [6, 9] or computed tomography [7, 10], both of which have limited sensitivity for detecting mild steatosis, while ultrasonography is additionally subject to operator dependency [11]. Moreover, these modalities do not provide information regarding liver fibrosis. In contrast, vibration-controlled transient elastography (VCTE) enables simultaneous, objective, and sensitive assessment of both hepatic steatosis and fibrosis across the full disease spectrum [12].

Therefore, in the present study, we aimed to evaluate the association between CAP-defined MASLD and multiple dimensions of coronary atherosclerosis assessed by CCTA, including plaque presence, burden, composition, and stenosis severity, in a cohort of individuals with contemporaneous VCTE assessment.

Methods

Study design and population

Participants were enrolled in a cross-sectional study conducted between February 2022 and December 2024 at an internal medicine outpatient center (NCT05194553). The study protocol was approved by the Istanbul Health Sciences University Clinical Research Ethics Committee (2021/224) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment, and all procedures were carried out in compliance with Good Clinical Practice guidelines.

Adult participants aged 18 to 80 years attending the study site for routine follow-up or initial evaluation of cardiometabolic conditions were recruited by their physicians. Eligible participants met at least one cardiometabolic risk factor required for MASLD diagnosis at the time of enrollment. Exclusion criteria included, excessive alcohol consumption (> 30 g/day for men and >20 g/day for women), current or prior use of hepatotoxic medications, other known causes of chronic liver disease, and current pregnancy or breastfeeding. A comprehensive list of inclusion and exclusion criteria for the cohort has been reported previously [13]. CCTA results of the eligible participants were retrieved from electronic medical records and were included if performed within three months of the VCTE assessment. CCTA had been requested by treating physicians for assessment of suspected or underlying cardiovascular conditions, cardiovascular risk stratification and coronary artery calcium assessment in individuals with increased atherosclerotic cardiovascular disease (ASCVD) risk, in accordance with contemporary guidance for adults with intermediate predicted cardiovascular risk [14].

Liver assessments

Hepatic steatosis was assessed using VCTE with the CAP, performed using a FibroScan device equipped with both M and XL probes. The M probe was used by default, with the XL probe applied when recommended by the device algorithm. Examinations were considered valid if participants had fasted for at least three hours, achieved a minimum of 10 valid liver stiffness measurements (LSM), and had an interquartile range to median ratio (IQR/median) of <30%. Steatosis was defined as CAP ≥ 248 dB/m, and significant fibrosis as LSM ≥ 8 kPa, consistent with established clinical guidance [15]. MASLD was defined as the presence of hepatic steatosis, as assessed by CAP, in addition to at least one of five predefined cardiometabolic risk factors [15].

CCTA assessments

CCTA was performed using a single-source 640-slice CT scanner (Aquilion ONE, Toshiba, Otawara, Japan). All scans were analyzed on a dedicated workstation (Vitrea Workstation, Toshiba, Otawara, Japan) by an experienced cardiovascular radiologist. Coronary artery segmentation was performed according to the recommendations of the Society of

Cardiovascular Computed Tomography using a standardized 16-segment coronary artery model [16]. Each coronary segment was assessed for the presence of stenosis and coronary atherosclerotic plaque. The contrast-enhanced coronary lumen was semi-automatically traced at the site of maximal stenosis and compared with the mean luminal diameter of the proximal and distal reference segments. Obstructive coronary stenosis was defined as luminal narrowing ≥50% [17]. Overall plaque presence was defined as the presence of any visible coronary atherosclerotic lesion in any coronary segment. Plaque burden was additionally assessed using the segment involvement score (SIS), calculated as the total number of coronary segments containing plaque; a SIS >4 was considered high segment involvement [16]. Plaque composition was evaluated visually, and Agatston score was calculated for coronary artery calcium. Plaques containing calcified tissue in >50% of the total plaque area with an attenuation of at least 130 Hounsfield Units were classified as calcified plaques [18]. Coronary plaque and stenosis severity were graded in accordance with the Coronary Artery Disease Reporting and Data System recommendations [17].

Covariate assessments

Anthropometric measurements, including waist circumference, weight, height, and blood pressure, were obtained on the day of VCTE evaluation. High waist circumference is defined as ≥94 cm for men and ≥80 cm for women [19]. A body mass index (BMI) of <25 kg/m^2, 25–30 kg/m^2, and >30 kg/m^2 were considered as normal weight, overweight, and obesity, respectively. Information on smoking status, alcohol consumption, lifestyle, medical history, medication use, and sociodemographic characteristics was collected using standardized questionnaires and extracted from participant's medical records when necessary. Mediterranean diet adherence was assessed with Mediterranean Diet Adherence Screener, a 14-point questionnaire translated and validated for the study population [20, 21]. Physical activity levels were evaluated using the short form of the International Physical Activity Questionnaire, which has also been translated and validated [22]. Blood samples were collected within one week of the VCTE assessment. Fasting blood glucose (FBG), fasting insulin, triglycerides (TAG), and high-density lipoprotein (HDL) cholesterol, liver function tests aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were analyzed using a biochemistry analyzer (Cobas, Roche Diagnostics, Basel, Switzerland) with commercial assay kits. Hypertension, dyslipidemia diagnosis was based on the International Diabetes Federation consensus [19]. Diabetes status was determined as normal glucose metabolism, prediabetes, or type 2 diabetes in accordance with the World Health Organization criteria [23].

Statistical analysis

The primary outcome of this study was the presence of overall plaque, and the primary exposure was MASLD. Secondary outcomes included obstructive stenosis, calcium plaques, high segment involvement, stenosis severity, and plaque severity, whereas secondary exposures included CAP and LSM. Analyses involving secondary outcomes and/or secondary exposures were exploratory in nature and were therefore not adjusted for multiple testing.

Continuous variables were summarized as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. Group comparisons were performed using Student's *t*-test for continuous variables and the chi-square test for categorical variables. Associations with CAD outcomes were examined using binary logistic regression, and associations with CAD severity using ordinal logistic regression. Multivariable models were progressively adjusted for age and sex, lifestyle (alcohol use, current smoking, adherence to Mediterranean diet, physical activity level), demographic (educational level, income categories), and metabolic (high waist circumference, diabetes status, hypertension, dyslipidemia, TAG, statin use) factors. Potential confounders were selected a priori based on their known influence on MASLD and potential associations with CAD.

Model assumptions were evaluated prior to analysis. Multicollinearity was assessed using variance inflation factors (VIFs); all VIFs <5 indicating no evidence of problematic collinearity. Influential observations were defined as those with a Cook's distance≥1. When such observations were detected, sensitivity analyses excluding these observations were performed to assess the robustness of the findings. Analyses both including and excluding the influential outliers were presented in the main text and in the supplements. Linearity assumptions were assessed for the continuous predictors (age, TAG, CAP, and LSM) by testing for a quadratic effect. Categorical variables were included using dummy coding and therefore were not subject to linearity assumptions. When a significant quadratic term was observed, the continuous predictor was mean-centered (X-mean (X)) and both the centered linear term and its quadratic term (X-mean (X))^2 were included in the model to account for non-linearity while reducing collinearity between the linear and quadratic components. For ordinal logistic regression models, the proportional odds assumption was tested and met. Unless otherwise noted in the Results section, all fitted models satisfied the relevant model assumptions.

A two-sided p value <0.05 was considered statistically significant. All analyses were performed using SPSS (version 30; IBM Corp., USA). Forest plots were obtained from the "forest" function of the "metafor" package in R (version 4.6.0, R Core Team, 2026).

Missing data

Missing data occurred only in the outcome variables (i.e., overall plaque, obstructive stenosis, calcium plaques, high segment involvement, stenosis severity, and plaque severity), due to the absence of CCTA results in 175 out of 640 recruited patients. Factors associated with outcome missingness were explored using logistic regression (Supplementary S1). Variables associated with missingness (i.e., age, education, income, TAG, hypertension, and statin use) were included in the main analyses to support the plausibility of the missing at random (MAR) assumption. Complete case analysis was performed for all analyses (n=425). Given that missingness was confined to the outcome variables and that models were adjusted for factors associated with missingness, complete case analysis was expected to yield results similar to those obtained using multiple imputation [24, 25], while being more straightforward to implement. However, results may still be biased if the untestable MAR assumption, which also underlies multiple imputation, does not hold.

Results

Study population

A total of 425 participants were included in the final analysis (Fig. 1). Of these, 201 (47.3%) were classified as having MASLD based on CAP ≥248 dB/m, while 224 (52.7%) did not have MASLD. A total of 34 (8%) participants presented with significant liver fibrosis (LSM≥ 8 kPa).

Baseline characteristics according to MASLD status are shown in Table 1. Age was similar between MASLD and non-MASLD groups, while the proportion of males was higher among participants with MASLD (p<0.001). Individuals with MASLD had a greater prevalence of central obesity and overall obesity (all p<0.001).

Education, income, alcohol consumption, and smoking status did not differ between groups. Participants with MASLD had lower adherence to the Mediterranean diet (p=0.002) and lower physical activity levels (p<0.001). Participants with MASLD had lower HDL-cholesterol and higher triglycerides, fasting glucose, HOMA-IR, liver enzyme levels, CAP, and LSM than those without MASLD (all p≤0.006), while LDL-cholesterol levels were similar between groups. Diabetes, hypertension, dyslipidemia, and obesity were more prevalent among participants with MASLD (all p<0.001).

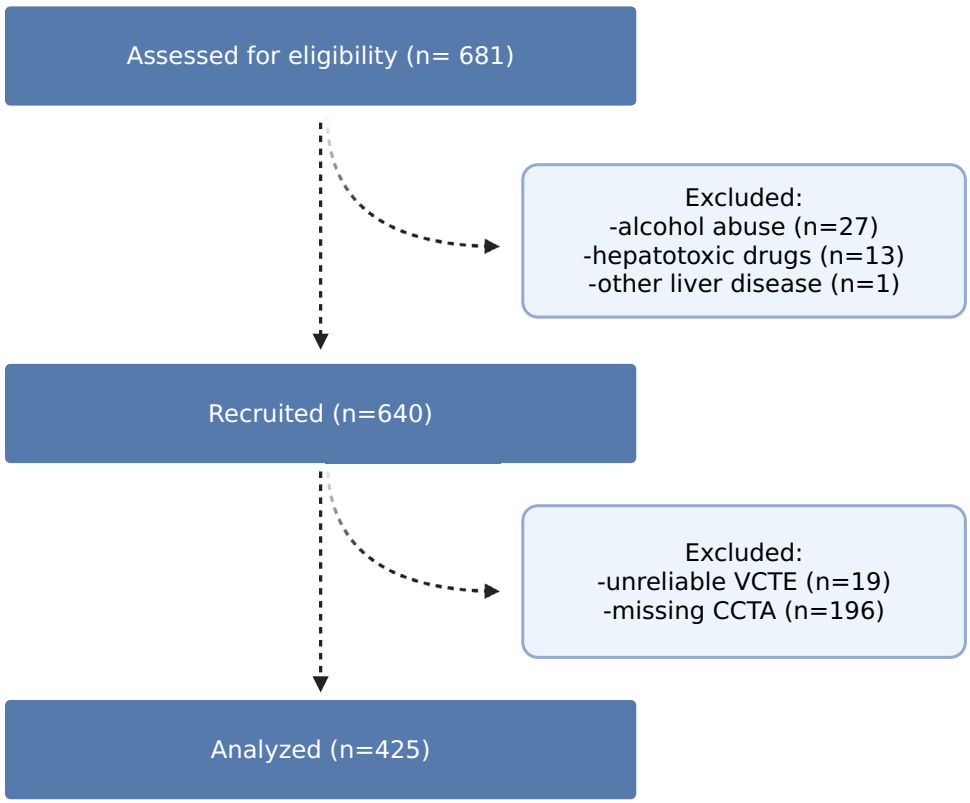


Fig. 1 Study flowchart. Abbreviations: CCTA, coronary computed tomography angiography; VCTE, vibration-controlled transient elastography

Table 1 Baseline characteristics of the study population according to MASLD status (defined by CAP ≥248 dB/m)

	All (*n*=425)	MASLD (*n*=201)	Non-MASLD (*n*=224)	*p*
Demographics				
Age	54.02 ± 11.77	54.55 ± 11.30	53.55 ± 12.19	0.383
Sex (% Male)	299 (70.4)	160 (79.6)	139 (62.1)	<0.001
High waist circumference (%)	284 (66.8)	183 (91.0)	101 (45.1)	<0.001
Normal weight (%)	67 (15.8)	5 (2.5)	62 (27.7)	<0.001
Overweight (%)	222 (52.2)	87 (43.3)	135 (60.3)	
Obese (%)	136 (32.0)	109 (54.2)	27 (12.1)	
Primary school (%)	13 (3.1)	7 (3.5)	6 (2.7)	0.869
Secondary school (%)	20 (4.7)	11 (5.5)	9 (4.0)	
High School (%)	119 (28.0)	57 (28.4)	62 (27.7)	
University or higher (%)	273 (64.3)	126 (62.7)	174 (65.6)	
Very low & Low Income (%)	28 (6.6)	12 (6.0)	16 (7.1)	0.908
Medium & Medium High Income (%)	206 (48.5)	98 (48.8)	108 (48.2)	
High Income (%)	191 (44.9)	91 (45.3)	100 (44.6)	
Lifestyle				
Alcohol (%)	259 (60.9)	122 (60.7)	137 (61.2)	0.922
Smoker (%)	142 (33.4)	68 (33.8)	74 (33.0)	0.862
Low adherence to Mediterranean diet (%)	140 (32.9)	82 (40.8)	58 (25.9)	0.002
Medium adherence to Mediterranean diet(%)	229 (53.9)	100 (49.8)	129 (57.6)	
High adherence to Mediterranean diet (%)	56 (13.2)	19 (9.5)	37 (16.5)	
Physically inactive (%)	154 (36.2)	104 (51.7)	50 (22.3)	<0.001
Physically Active (%)	222 (52.2)	89 (44.3)	133 (59.4)	
Physically Highly active (%)	49 (11.5)	8 (4.0)	41 (18.3)	
Biochemical measurements				
Total cholesterol (mg/dl)	197.64 ± 56.22	191.72 ± 59.25	202.97 ± 52.98	0.040
HDL-cholesterol (mg/dl)	49.72 ± 14.75	44.43 ± 12.73	54.46 ± 14.67	<0.001
LDL-cholesterol (mg/dl)	116.53 ± 47.30	114.62 ± 50.42	118.25 ± 44.28	0.433
TAG (mg/dl)	164.67 ± 108.03	183.29 ± 110.84	147.96 ± 101.43	<0.001
FBS (mg/dl)	98.23 ± 30.96	102.56 ± 33.18	94.35 ± 28.42	0.006
HOMA-IR	3.73 ± 4.28	4.57 ± 3.92	2.99 ± 4.44	<0.001
ALT (UI/l)	27.40 ± 18.04	31.60 ± 20.59	23.64 ± 14.49	<0.001
AST (UI/l)	23.70 ± 14.45	25.79 ± 17.27	21.83 ± 10.68	0.005
GGT (UI/l)	31.33 ± 36.41	37.94 ± 41.22	25.40 ± 29.83	<0.001
Liver measurements				
CAP (dB/m)	244.85 ± 50.23	287.57 ± 33.25	206.51 ± 27.91	<0.001
LSM (kPa)	5.38 ± 2.43	5.83 ± 2.39	4.97 ± 2.39	<0.001
Cardiac measurements				
Overall plaque (%)	300 (70.6)	164 (81.6)	136 (60.7)	<0.001
Obstructive stenosis (%)	108 (25.4)	57 (28.4)	51 (22.8)	0.186
Segment involvement score	6.18 ± 4.67	7.11 ± 4.52	5.35 ± 4.64	<0.001
Agatston score	130.03 ± 407.88	157.80 ± 520.61	106.56 ± 271.15	0.241
Medical history				
Obesity (%)	138 (32.5)	109 (54.2)	29 (12.9)	<0.001
Diabetes (%)	142 (33.4)	93 (46.3)	49 (21.9)	<0.001
Hypertension (%)	318 (74.8)	170 (84.6)	148 (66.1)	<0.001
Dyslipidemia (%)	374 (88.0)	187 (93.0)	187 (83.5)	<0.001
CMRF (out of 5)	3.0±1.4	3.7±1.1	2.4±1.4	<0.001

The prevalence overall plaque was higher among participants with MASLD (p<0.001), whereas obstructive coronary artery disease did not differ between groups. Segment involvement score was higher in the MASLD group (p<0.001), while Agatston score was similar between groups. Clinical characteristics of the participants with and without plaque is provided in the Supplementary S2.

Data are presented as mean±standard deviation and frequencies (percentages); p < 0.05 considered as statistically significant. ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CAP, controlled attenuation parameter; CMRF, cardiometabolic risk factor; FBG, fasting blood glucose; GGT; Gamma-glutamyl transferase, HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; TAG, triglycerides; TC, total cholesterol.

Primary analyses: MASLD and overall plaque

MASLD was more frequent among participants with coronary stenosis and plaque (Fig. 2). MASLD was present in 54.7% of participants with plaque compared with 29.6% of those without plaque.

In binary logistic regression analyses, MASLD was independently associated with the presence of overall coronary plaque (Table 2, Fig. 3). Participants with MASLD had nearly threefold greater odds of plaque in crude analyses (OR 2.87, 95% CI 1.84–4.48; p<0.001), and the association remained statistically significant, with a substantial effect size, after full adjustment for demographic, lifestyle, and cardiometabolic factors. Even in the fully adjusted model, MASLD was associated with more than twofold greater odds of overall plaque presence (OR 2.22, 95% CI 1.04–4.73; p=0.038).

In the primary analysis of overall plaque presence, two influential observations were identified. Nevertheless, sensitivity analyses excluding these observations yielded similar results (Supplementary S3). Furthermore, sensitivity analyses modeling hepatic steatosis as a continuous exposure yielded consistent findings with results in Table 2. Each 10 dB/m increase in CAP was independently associated with higher odds of overall plaque presence in the fully adjusted model (OR 1.12, 95% CI 1.03–1.23; p=0.007), corresponding to a 12% increase in the odds. Similar effect estimates (15%-17% higher odds) were observed in the crude and partially adjusted models (Supplementary S4). Sensitivity analyses modeling hepatic steatosis as a continuous exposure and excluding influential observations (n=3) also yielded similar results (Supplementary S5).

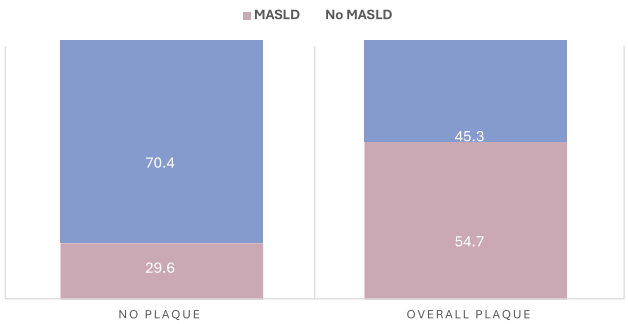


Fig. 2 Prevalence of MASLD (defined by CAP ≥248 dB/m) in coronary artery disease according to overall plaque status

Table 2 Binary logistic regression showing the impact of MASLD (defined by CAP ≥248 dB/m) on the presence of coronary artery disease outcomes (n=425)

		OR (95% CI)	p
Overall plaque	Crude Model	2.87 (1.84, 4.48)	<0.001
	Model 1	3.31 (1.85, 5.92)	<0.001
	Model 2	2.94 (1.55, 5.57)	<0.001
	Model 3	2.22 (1.04, 4.73)	0.038

Model 1: adjusted for age and sex

Model 2: Model 1 plus lifestyle factors (Mediterranean diet adherence level, physical activity level, alcohol, smoker) and demographic factors (educational level, income categories)

Model 3: Model 2 plus health-related factors (high waist circumference, diabetes status, hypertension, dyslipidemia, TAG, statin use). NB: Model 3 adjusted for all observed factors associated with outcome missingness and is therefore considered most consistent with the MAR assumption

Secondary analyses

The following analyses were prespecified as exploratory to evaluate the associations between MASLD, liver disease severity, and individual coronary artery disease phenotypes. Given their exploratory nature, no adjustment for multiple testing was applied. Accordingly, these findings are considered hypothesis-generating and should be interpreted cautiously rather than as confirmatory evidence.

MASLD and other coronary artery disease outcomes

MASLD prevalence increased from 33.8% in those without stenosis to 49.4% and 52.8% in those with non-obstructive and obstructive stenosis, respectively. MASLD was not positively associated with obstructive coronary stenosis in any adjusted model, but it was associated with moderately increased odds of coronary calcium plaque and high segment involvement in crude analyses, corresponding to 53% higher odds of calcium plaque and 85% higher odds of high segment involvement. However, the magnitude of these associations was substantially attenuated after adjustment

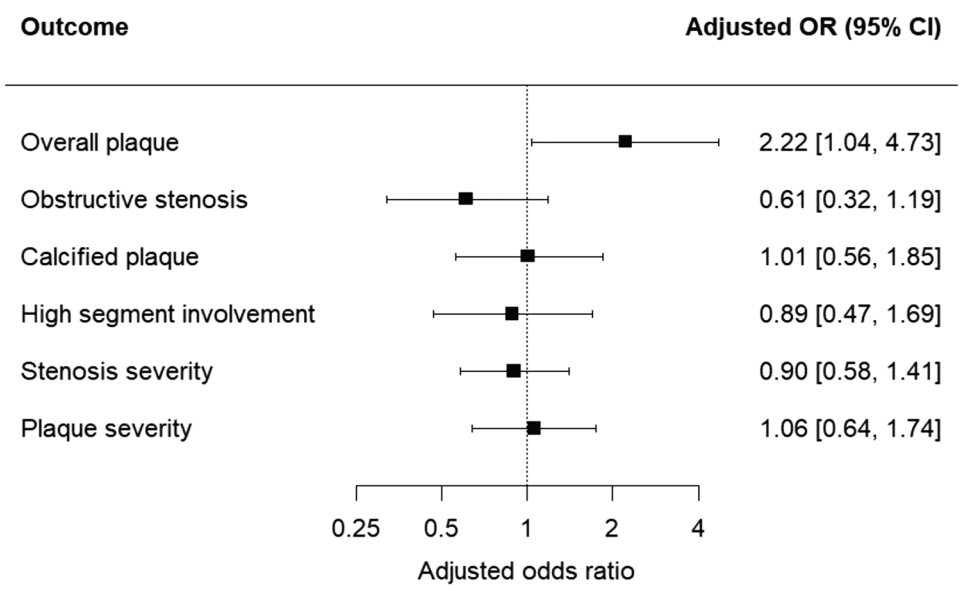


Fig. 3 Adjusted odds ratios (OR) for the association between MASLD and the primary and secondary coronary artery disease outcomes from the fully adjusted models (n=425). The models were adjusted for age, sex, Mediterranean diet adherence, physical activity level, alcohol, smoking status, educational level, income category, high waist circumference, diabetes status, hypertension, dyslipidemia, TAG, and statin use

for cardiometabolic factors (calcium plaque: OR 1.01, 95% CI 0.56–1.85, p=0.962; high segment involvement: OR 0.89, 95% CI 0.47–1.69, p=0.731) (Fig. 3, Supplementary S6).

MASLD and coronary artery disease severity

The association between MASLD and coronary artery disease severity is presented in Fig. 3 and Supplementary S7. In the crude analysis, MASLD was associated with higher stenosis severity, with 63% higher odds of belonging to a more severe stenosis category (OR 1.63, 95% CI 1.16–2.30; p=0.005). Adjustment for age and sex only modestly attenuated the odds ratio (OR 1.43, 95% CI 0.99–2.05; p=0.053), and further adjustment resulted in gradual attenuation of the association. Similarly, MASLD was associated with nearly twofold higher odds of more severe plaque burden in crude analysis (OR 1.98, 95% CI 1.39–2.82; p<0.001). The magnitude of association remained considerable after adjustment for age and sex (OR 1.88, 95% CI 1.26–2.80; p=0.002) and after additional adjustment in Model 2 (OR 1.63, 95% CI 1.06–2.52; p=0.026), corresponding to approximately 60–90% higher odds of greater plaque severity across these models. However, the odds ratio was markedly reduced in the fully adjusted model (OR 1.06, 95% CI 0.64–1.74; p=0.829).

Fibrosis and coronary artery disease

Given the low number of participants with significant fibrosis in the study population (n=34), fibrosis analyses were performed using LSM as a continuous variable. In analyses with obstructive stenosis and calcium plaques as outcomes, one influential observation was identified. Although evidence of an association between LSM and these outcomes was observed both with and without this observation, its inclusion meaningfully altered the estimated functional form of the association. Specifically, models including the influential observation suggested a nonlinear relationship, whereas models excluding it supported a linear association. Therefore, the following analyses for LSM were performed after excluding this influential observation, as this yielded a linear association and enabled a more consistent comparison with the results for the other outcomes (Supplementary S8). Sensitivity analyses including the influential observation are also presented in the Supplementary S9.

While higher LSM was not independently associated with overall plaque presence, it remained associated with obstructive stenosis and calcium plaque after full adjustment (Fig. 4, Supplementary S8). Across models, higher LSM was associated with increased odds of obstructive stenosis (ORs 1.14–1.19) and calcium plaque (ORs 1.18–1.24), corresponding in fully adjusted models to approximately 14% and 18% higher odds per 1 kPa increase, respectively. Associations between LSM and high segment involvement were of similar magnitude in crude and age- and sex-adjusted models (OR 1.15–1.20), but were attenuated after adjustment for lifestyle, demographic, and cardiometabolic factors (OR 1.05–1.09). Likewise, higher LSM was associated with greater odds of higher stenosis severity in crude and partially adjusted models (OR 1.10–1.15); however, this association was attenuated after adjustment for health-related factors (OR 1.06, 95% CI 0.97–1.15). For plaque severity, the association with LSM was weakened following adjustment for lifestyle and demographic factors. In the full model, the association was small (OR 1.03, 95% CI 0.93–1.13), providing limited evidence of an independent association between LSM and plaque severity (Fig. 4, Supplementary S10).

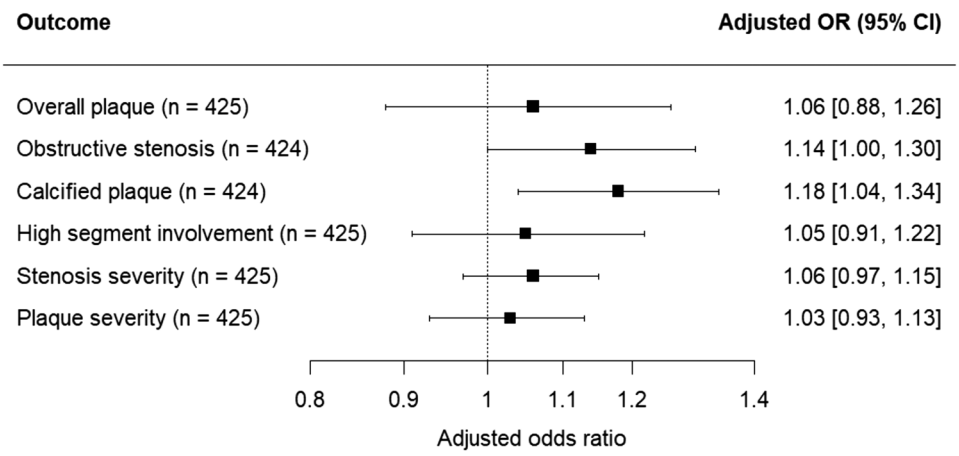


Fig. 4 Adjusted odds ratios (OR) for the association between 1 kPa increase in LSM and the presence and severity of coronary artery disease from the fully adjusted model. The model was adjusted for age, sex, Mediterranean diet adherence, physical activity level, alcohol, smoking status, educational level, income category, high waist circumference, diabetes status, hypertension, dyslipidemia, TAG, and statin use

Discussion

In this matched VCTE–CCTA study, we found that MASLD was independently associated with coronary atherosclerotic plaque presence. In exploratory analyses, higher liver stiffness was associated with higher odds of obstructive stenosis and calcified plaques. These findings suggest that MASLD may be associated with coronary plaque development, whereas more advanced liver disease may be linked to specific features of advanced coronary artery disease.

The existing literature generally supports our observation that hepatic steatosis is more closely linked to atherosclerosis initiation, whereas fibrosis may be associated with more advanced coronary disease. A cross-sectional study reported that MASLD was associated with non-calcified plaques, but not with obstructive CAD or calcified plaques [9]. In the ROMICAT trial, MASLD was independently associated with high-risk coronary plaque irrespective of plaque burden, coronary calcium, or stenosis severity, supporting a relationship with plaque vulnerability rather than advanced luminal obstruction [7]. Prior CCTA studies have similarly suggested that MASLD is more strongly associated with plaque phenotype than stenosis severity alone [6–8, 10, 26]. Collectively, these findings support the notion that MASLD may preferentially relate to early atherogenesis and plaque development rather than later stages of coronary artery disease. This interpretation is consistent with our observation that MASLD was associated with more than twofold higher odds of coronary plaque presence. Moreover, our exploratory findings suggest that more advanced liver disease could be linked to more advanced coronary atherosclerosis. Evidence regarding the relationship between fibrosis and coronary artery disease remains limited and methodologically heterogeneous. Kubotsu et al. reported an association between LSM and increased carotid intima–media thickness [27], while another cross-sectional study found 24% higher odds of plaque presence among individuals with significant fibrosis defined by LSM [28]. However, atherosclerosis in the latter was assessed using carotid ultrasonography or vascular stiffness indices rather than direct coronary imaging. Chen et al. and Xin et al. also reported associations between fibrosis and subclinical atherosclerosis, although fibrosis was assessed using blood-based indices and atherosclerosis was defined by carotid intima media thickness [29, 30]. Thus, evidence directly linking fibrosis with detailed coronary plaque phenotypes and stenosis severity remains scarce. Our study extends the existing literature by simultaneously evaluating hepatic steatosis and fibrosis using VCTE alongside detailed coronary phenotyping by CCTA. Given the relatively small number of participants with significant fibrosis, and exploratory nature of our secondary analyses, these findings should be considered hypotheses-generating and warrant confirmation in larger prospective studies. Furthermore, the non-MASLD group comprised individuals with cardiometabolic risk factors who did not have CAP-defined hepatic steatosis rather than metabolically healthy controls. Therefore, the observed associations should be interpreted within the context of comparisons between at-risk individuals, and future studies including healthy control populations are needed to better define the incremental contribution of MASLD to coronary atherosclerosis.

Several mechanisms may explain the distinct pattern of associations observed between steatosis, fibrosis, and coronary artery disease phenotypes. Hepatic steatosis may be preferentially associated with coronary plaque development through metabolic and inflammatory pathways proposed in experimental and clinical studies. MASLD is strongly linked to hepatic insulin resistance, which promotes increased de novo lipogenesis and an atherogenic lipoprotein profile characterized by hypertriglyceridemia, reduced HDL-cholesterol, and a predominance of small dense LDL particles [3]. This dyslipidemic milieu may facilitate lipid deposition within the arterial wall and promote early atherogenesis [31]. In parallel, hepatic fat accumulation activates inflammatory signaling pathways, leading to increased systemic release of pro-inflammatory mediators, including tumor

necrosis factor-α and interleukins, which contribute to oxidative stress and vascular inflammation [32]. MASLD could further exacerbate endothelial dysfunction through impaired nitric oxide bioavailability, promoting leukocyte recruitment and facilitating foam cell formation [33]. Furthermore, early stages of MASLD preceding advanced fibrosis have been associated with active angiogenesis and increased circulating vascular endothelial growth factor levels, which theoretically contribute to atherogenesis and plaque instability [34]. Fibrosis, on the other hand, has been proposed to represent a marker of cumulative metabolic injury and prolonged inflammatory burden rather than hepatic steatosis alone [35]. It is characterized by sustained immune activation, chronic inflammation, and more severe metabolic dysfunction [36], factors that contribute to plaque maturation, vascular remodeling, calcification, and eventual luminal obstruction. From this perspective, fibrosis may reflect a later stage of the cardiometabolic disease spectrum, corresponding to more advanced phases of coronary atherosclerosis. This interpretation is consistent with a meta-analysis of studies in which the risk of fatal and non-fatal cardiovascular events appeared to increase further with greater severity of fibrosis [37]. Likewise, in our exploratory analyses, higher liver stiffness measurement values were associated with higher odds of obstructive stenosis and calcified plaque, but not overall plaque presence. Nevertheless, given the cross-sectional nature of our study, these mechanisms remain speculative and cannot establish a causal or temporal relationship between liver disease progression and coronary artery disease.

From a clinical perspective, our findings suggest a potential stage-specific relationship between liver disease severity and coronary atherosclerosis. Current clinical pathways in MASLD emphasize fibrosis assessment using widely accessible and non-invasive tools such as fibrosis scores and VCTE, primarily to identify individuals at risk of liver-related complications. Our primary findings demonstrate an independent association between MASLD and coronary plaque burden, whereas the exploratory analyses raise the possibility that liver stiffness may provide additional information regarding more advanced manifestations of coronary artery disease. Given that coronary atherosclerosis precedes the development of obstructive disease and subsequent cardiovascular events, early identification of plaque burden is a central objective of preventive cardiology. Notably, neither steatosis nor fibrosis is currently incorporated into widely used cardiovascular risk prediction tools such as Systematic Coronary Risk Evaluation (SCORE2) [38] or Atherosclerosis Cardiovascular Disease (ASCVD) risk estimator [39], despite growing evidence linking advanced liver disease with adverse cardiovascular outcomes. The absence of liver disease parameters in cardiovascular risk stratification models may lead to underrecognition of cardiovascular risk related to MASLD-specific pathways that appear to contribute independently to coronary artery disease. Although Japanese clinical practice guidelines recommend cardiology consultation in patients with elevated fibrosis risk, current AASLD and EASL guidance lacks fibrosis-based recommendations for cardiovascular evaluation [40]. While our findings are exploratory and do not support routine coronary screening in all patients with MASLD, they suggest that further research should evaluate whether VCTE-derived measures provide incremental value for cardiovascular risk assessment and whether individuals with significant fibrosis warrant closer cardiovascular evaluation.

Our study has several strengths. First, we leveraged paired VCTE and CCTA, allowing detailed assessment of both liver disease and coronary artery disease phenotypes. Second, unlike much of the earlier literature conducted in the NAFLD era and relying on ultrasonography or computed tomography for steatosis assessment, we applied the contemporary MASLD framework and used CAP, a more sensitive and objective modality for hepatic steatosis quantification. Third, detailed coronary phenotyping by CCTA enabled evaluation of plaque presence, calcification, burden, and stenosis severity beyond surrogate measures such as coronary calcium score or carotid intima–media thickness. Nevertheless, several limitations merit consideration. The single-center and cross-sectional design and the lack of mechanistic biomarkers precludes causal inference and does not allow determination of causal or temporal relationships between liver disease progression and coronary atherosclerosis. Furthermore, analyses involving secondary outcomes and secondary exposures were prespecified as exploratory and were intended to characterize different manifestations of coronary atherosclerosis across the spectrum of liver disease severity. Consequently, formal adjustment for multiple comparisons was not performed. Their findings should therefore be interpreted cautiously because of the increased risk of type I error. Furthermore, because CCTA examinations were performed only when clinically indicated rather than systematically in all eligible participants, referral bias cannot be excluded. Given that all analyses were performed within a clinically referred population and multivariable models adjusted for major cardiometabolic risk factors, the internal comparisons remain informative, although external generalizability of the findings should be interpreted with caution. In addition, this referral strategy resulted in the lack of CCTA data for 196 participants. Factors associated with CCTA availability were identified using multivariable logistic regression and incorporated into all fully adjusted analyses to account for systematic differences between participants with and without CCTA data, thereby strengthening the plausibility of the MAR assumption. However, the validity of the findings depends on the tenability of this untestable assumption. One participant with markedly elevated liver

stiffness exerted substantial influence on model estimates and altered the estimated functional form of the association between liver stiffness and both obstructive stenosis and calcium plaque. Although the overall conclusions regarding the presence of an association were consistent, the shape of the association differed depending on whether this observation was included. We therefore present primary analyses excluding this influential observation and provide corresponding sensitivity analyses including the observation, with appropriate modeling of the non-linear association, in the supplementary material. Additionally, the study population was characterized by generally low liver stiffness values and a limited number of participants with significant fibrosis, which may limit the generalizability of fibrosis-related findings. Finally, residual confounding cannot be excluded despite extensive multivariable adjustment.

In conclusion, MASLD was independently associated with the presence of coronary atherosclerotic plaque in this matched VCTE–CCTA study, greater liver stiffness may increase the odds of advanced coronary artery disease. Future longitudinal studies are warranted to investigate the temporal relationship between liver disease progression and coronary artery disease.

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Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval The study was conducted in accordance with the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of Istanbul Health Sciences University (protocol code 2021/244 and 08.12.2021).

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