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Inflammation mediates the relationship between cardiometabolic index and vulnerable plaque in patients with acute coronary syndrome

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Abstract

Background As a novel indicator reflecting metabolic status and visceral adiposity distribution, the cardiometabolic index (CMI) has gained attention in cardiovascular risk stratification. This investigation employed optical coherence tomography (OCT) to examine potential associations between CMI and vulnerable plaque, as well as the role of inflammation.

Methods This study conducted a cross-sectional analysis of 270 acute coronary syndrome (ACS) patients who had OCT imaging evaluation. Patients were categorized based on CMI tertiles, with CMI calculated using the formula [waist (cm)/height (cm)]×[triglycerides (mmol/L)/HDL-C (mmol/L)]. OCT was used to assess plaque events in culprit lesions and plaque components in non-culprit lesions, and inflammatory markers were measured. A mediation analysis framework was implemented to investigate inflammatory pathways in CMI-vulnerable plaque relationships.

Results CMI tertiles were linked to vulnerable plaque traits: thin-cap fibroatheromas (TCFA), macrophages (Tertiles1 vs. Tertiles2 vs. Tertiles3, TCFA: 10.0% vs. 20.0% vs. 26.7%, $P=0.016$; macrophages: 17.8% vs. 28.9% vs. 36.7%, $P=0.019$). Multivariate regression demonstrated CMI elevation independently predicted a higher prevalence of TCFA (OR:1.40, 95%CI: 1.25–2.89, $P=0.003$), more macrophage infiltration (OR:1.61, 95% CI:1.09–2.37, $P=0.017$), reduced FCT (β:-30.65, 95% CI:-50.72-10.57, $P=0.003$), and enlarged maximum lipid arc (β:20.78, 95% CI:6.55–35.01, $P=0.004$). Moreover, CMI was positively related to hsCRP, WBC, and neutrophils. Mediation analysis revealed that hsCRP mediated about 17.0% of the association between CMI and minimum FCT [Indirect effect=-5.21, 95% CI=(-12.70, -1.27), $P=0.016$].

Conclusions CMI is a key forecaster of vulnerable plaque in patients with ACS. Systemic inflammation is associated with the relationship between CMI and vulnerable plaque features, suggesting a potential mechanistic link.

Keywords Vulnerable plaque, Inflammation, Cardiometabolic index

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Introduction

Acute Coronary Syndrome (ACS) is a critical condition with rapid onset. Despite improved cardiovascular disease prognosis due to advancements in percutaneous coronary intervention and medications, ACS remains a leading global cause of death. Early identification of its pathogenic mechanisms and prognostic risk markers is crucial [1, 2].

Cardiometabolic diseases encompass a range of metabolic dysfunctions that accelerate the progression of atherosclerosis [3]. The Cardiometabolic Index (CMI), as an easily accessible indicator, was initially used for the prediction of diabetes and serves as a marker of individual cardiometabolic health status and a reflection of visceral fat distribution. Based on this, recent studies have found that CMI serves as a strong indicator for predicting metabolic syndrome (MetS) and demonstrates significant correlations with cardiovascular disease (CVD) over extended follow-up periods [4–6]. Optical Coherence Tomography (OCT) provides superior spatial resolution (10–15 μm) that can clearly identify atherosclerotic plaque characteristics, including such as Thin-Cap Fibroatheromas (TCFA) and macrophages [7, 8]. These vulnerable plaques increase the risk of ACS and can significantly worsen patient prognosis. However, current research gaps persist regarding the relationship between CMI and OCT-identified plaque components.

Inflammation drives the advancement of atherosclerosis and the formation of vulnerable plaques through various pathways and is present from the earliest stages of the pathology. The pro-inflammatory process of atherosclerosis is associated with metabolic dysfunction and is currently considered a result of chronic inflammation, with high-sensitivity C-reactive protein (hsCRP) being the most commonly utilized biomarker [9–11]. In addition, the Neutrophil-to-lymphocyte ratio (NLR) and several other inflammatory indicators are also confirmed to be correlated with atherosclerosis [12, 13].Recent studies have found a connection between CMI and systemic inflammation, suggesting that CMI may have a potential role in inflammation-promoted atherosclerosis [14].

This study hypothesizes that CMI is associated with vulnerable plaques identified by OCT, with inflammatory markers acting as intermediaries. We innovatively use intravascular imaging OCT to explore this correlation and assess the intermediary role of inflammatory markers, clarifying how CMI affects atherosclerosis progression in ACS patients. These findings propose novel insights and introduce a candidate biomarker to enhance early risk stratification, advance precision medicine in ACS management.

Methods

Study population

At the Cardiology Department of Beijing Jishuitan Hospital, 366 ACS patients who had percutaneous coronary intervention (PCI) and OCT examination between January 2023 and January 2024 were initially enrolled. Participants were selected based on: ACS diagnosis; age ≥ 18 years; and first - time coronary angiography and OCT. The exclusion criteria were lack of preintervention OCT examination, prior PCI or coronary artery bypass graft (CABG), poor OCT imaging, cardiogenic shock, severe hepatorenal insufficiency, severe coronary calcification, and incomplete clinical data. Finally, 270 eligible ACS patients' OCT images were analyzed. ACS was diagnosed based on current guideline standards [15]. The patients' general information, laboratory results, and medication usage during hospitalization were collected. Ethical approval was obtained from the Ethics Committee of Beijing Jishuitan Hospital, Capital Medical University (K2024-162-00) (Fig. 1).

CMI assessment

The CMI is defined as [triglycerides (TG, mmol/L) / high-density lipoprotein cholesterol (HDL-C, mmol/L)] × [Waist (cm) / Height (cm)] [4]. All participants were divided into tertiles based on CMI for subsequent analysis.

OCT procedure and imaging analysis

The culprit vessel related to the infarction was determined by two highly qualified cardiologists using the ILUMIEN OPTIS OCT system. All OCT results were conducted by two interventional cardiologists blinded from angiographic findings and baseline clinical data. They used image analysis software (Abbott, USA) to analyze results, resolving discrepancies through consensus. Culprit vessels were evaluated per consensus standards [16]; including the plaque events for culprit lesions (Plaque rupture or no) and plaque components for non-culprit lesions (Non-culprit lesions were selected based on the most stenotic site within the proximal/distal segments ≥ 5 mm from the culprit lesion): TCFA, lipid-rich plaque, minimum lumen area (MLA), minimum fibrous cap thickness (FCT), microvessels, etc. (Fig. 2, Supplementary appendix)

Statistical analysis

Data processing was conducted using IBM SPSS Statistics 26.0 (IBM Corp., USA) and R programming language v4.4.2. Baseline demographic and clinical characteristics were stratified based on CMI tertile distributions. Descriptive statistics were computed with categorical data presented as frequency counts (percentages), while continuous measures were reported as median values

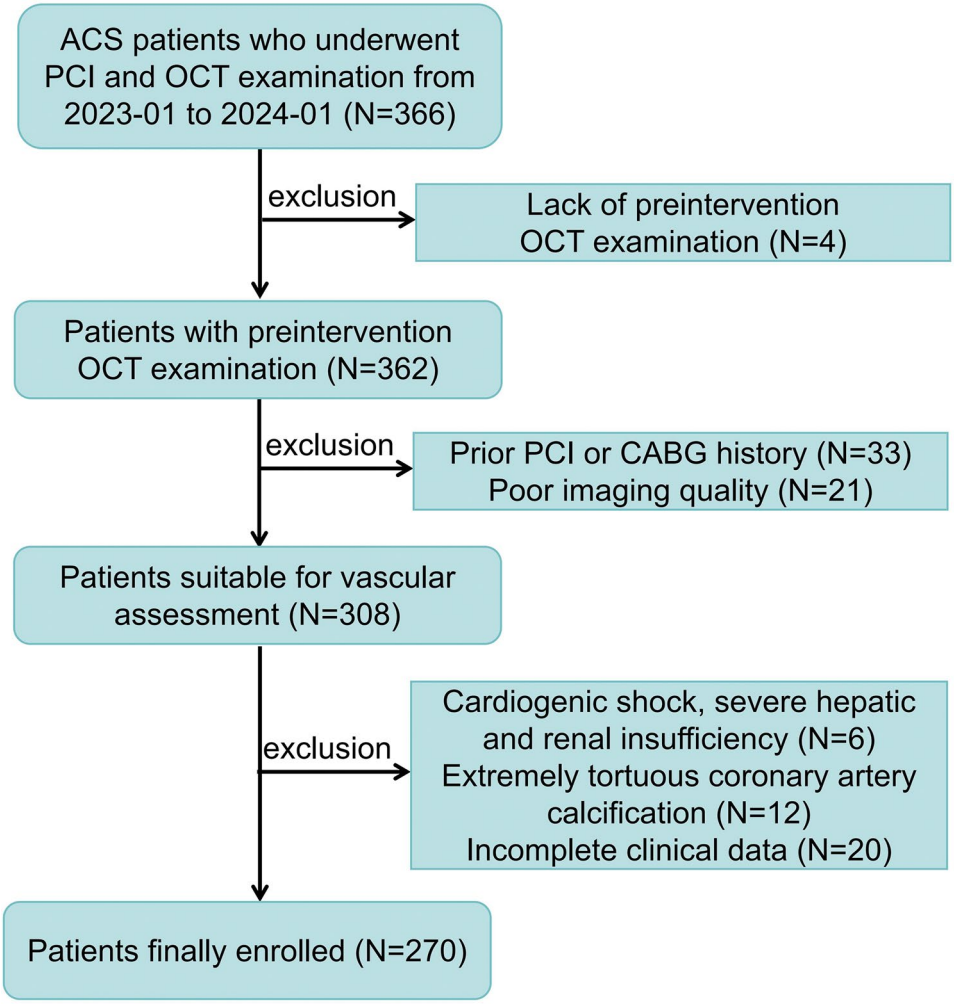

Fig. 1 Flowchart of study participants

with interquartile ranges following distributional assessment. Group comparisons used χ^2 or Fisher's tests for categorical data, and ANOVA or Kruskal-Wallis tests for continuous data, depending on normality. Multivariable regression models, including linear and logistic approaches, were implemented to examine associations between CMI and inflammatory markers [white blood cells(WBC), neutrophils, lymphocytes, NLR, and hsCRP] and plaque characteristics, adjusted for gender, age, body mass index (BMI), hypertension, hyperlipidemia, diabetes, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), current smoking, and family history [17]. Mediation effects were evaluated using the 'mediation' package, with significance defined by significant direct and total effects and a measurable indirect effect. Inter- and intra-observer variability was assessed by Cohen's Kappa and means of the intraclass correlation coefficient (ICC) for the absolute value. Statistical significance was determined as a two-sided $P<0.05$.

Results

Baseline data comparison of patients with different CMI tertiles

Among the 270 patients enrolled, 31 had STEMI (11.5%), 58 had NSTEMI (21.5%), and 181 (67.0%) had unstable angina (Table 1). In all participants, the CMI value was 0.95 ± 0.78, with T1 group at 0.42 ± 0.10, T2 group at 0.74 ± 0.10, and T3 group at 1.68 ± 0.96. Participants in the higher CMI tertiles exhibited younger age, had higher BMI, hsCRP, WBC, neutrophil, and NLR, fasting blood glucose, and lipid marker levels. Additionally, diabetes mellitus (DM) and hypertension prevalence exhibited positive association with elevated CMI levels.

Characterization of vulnerable plaques across different CMI tertiles

Analysis of OCT plaque characteristics revealed that as CMI tertiles increased, TCFA and macrophage infiltration significantly increased. FCT was significantly reduced in the highest CMI tertile, while the maximum

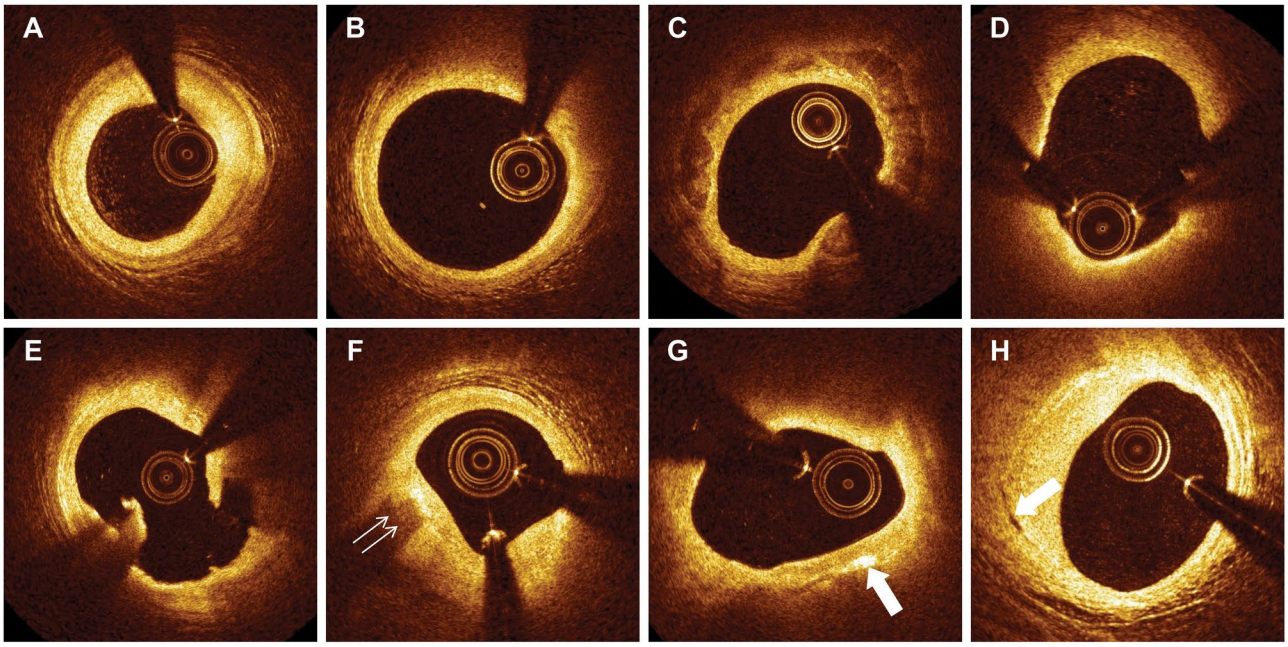

Fig. 2 Representative cross-sectional optical coherence tomography images. A Fibrous plaque B Lipid plaque C Calcified plaque D Thin-cap fibroatheroma E Plaque rupture F Macrophage infiltration (arrow) G Cholesterol crystal (arrow) H Microvessel (arrow)

lipid arc significantly increased. Regression analysis revealed that in a fully adjusted model, TCFA [Odds Ratio (OR):1.400, 95% Confidence Interval (CI): 1.25–2.89, $P = 0.003$], macrophages (OR: 1.61, 95% CI 1.09–2.37, $P = 0.017$), minimal FCT (β: -30.65, 95% CI -50.72–10.57, $P = 0.003$), and maximum lipid arc (β: 20.78, 95% CI 6.55–35.01, $P = 0.004$) all significantly increased with increasing CMI values(Tables 2 and 3). Restricted Cubic Spline (RCS) modeling revealed linear correlations of CMI with TCFA, minimal FCT, and maximum lipid arc (Fig. 3A). A non-linear relationship between CMI and macrophage was identified in this study, with a turning point observed at a CMI of 1.15 (Supplementary Table S1). And stratified analysis revealed a 5.76-fold increased probability of macrophage formation (95% CI 1.08–30.72, $P = 0.040$) when CMI remained below the 1.15 threshold. However, this relationship lost statistical significance when CMI values exceeded 1.15 ($P = 0.671$). Figure 3B provides OCT typical images from patients with CMI levels in the three groups. Inter - and intra - observer agreement for the four key plaque characteristics were shown in Supplementary Table S2.

Associations of inflammatory markers with CMI and plaque characteristics

The results of the association analysis between inflammatory markers and CMI are shown in Table 4. After implementing multivariable adjustment for covariates, significant positive associations were identified between CMI and inflammatory markers, including WBC ($P = 0.029$), neutrophil ($P = 0.046$), and hsCRP ($P < 0.001$). RCS modeling demonstrated linear dose-response patterns for CMI with WBC (Poverall = 0.024), neutrophils (Poverall = 0.028), and hsCRP (Poverall < 0.001).(Fig. 4).

The results of the association analysis between inflammatory markers and plaque characteristics are shown in Table 5. Following comprehensive adjustment for potential confounders, TCFA was associated with NLR and hsCRP, macrophage was associated with WBC and neutrophils, and minimal FCT and maximum lipid arc were associated with hsCRP.

Mediation analysis of inflammation

Mediation analysis of inflammatory markers associated with CMI demonstrated that hsCRP mediated 17.0% of the association between CMI and minimal FCT [Indirect effect= -5.21, 95% CI= (-12.70, -1.27), $P = 0.016$]. However, no significant mediating effects were found in TCFA ($P = 0.124$), Macrophage ($P = 0.166$), Maximum lipid arc ($P = 0.312$). Additionally, none of the other inflammatory markers exhibited significant mediating effects across plaque characteristics (Table 6; Fig. 5).

Discussion

This study is the first exploration into the correlation between CMI and vulnerable plaques identified by OCT, and mediation analysis reveals the significant role of the inflammatory marker hsCRP in the association between CMI and minimal FCT, suggesting that inflammation is a potential mechanism linking CMI to vulnerable plaques.

Initially proposed by Wakabayashi et al. in 2015, the CMI has been indicated to be associated with DM

Table 1 Baseline characteristics

Variables	Tertiles1 ($n=90$)	Tertiles 2 ($n=90$)	Tertiles 3 ($n=90$)	*P* value	*P* for trend
Age (years)	66.00 (59.00, 72.25)	62.00 (52.75, 72.00)	58.50 (47.00, 69.00)	< 0.001	< 0.001
Male (n, %)	65 (72.2%)	63 (70.0%)	65 (72.2%)	0.930	1.000
BMI (kg/m2)	24.20 (22.44, 25.58)	25.94 (23.88, 27.85)	26.05 (24.51, 28.16)	< 0.001	< 0.001
Diagnosis (n, %)				0.606	
STEMI	10 (11.1)	8 (8.9)	13 (14.4)		-
NSTEMI	19 (21.1)	17 (18.9)	22 (24.4)		0.804
Unstable angina	61 (67.8)	65 (72.2)	55 (61.1)		0.414
Waist (cm)	89.00 (82.00, 95.00)	94.00 (88.75, 101.00)	96.00 (90.00, 102.25)	< 0.001	< 0.001
SBP (mmHg)	133.00 (120.00, 144.25)	127.50 (119.00, 143.00)	128.50 (120.75, 141.25)	0.665	0.604
DBP (mmHg)	71.50 (63.50, 79.25)	73.00 (64.00, 84.25)	75.00 (67.75, 81.25)	0.069	0.060
NT-proBNP (pg/ml)	106.70 (43.40, 344.70)	95.72 (45.93, 319.63)	74.94 (29.90, 268.93)	0.316	0.673
hsCRP	0.98 (0.39, 3.10)	1.43 (0.58, 4.66)	2.93 (0.89, 8.94)	< 0.001	0.025
White blood cells (×109/L)	6.13 (4.96, 7.21)	6.56 (5.51, 8.49)	7.52 (6.13, 9.26)	< 0.001	< 0.001
Neutrophil (×109/L)	3.70 (2.73, 4.57)	4.13 (3.17, 5.30)	4.65 (3.73, 6.23)	< 0.001	< 0.001
Lymphocyte (×109/L)	1.63 (1.34, 2.18)	1.75 (1.47, 2.34)	1.87 (1.47, 2.29)	0.335	0.556
NLR	2.08 (1.47, 2.94)	2.08 (1.59, 2.84)	2.46 (1.82, 3.52)	0.027	0.005
Albumin (g/L)	41.35 (39.08, 43.88)	42.45 (39.65, 44.75)	42.40 (40.48, 44.43)	0.141	0.086
Fasting blood glucose (mmol/L)	5.45 (4.50, 7.63)	5.85 (5.00, 7.03)	6.20 (5.08, 8.30)	0.020	0.027
TC (mmol/L)	3.61 (2.78, 4.33)	3.64 (3.06, 4.44)	4.31 (3.50, 5.00)	< 0.001	< 0.001
TG (mmol/L)	0.90 (0.78, 1.08)	1.34 (1.19, 1.58)	2.12 (1.86, 2.89)	< 0.001	< 0.001
HDL-C (mmol/L)	1.17 (1.01, 1.39)	1.06 (0.92, 1.19)	0.93 (0.82, 1.01)	< 0.001	< 0.001
LDL-C (mmol/L)	2.08 (1.52, 2.67)	2.22 (1.73, 2.89)	2.60 (1.99, 3.47)	< 0.001	< 0.001
eGFR (ml/min/1.73m2)	92.42 (81.96, 99.90)	92.15 (80.87, 101.34)	90.59 (76.19, 102.28)	0.945	0.446
Lipoprotein a (mg/L)	203.00 (109.50, 477.25)	188.50 (90.25, 373.25)	163.50 (89.00, 350.00)	0.184	0.241
LVEF (%)	63.00 (59.75, 66.00)	63.31 (60.00, 66.00)	63.00 (59.83, 67.00)	0.870	0.774
Hypertension (n, %)	46 (51.1)	61 (67.8)	64 (71.1)	0.012	0.006
Diabetes Mellitus (n, %)	34 (37.8)	48 (53.3)	51 (56.7)	0.026	0.012
Dyslipidemia (n, %)	83 (92.2)	84 (93.3)	85 (94.4)	0.836	0.551
Family history of CVD (n, %)	6 (6.7)	11 (12.2)	12 (13.3)	0.302	0.152
Current smoking (n, %)	45 (50.0)	47 (52.2)	44 (48.9)	0.901	1.000
TIMI flow (n, %)				0.086	0.056
0–1	8 (8.9)	9 (10.0)	17 (18.9)		
2–3	82 (91.1)	81 (90.0)	73 (81.1)		
No. of coronary artery narrowed *(n, %)				0.830	
1	28 (31.1)	28 (31.1)	30 (33.3)		-
2	29 (32.2)	35 (38.9)	29 (32.2)		0.849
3	33 (36.7)	27 (30.0)	31 (34.4)		0.713
Aspirin (n, %)	90 (100)	90 (100)	90 (100)	-	-
P2Y12 receptor antagonist (n, %)	89 (98.9)	88 (97.8)	87 (96.7)	0.600	0.323
Statins (n, %)	84 (93.3)	85 (94.4)	85 (94.4)	0.936	0.322

SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; NLR, Neutrophil-to-Lymphocyte Ratio;

*Narrowed coronary artery was quantified using quantitative coronary angiography, with > 50% diameter narrowing considered significant.

P for trend was unadjusted

through reflecting body's obesity and blood lipid levels [4]. Subsequently, a 2023 cohort study further revealed the potential relationship between CMI and DM events [18]. CMI reflects metabolic disorders to a certain extent. Previous studies had reported that CMI can identify metabolic obesity among young adults with normal BMI and were correlated with the risk of new chronic diseases [19, 20]. Additionally, CMI has shown excellent diagnostic accuracy for MetS and its severity in obese patients, helping to detect and assess MetS early in clinical practice [21, 22]. Patients in higher CMI tertiles exhibited a higher incidence of diabetes and hypertension at baseline, further confirming the association with metabolic diseases. However, no inter-group difference in hyperlipidemia was observed, which be attributed to the high prevalence

Table 2 Optical coherence tomography characteristics

	Tertiles 1 ($n=90$)	Tertiles 2 ($n=90$)	Tertiles 3 ($n=90$)	*P* value
Plaque rupture (n, %)	21 (23.3)	26 (28.9)	27 (30.0)	0.562
Lipid-rich plaques (n, %)	63 (70.0)	74 (82.2)	68 (75.6)	0.158
TCFA (n, %)	9 (10.0)	18 (20.0)	24 (26.7)	0.016
Cholesterol crystals (n, %)	29 (32.2)	39 (43.3)	40 (42.2)	0.180
Thrombus (n, %)	27 (30.0)	29 (32.2)	35 (38.9)	0.422
Microvascular (n, %)	48 (53.3)	44 (48.9)	45 (50.0)	0.825
Macrophage (n, %)	16 (17.8)	26 (28.9)	33 (36.7)	0.019
Calcification (n, %)	43 (47.8)	41 (45.6)	50 (55.6)	0.371
Minimal FCT (μm)	205.00 (130.00, 312.50)	175.00 (90.00, 280.00)	155.00 (60.00, 242.50)	0.001
Maximum lipid arc, °	121.10 (81.05, 167.30)	142.60 (99.10, 195.50)	144.80 (90.00, 201.65)	0.031
MLA (mm2)	1.73 (1.33, 2.56)	1.75 (1.13, 2.39)	1.52 (1.10, 2.37)	0.180
RLA (mm2)	6.16 (4.95, 8.38)	6.59 (4.83, 8.43)	6.29 (4.27, 8.44)	0.782
Stenosis (%)	68.46 (58.80, 78.59)	72.40 (65.10, 78.41)	73.85 (64.10, 81.77)	0.077

TCFA, thin-cap fibroatheroma; FCT, fibrous cap thickness; MLA, minimal lumen area; RLA, reference lumen area;

Table 3 Logistic and linear regression analysis of CMI with vulnerable plaque

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
TCFA	1.65 (1.17, 2.33)	0.004	1.68 (1.18, 2.40)	0.004	1.90 (1.25, 2.89)	0.003
Macrophage	1.45 (1.05, 2.02)	0.025	1.34 (0.96, 1.88)	0.089	1.61 (1.09, 2.37)	0.017
Minimal FCT	-28.11 (-46.02, -10.21)	0.002	-30.23 (-48.67, -11.80)	0.001	-30.65 (-50.72, -10.57)	0.003
Maximum lipid arc	16.36 (3.27, 29.46)	0.015	15.50 (2.14, 28.86)	0.023	20.78 (6.55, 35.01)	0.004

Model 1: -

Model 2: age, gender

Model 3: age, gender, BMI, hypertension, DM, dyslipidemia, current smoking, family history of CVD, TC, LDL-C

of dyslipidemia in ACS patients, potentially affecting the statistical outcome.

Metabolic disorders are associated with cardiovascular diseases and atherosclerosis, with pathophysiological mechanisms involving the complex interaction of multiple factors, such as insulin resistance, immune responses, oxidative stress, and inflammatory reactions [23, 24]. A multi-ethnic atherosclerosis study found that changes in cardiometabolic parameters in individuals with higher baseline cardiometabolic risk were significantly linked to a greater likelihood of subsequent CVD events [25]. As an indicator reflecting metabolic activity and visceral fat distribution, CMI has been confirmed in the Suita Study to be a potent predictor of ischemic CVD [5]. Another study exploring the association between peripheral arterial disease and atherosclerosis progression suggests that CMI exhibits significant correlations with both carotid atherosclerotic burden and peripheral ischemia severity [26]. This study clarify the association of CMI with coronary vulnerable plaques through intravascular imaging, including linear positive correlations with TCFA, minimal FCT, and maximum lipid arc, as well as a nonlinear positive correlation with macrophages when CMI is below 1.15. The CLIMA study, analyzing coronary plaque morphology by OCT, established four morphometric predictors of adverse coronary outcomes: lipid arcs > 180°, FCT < 75 μm, macrophage, and MLA < 3.5 mm^2 [27]. TCFA is not only an early signal of plaque rupture but also a key indicator in assessing whether a lesion will progress rapidly [7, 8, 28]. The COMBINE OCT-FFR trial revealed that TCFA detection independently correlates with heightened major coronary event risk in diabetic patients exhibiting preserved fractional flow reserve [29]. Although an increasing trend in plaque rupture incidence was observed with elevated CMI levels among the three groups, no statistically significant difference was found. It may partly stem from the exclusion of patients with severe plaque rupture due to poor-quality OCT imaging and the limited cohort size. Similarly, lipid-rich plaques showed no significant intergroup differences, which could be explained by the low diagnostic threshold (maximum lipid arc > 90°) used for binary classification. In our cohort, the median maximum lipid arc was notably elevated at 137.3°(94.5°–183.7°), leaving limited scope to detect meaningful associations. The post-hoc analysis of the CLIMA showed that the circumferential extension of macrophages and their location are related to adverse cardiovascular outcomes [30]. Accumulated evidence demonstrates an inverse relationship between macrophage infiltration density in FCT [31]. Oxidative transformation of intimal LDL particles is prerequisite for macrophage phagocytosis, initiating their differentiation into foam cells. As macrophages undergo apoptosis and inhibit exocytosis, this leads to necrosis of the plaque

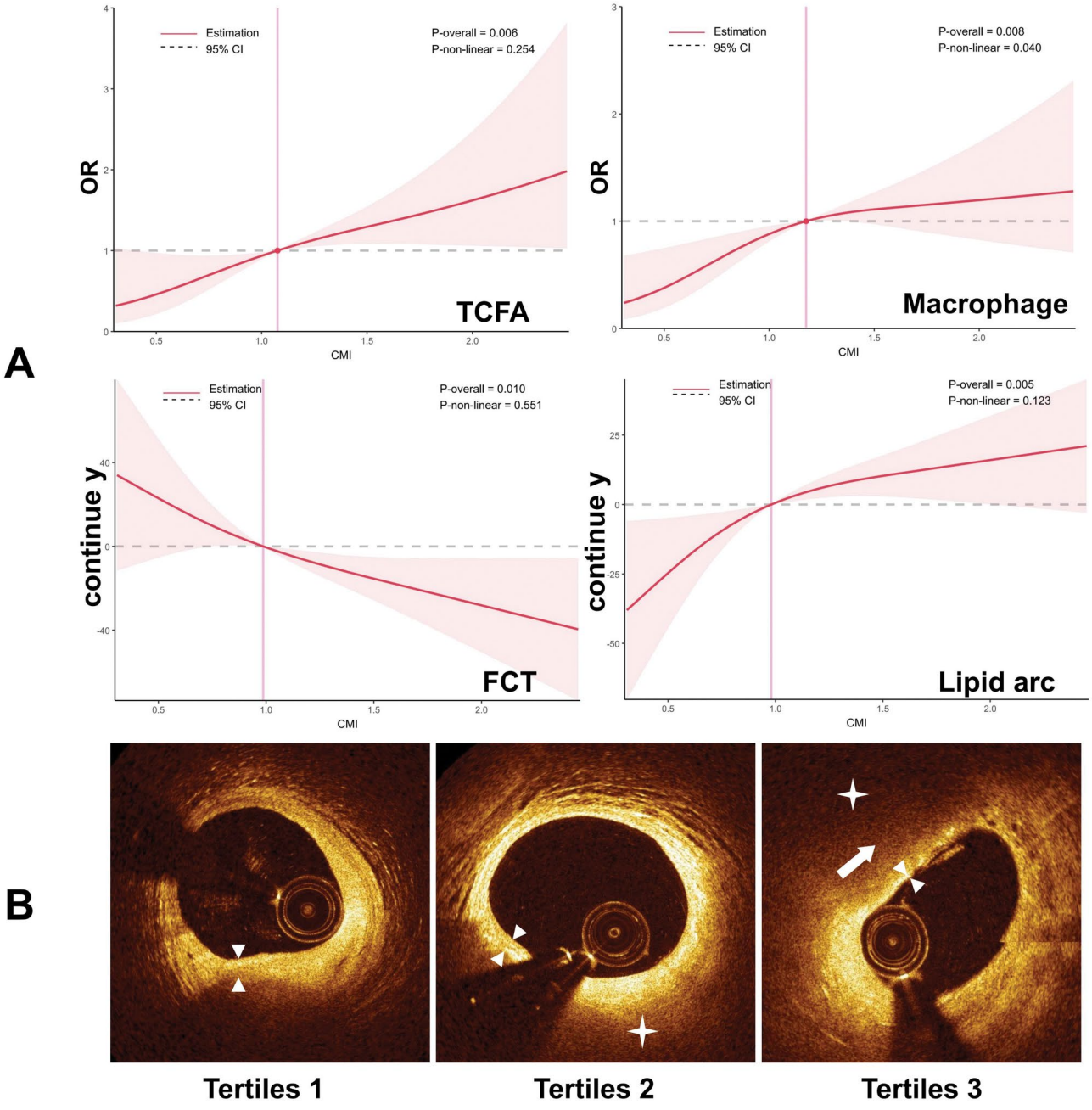

Fig. 3 Analysis of vulnerable plaque across different CMI tertiles in patients. TCFA (arrow): FCT ≤ 65 μm and lipid arc ≥ 90°; fibrous cap (triangle); lipid plaque (asterisk)

core and adverse remodeling of plaque structure, further promoting the progression of plaque vulnerability [32, 33]. We observed a nonlinear association between CMI and macrophage. Previous studies have shown that type 2 diabetes reduces the population of M2 macrophages, leading to polarization imbalance [34]. We hypothesize that this phenomenon may be attributed to a significant reduction in M2 macrophages when CMI exceeds 1.15 (indicating severe metabolic dysfunction), while M1 macrophages remains unchanged, leading to an imbalance in macrophage polarization rather than a quantitative increase. This study suggests that patients with high CMI exhibit more pronounced high-risk plaque characteristics and more severe progression of atherosclerosis.

Inflammation acts throughout the entire process of atherosclerosis and involves various immune cells within the body. Neutrophils form neutrophil extracellular traps, which promote inflammation through cholesterol crystal-induced neutrophil extracellular traps release [35]. CD4 + T cells can differentiate into various

Table 4 Linear regression analysis of CMI with inflammatory markers

	Model 1		Model 2		Model 3	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
WBC	0.68 (0.30, 1.06)	< 0.001	0.55 (0.17, 0.93)	0.005	0.45 (0.05, 0.86)	0.029
Neutrophil	0.53 (0.19, 0.86)	0.002	0.41 (0.08, 0.75)	0.016	0.37 (0.01, 0.73)	0.046
Lymphocyte	0.08 (-0.14, 0.30)	0.470	0.07 (-0.16, 0.30)	0.559	-0.03 (-0.22, 0.27)	0.826
NLR	0.21 (-0.14, 0.55)	0.233	0.19 (-0.16, 0.55)	0.284	0.28 (-0.10, 0.66)	0.147
hsCRP	4.95 (2.19, 7.71)	< 0.001	5.83 (3.01, 8.64)	< 0.001	6.78 (3.67, 9.90)	< 0.001

Model 1: -

Model 2: gender, age

Model 3: gender, age, BMI, hypertension, DM, dyslipidemia, current smoking, family history of CVD, TC, LDL-C

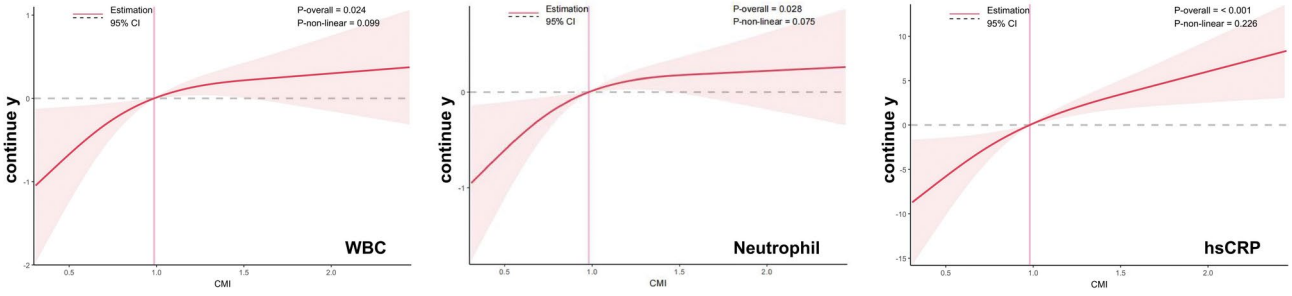

Fig. 4 Restricted cubic spline analysis of CMI with inflammatory markers

Table 5 Logistic and linear regression analysis of inflammatory markers with vulnerable plaque

Variable	Model 1		Model 2	
	OR (95% CI)	*P*	OR (95% CI)	*P*
TCFA				
WBC	1.12 (1.00, 1.25)	0.054	1.10 (0.97, 1.24)	0.139
Neutrophil	1.15 (1.01, 1.30)	0.030	1.13 (0.98, 1.29)	0.083
Lymphocyte	0.81 (0.55, 1.19)	0.287	0.78 (0.52, 1.16)	0.216
NLR	1.16 (1.03, 1.30)	0.017	1.15 (1.02, 1.31)	0.027
hsCRP	1.03 (1.01, 1.06)	0.019	1.03 (1.00, 1.06)	0.026
Macrophage				
WBC	1.17 (1.05, 1.31)	0.003	1.15 (1.03, 1.30)	0.018
Neutrophil	1.18 (1.04, 1.33)	0.008	1.16 (1.02, 1.33)	0.029
Lymphocyte	0.99 (0.81, 1.20)	0.885	0.95 (0.76, 1.19)	0.638
NLR	1.07 (0.96, 1.20)	0.220	1.06 (0.94, 1.19)	0.380
hsCRP	1.01 (0.99, 1.03)	0.227	1.01 (1.00, 1.03)	0.130
Minimal FCT				
WBC	-5.96 (-11.59, -0.33)	0.038	-3.64 (-9.71, 2.42)	0.238
Neutrophil	-5.07 (-11.52, 1.38)	0.123	-2.17 (-9.06, 4.71)	0.535
Lymphocyte	8.02 (-1.78, 17.83)	0.108	8.87 (-1.28, 19.02)	0.086
NLR	-5.38 (-11.71, 0.95)	0.095	-3.44 (-9.97, 3.08)	0.300
hsCRP	-1.07 (-1.83, -0.30)	0.006	-1.02 (-1.78, -0.25)	0.009
Maximum lipid arc				
WBC	5.46 (1.39, 9.53)	0.009	2.72 (-1.57, 7.02)	0.213
Neutrophil	6.06 (1.41, 10.72)	0.011	2.92 (-1.95, 7.79)	0.238
Lymphocyte	-6.44 (-13.55, 0.68)	0.076	-5.69 (-12.88, 1.50)	0.121
NLR	5.09 (0.51, 9.67)	0.029	2.61 (-2.01, 7.23)	0.267
hsCRP	0.81 (0.25, 1.36)	0.004	0.27 (0.25, 1.33)	0.004

Model 1: -

Model 2:age, gender, BMI, hypertension, DM, current smoking, dyslipidemia, family history of CVD, TC, LDL-C

Table 6 Mediation analysis of inflammation

	Mediation effect (95% CI), *P* value			
	Total	**Direct**	**Indirect**	**Mediation**
TCFA				
WBC	0.12 (0.03, 0.19) 0.012	0.11 (0.02, 0.19) 0.016	0.005 (-0.007, 0.03) 0.516	4.3%
Neutrophil	0.12 (0.03, 0.18) 0.010	0.11 (0.02, 0.18) 0.014	0.006 (-0.006, 0.02) 0.396	5.3%
hsCRP	0.12 (0.03, 0.19) 0.010	0.09 (0.01, 0.18) 0.048	0.02 (-0.01, 0.05) 0.124	18.8%
Macrophage				
WBC	0.09 (0.01, 0.17) 0.020	0.08 (0.005, 0.16) 0.034	0.01 (-0.001, 0.04) 0.104	12.5%
Neutrophil	0.09 (0.01, 0.18) 0.030	0.08 (0.007, 0.16) 0.038	0.01 (-0.002, 0.03) 0.116	10.6%
hsCRP	0.09 (0.02, 0.18) 0.008	0.08 (-0.01, 0.17) 0.096	0.01 (-0.01, 0.08) 0.166	12.8%
Minimal FCT				
WBC	-30.61 (-48.55, -12.04) 0.002	-29.50 (-48.59, -10.22)0.004	-1.11 (-6.44, 2.10) 0.484	3.6%
Neutrophil	-30.61 (-47.52, -11.05) < 0.001	-30.28 (-47.49,-10.92) < 0.001	-0.33 (-5.05, 3.53) 0.830	1.1%
hsCRP	-30.61 (-47.44, -12.53) 0.002 0.240	-25.40 (-42.94, -4.53) 0.018	-5.21 (-12.70, -1.27) 0.016	17.0%
Maximum lipid arc				
WBC	20.76 (9.74, 34.46) < 0.001	19.89 (9.05, 34.03) 0.002	0.87 (-2.25, 4.66) 0.610	4.2%
Neutrophil	20.76 (10.06, 35.74) < 0.001	20.00 (9.04, 35.31) < 0.001	0.76 (-2.32, 4.55) 0.580	3.7%
hsCRP	20.76 (10.16, 36.13) < 0.001	16.49 (4.85, 32.82) 0.004	4.27 (-3.10, 8.75) 0.312	20.6%

adjust for: gender, age, BMI, hypertension, DM, current smoking, dyslipidemia, family history of CVD, TC, LDL-C

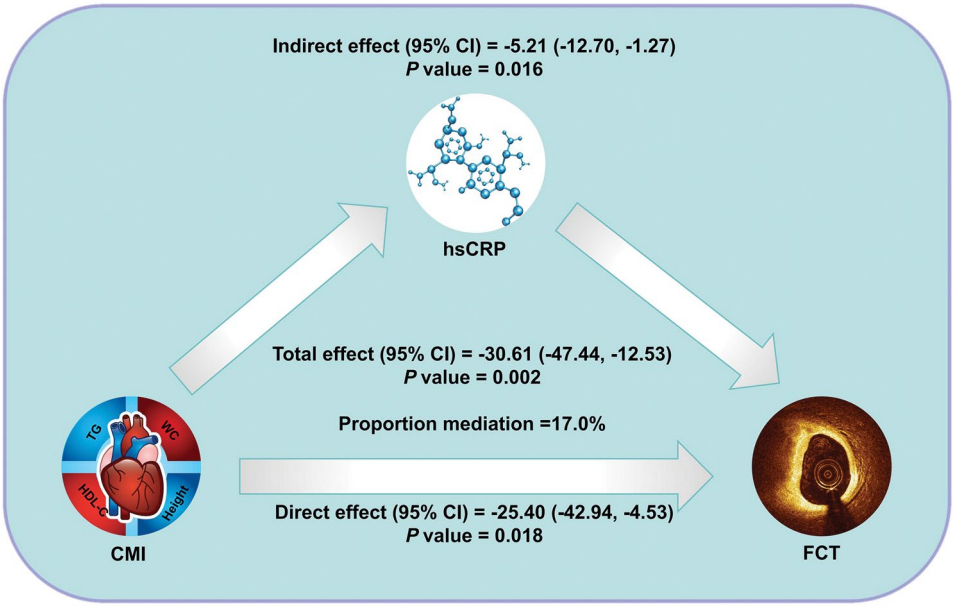

Fig. 5 Analysis of the mediation of hsCRP in the associations between CMI and FCT

subtypes, thereby suppressing immune actions or activating other T cells, exerting direct anti-inflammatory or pro-inflammatory effects on cells located in tissues [36]. Emerging evidence implicated neutrophilic and lymphocytic (T/B cell) infiltration in the pathophysiology of vulnerable plaque development [37–39]. Qi et al. found that the NLR correlates with perivascular fat inflammation. Subsequent investigations by Mariaca et al. further established NLR as an independent predictor of carotid atherosclerotic burden in type 1 diabetes cohorts [12, 13]. Elevated hsCRP levels exhibit consistent correlations with adverse cardiovascular outcomes in clinical studies [40–42]. Current investigations demonstrate that CMI exhibits a correlation with systemic inflammatory levels, thereby inducing the progression of insulin resistance and increasing all-cause mortality in geriatric populations [14, 43]. Metabolic disorders may represent potential clinical manifestations of underlying systemic inflammation [9]. This study found that CMI levels are correlated with systemic inflammatory markers, consistent with previous studies, and different inflammatory markers are associated with plaque characteristics such as TCFA, macrophages, minimal FCT, and maximum lipid arc. Notably, mediation analysis suggested that

hsCRP accounted for 17.0% of the association between CMI and minimal FCT. A clinical study reported an inverse correlation between cholesterol metabolism and hsCRP with FCT and that they promote plaque instability, which is consistent with this study [44]. As an inflammatory marker related to metabolic disorders, CRP synthesis can be induced by various pro-inflammatory cytokines [45, 46]. IL-1 serves as a master pro-inflammatory cytokine. Studies have shown that IL-1 can induce smooth muscle cell to produce IL-6 during atherosclerosis development. Subsequently, IL-6 can stimulate hepatocytes and promote the synthesis of acute-phase reactants, including CRP. Therefore, targeting inflammation in high CMI patients (e.g., IL-1β inhibitors like canakinumab) may stabilize vulnerable plaques by attenuating hsCRP involved cap thinning. Future trials should explore whether CMI guided anti-inflammatory therapy reduces ACS recurrence [47].These findings highlight the undeniable importance of inflammation in optimizing atherosclerotic disease management and provide a new perspective for understanding the complex mechanisms between CMI and atherosclerosis.

Strengths and limitations

This study first explores the relationship between metabolic dysfunction, inflammation levels, and vulnerable plaque formation, shedding new light on the underlying mechanisms. It also clarifies the intermediary role of CMI, inflammation, and FCT. Nonetheless, certain limitations exist in this study. The cross-sectional design precludes causal conclusions. While mediation analysis suggests plausible pathways, longitudinal studies are required to confirm directional relationships. Multivariable regression models were implemented to adjust for key covariates, yet residual confounders persist as potential sources of bias. Additionally, the lack of assessment of non-culprit vessels may introduce bias into the analysis. Furthermore, the monocentric design with a limited cohort size ($n = 270$) and the strict exclusion criteria restricted the statistical power to detect differences, underscoring the need for multicenter validation studies. CMI levels and OCT imaging data were only observed at baseline, with no monitoring of dynamic CMI changes or plaque progression during follow-up. This resulted in a lack of imaging evidence for prognostic evaluation, thereby precluding definitive determination of CMI's predictive value in the long-term evolution of atherosclerosis.

Conclusions

This study suggests that CMI is associated with vulnerable plaque characteristics in ACS patients. Systemic inflammation is associated with the relationship between CMI and vulnerable plaque features, suggesting a potential mechanistic link. These findings support the incorporation of CMI into clinical practice, where its integration with intravascular imaging enhances risk prediction and guides personalized management strategies for ACS patients.

Abbreviations

ACS	Acute Coronary Syndrome
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CMI	Cardiometabolic Index
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
FCT	Fibrous Cap Thickness
eGFR	Estimated Glomerular Filtration Rate
HDL-C	High-Density Lipoprotein Cholesterol
HsCRP	High-sensitivity C-reactive protein
ICC	Intraclass Correlation Coefficient
LDL-C	Low-Density Lipoprotein Cholesterol
LVEF	Left Ventricular Ejection Fraction
MetS	Metabolic Syndrome
MLA	Minimum Lumen Area
NLR	Neutrophil-to-Lymphocyte Ratio
NT-proBNP	N-terminal pro-B-type Natriuretic Peptide
OCT	Optical Coherence Tomography
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
RCS	Restricted Cubic Spline
RLA	Reference Lumen Area
SBP	Systolic Blood Pressure
TC	Total Cholesterol
TCFA	Thin-Cap Fibroatheromas
TG	Triglycerides
WBC	White Blood Cells

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions

Conceptualization: HY, SL, HY, YL, WL; Data collection: HY, SL, HP, YW, WL; Statistical analysis: HY, YW, YL, WL; Original draft: HY, HP, HY, WY, WL; Review & editing: YW, YL, WL; Project administration: HY, YW, YL, WL.

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Data availability

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Helsinki Declaration and was approved by the ethics committee of Beijing Jishuitan Hospital, Capital Medical University.(Number: K2024-162-00).

Consent for publication
All the authors gave their consent to publication.

Competing interests
The authors declare no competing interests.

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References

1. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. Lancet. 2017;389(10065):197–210.
2. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke Statistics-2022 update: A report from the American heart association. Circulation. 2022;145(8):e153–639.
3. Guo F, Moellering DR, Garvey WT. The progression of cardiometabolic disease: validation of a new cardiometabolic disease staging system applicable to obesity. Obes (Silver Spring). 2014;22(1):110–8.
4. Wakabayashi I, Daimon T. The cardiometabolic index as a new marker determined by adiposity and blood lipids for discrimination of diabetes mellitus. Clin Chim Acta. 2015;438:274–8.
5. Higashiyama A, Wakabayashi I, Okamura T, et al. The risk of fasting triglycerides and its related indices for ischemic cardiovascular diseases in Japanese community dwellers: the suita study. J Atheroscler Thromb. 2021;28(12):1275–88.
6. Lazzer S, D'Alleva M, Isola M, et al. Cardiometabolic index (CMI) and visceral adiposity index (VAI) highlight a higher risk of metabolic syndrome in women with severe obesity. J Clin Med. 2023;12(9):3055.
7. Aguirre AD, Arbab-Zadeh A, Soeda T, Fuster V, Jang IK. Optical coherence tomography of plaque vulnerability and rupture: JACC focus seminar part 1/3. J Am Coll Cardiol. 2021;78(12):1257–65.
8. Araki M, Yonetsu T, Kurihara O, et al. Predictors of rapid plaque progression: an optical coherence tomography study. JACC Cardiovasc Imaging. 2021;14(8):1628–38.
9. Gusev E, Sarapultsev A. Atherosclerosis and inflammation: insights from the theory of general pathological processes. Int J Mol Sci. 2023;24(9):7910.
10. Yuki H, Sugiyama T, Suzuki K, et al. Coronary inflammation and plaque vulnerability: A coronary computed tomography and optical coherence tomography study. Circ Cardiovasc Imaging. 2023;16(3):e014959.
11. Waksman R, Merdler I, Case BC, Waksman O, Porto I. Targeting inflammation in atherosclerosis: overview, strategy and directions. EuroIntervention. 2024;20(1):32–44.
12. Mariaca K, Serés-Noriega T, Viñals C, et al. Neutrophil-to-lymphocyte ratio is independently associated with carotid atherosclerosis burden in individuals with type 1 diabetes. Nutr Metab Cardiovasc Dis. 2024;34(2):395–403.
13. Qi L, Li Y, Kong C, et al. Morphological changes of Peri-Coronary adipose tissue together with elevated NLR in acute myocardial infarction patients in-Hospital. J Inflamm Res. 2024;17:4065–76.
14. Xu B, Wu Q, La R, et al. Is systemic inflammation a missing link between cardiometabolic index with mortality? Evidence from a large population-based study. Cardiovasc Diabetol. 2024;23(1):212.
15. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J. 2023;44(38):3720–826.
16. Araki M, Park SJ, Dauerman HL, et al. Optical coherence tomography in coronary atherosclerosis assessment and intervention. Nat Rev Cardiol. 2022;19(10):684–703.
17. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295(2):180–9.
18. Zha F, Cao C, Hong M, et al. The nonlinear correlation between the cardiometabolic index and the risk of diabetes: A retrospective Japanese cohort study. Front Endocrinol (Lausanne). 2023;14:1120277.
19. Liu X, Wu Q, Yan G, et al. Cardiometabolic index: a new tool for screening the metabolically obese normal weight phenotype. J Endocrinol Invest. 2021;44(6):1253–61.
20. Zhuo L, Lai M, Wan L, Zhang X, Chen R. Cardiometabolic index and the risk of new-onset chronic diseases: results of a National prospective longitudinal study. Front Endocrinol (Lausanne). 2024;15:1446276.
21. Chen X, Zhao Y, Sun J, Jiang Y, Tang Y. Identification of metabolic syndrome using lipid accumulation product and cardiometabolic index based on NHANES data from 2005 to 2018. Nutr Metab (Lond). 2024;21(1):96.
22. Tamini S, Bondesan A, Caroli D, Sartorio A. The lipid accumulation product index (LAP) and the cardiometabolic index (CMI) are useful for predicting the presence and severity of metabolic syndrome in adult patients with obesity. J Clin Med. 2024;13(10):2843.
23. Gonzalez-Chávez A, Chávez-Fernández JA, Elizondo-Argueta S, González-Tapia A, León-Pedroza JI, Ochoa C. Metabolic syndrome and cardiovascular disease: A health challenge. Arch Med Res. 2018;49(8):516–21.
24. Xu J, Kitada M, Ogura Y, Koya D. Relationship between autophagy and metabolic syndrome characteristics in the pathogenesis of atherosclerosis. Front Cell Dev Biol. 2021;9:641852.
25. Merkin SS, Karlamangla A, Elashoff D, Grogan T, Seeman T. Change in cardiometabolic score and incidence of cardiovascular disease: the multi-ethnic study of atherosclerosis. Ann Epidemiol. 2015;25(12):912–e71.
26. Wakabayashi I, Sotoda Y, Hirooka S, Orita H. Association between cardiometabolic index and atherosclerotic progression in patients with peripheral arterial disease. Clin Chim Acta. 2015;446:231–6.
27. Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. Eur Heart J. 2020;41(3):383–91.
28. Jiang S, Fang C, Xu X, et al. Identification of High-Risk coronary lesions by 3-Vessel optical coherence tomography. J Am Coll Cardiol. 2023;81(13):1217–30.
29. Kedhi E, Berta B, Roleder T, et al. Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. Eur Heart J. 2021;42(45):4671–9.
30. Gatto L, Alfonso F, Paoletti G, et al. Relationship betweeen the amount and location of macrophages and clinical outcome: subanalysis of the CLIMA-study. Int J Cardiol. 2022;346:8–12.
31. Raffel OC, Tearney GJ, Gauthier DD, Halpern EF, Bouma BE, Jang IK. Relationship between a systemic inflammatory marker, plaque inflammation, and plaque characteristics determined by intravascular optical coherence tomography. Arterioscler Thromb Vasc Biol. 2007;27(8):1820–7.
32. Simion V, Zhou H, Haemmig S, et al. A macrophage-specific LncRNA regulates apoptosis and atherosclerosis by tethering HuR in the nucleus. Nat Commun. 2020;11(1):6135.
33. Björkegren J, Lusis AJ, Atherosclerosis. Recent developments. Cell. 2022;185(10):1630–45.
34. Fadini GP, de Kreutzenberg SV, Boscaro E, et al. An unbalanced monocyte polarisation in peripheral blood and bone marrow of patients with type 2 diabetes has an impact on microangiopathy. Diabetologia. 2013;56(8):1856–66.
35. Silvestre-Roig C, Braster Q, Ortega-Gomez A, Soehnlein O. Neutrophils as regulators of cardiovascular inflammation. Nat Rev Cardiol. 2020;17(6):327–40.
36. Bonilla FA, Oettgen HC. Adaptive immunity. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S33–40.
37. Ammirati E, Moroni F, Magnoni M, Camici PG. The role of T and B cells in human atherosclerosis and atherothrombosis. Clin Exp Immunol. 2015;179(2):173–87.
38. Bonaventura A, Montecucco F, Dallegri F, et al. Novel findings in neutrophil biology and their impact on cardiovascular disease. Cardiovasc Res. 2019;115(8):1266–85.
39. Wolf D, Ley K. Immunity and inflammation in atherosclerosis. Circ Res. 2019;124(2):315–27.
40. Carrero JJ, Andersson Franko M, Obergfell A, Gabrielsen A, Jernberg T. HsCRP level and the risk of death or recurrent cardiovascular events in patients with myocardial infarction: a Healthcare-Based study. J Am Heart Assoc. 2019;8(11):e012638.
41. Ridker PM, Bhatt DL, Pradhan AD, et al. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving Statin therapy: a collaborative analysis of three randomised trials. Lancet. 2023;401(10384):1293–301.

42. Mazhar F, Faucon AL, Fu EL, et al. Systemic inflammation and health outcomes in patients receiving treatment for atherosclerotic cardiovascular disease. Eur Heart J. 2024;45(44):4719–30.
43. Xu B, Wu Q, Yin G, et al. Associations of cardiometabolic index with diabetic statuses and insulin resistance: the mediating role of inflammation-related indicators. BMC Public Health. 2024;24(1):2736.
44. Nasu K, Terashima M, Habara M, et al. Impact of cholesterol metabolism on coronary plaque vulnerability of target vessels: a combined analysis of virtual histology intravascular ultrasound and optical coherence tomography. JACC Cardiovasc Interv. 2013;6(7):746–55.
45. Libby P. Interleukin-1 Beta as a target for atherosclerosis therapy: biological basis of CANTOS and beyond. J Am Coll Cardiol. 2017;70(18):2278–89.
46. Mukherjee S, Im SS. Decoding health: exploring essential biomarkers linked to metabolic Dysfunction-Associated steatohepatitis and type 2 diabetes mellitus. Biomedicines. 2025;13(2):359. Published 2025 Feb 4.
47. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with Canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119–31.

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