

ORIGINAL RESEARCH

Characterizing Nonculprit Lesions and Perivascular Adipose Tissue of Patients Following Acute Myocardial Infarction Using Coronary Computed Tomography Angiography: A Comparative Study

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BACKGROUND: The comparison of coronary computed tomography angiography plaques and perivascular adipose tissue (PVAT) between patients with acute myocardial infarction (AMI) posttreatment and patients with stable coronary artery disease is poorly understood. Our objective was to evaluate the differences in coronary computed tomography angiography–quantified plaque and PVAT characteristics in patients post-AMI and identify signs of residual inflammation.

METHODS AND RESULTS: We analyzed 205 patients (age, 59.77 ± 9.24 years; 92.20% men) with AMI ≤ 1 month and matched them with 205 patients with stable coronary artery disease (age, 60.52 ± 10.04 years; 90.24% men) based on age, sex, and cardiovascular risk factors. Coronary computed tomography angiography scans were assessed for nonculprit plaque and vessel characteristics, plaque volumes by composition, high-risk plaques, and PVAT mean attenuation. Both patient groups exhibited similar noncalcified plaque volumes (383.35 ± 313.23 versus 378.63 ± 426.25 mm³, $P=0.899$). However, multivariable analysis revealed that patients post-AMI had a greater patient-wise noncalcified plaque volume ratio (estimate, 0.089 [95% CI, 0.053–0.125], $P<0.001$), largely attributed to a higher fibrofatty and necrotic core volume ratio, along with higher peri-lesion PVAT mean attenuation (estimate, 3.968 [95% CI, 2.556–5.379], $P<0.001$). When adjusted for vessel length, patients post-AMI had more high-risk plaques (estimate, 0.417 [95% CI, 0.298–0.536], $P<0.001$) per patient.

CONCLUSIONS: Patients post-AMI displayed heightened noncalcified plaque components, largely due to fibrofatty and necrotic core content, more high-risk plaques, and increased PVAT mean attenuation on a per-patient level, highlighting the necessity for refined risk assessment in patients with AMI after treatment.

Key Words: acute myocardial infarction ■ coronary atheroma ■ coronary computed tomography angiography ■ high-risk plaques ■ residual inflammatory risk

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CLINICAL PERSPECTIVE

What Is New?

- This study reveals that following acute myocardial infarction, patients have increased non-calcified plaque components, more high-risk plaques, and higher peri-lesion perivascular adipose tissue mean attenuation compared with patients with stable coronary artery disease, indicating a heightened inflammatory state in nonculprit lesions.

What Are the Clinical Implications?

- The findings suggest that comprehensive coronary computed tomography angiography assessments in patients following acute myocardial infarction are essential for identifying residual inflammatory risks and guiding more tailored and effective therapeutic strategies to prevent future cardiovascular events.

Nonstandard Abbreviations and Acronyms

CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcomes Study
CVS.AI	CardioVascular Systems Imaging and Artificial Intelligence
DS	diameter stenosis
HRP	high-risk plaque
ICONIC	Incident Coronary Syndromes Identified by Computed Tomography
LAP	low attenuation plaque
NC	necrotic core
NCPV	noncalcified plaque volume
NHCS	National Heart Center Singapore
PREVENT	Preventive Percutaneous Coronary Intervention Versus Optimal Medical Therapy Alone for the Treatment of Vulnerable Atherosclerotic Coronary Plaques
PV	plaque volume
PVAT	perivascular adipose tissue
SC	spotty calcification
SCCT	Society of Cardiovascular Computed Tomography
SCOT-HEART	Scottish Computed Tomography of the Heart

Coronary artery disease (CAD) and acute myocardial infarction (AMI) represent major global health challenges, with coronary computed tomography

angiography (CCTA) serving as a pivotal noninvasive tool for assessing CAD.¹ CCTA allows for a comprehensive evaluation of coronary vessels and plaques, including arterial stenosis and remodeling, plaque characteristics, and perivascular adipose tissue (PVAT).^{2–4} CCTA has become instrumental in understanding the pathogenesis of acute coronary syndromes by identifying high-risk features that implicate coronary inflammation, atheroma progression, and acute cardiovascular event risk.^{3,4}

Recent studies have highlighted the clinical importance of nonculprit lesions in patients post-AMI. Although not directly involved in the precipitating event, these lesions hold prognostic value and are often overlooked in research, representing a significant gap in our understanding.^{5,6} Nonculprit lesions are viable targets for further treatment, aligning with the holistic approach of treating the patient, not just individual lesions. In addition, residual inflammatory risk, the risk of further cardiovascular events caused by ongoing vascular inflammation, remains a concern in over 30% of patients with AMI posttreatment^{7,8} and exhibited a stronger association with future cardiovascular events than residual cholesterol risk in patients receiving statin therapy.⁹ Traditional measures such as high-sensitivity C-reactive protein provide a systemic rather than a localized indication of inflammation, prompting the need for methods such as CCTA that could directly assess inflammation within coronary arteries.^{10–12}

This study seeks to identify this residual inflammatory risk in patients with recent AMI using CCTA for plaque and PVAT characterization and quantification. Via CCTA plaque characterization focusing on uninvolved nonculprit lesions, we can identify unattended inflamed coronary plaques and reveal the residual inflammatory risk of coronary vessels in patients post-AMI. We hypothesize that patients with recent AMI exhibit more plaque and PVAT characteristics suggestive of inflammation than patients with stable CAD.

METHODS

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Study Design and Study Population

A total of 207 patients post-AMI were recruited from 8 centers from 2 countries (Singapore and New Zealand) from July 2021 to March 2023. Enrollment was contingent upon patients' consent to undergo CCTA within 1 month following their AMI event, as defined by the universal definition (Figure 1).¹³ All participants were required to have no history of prior AMI events or coronary revascularization before the index AMI event. This

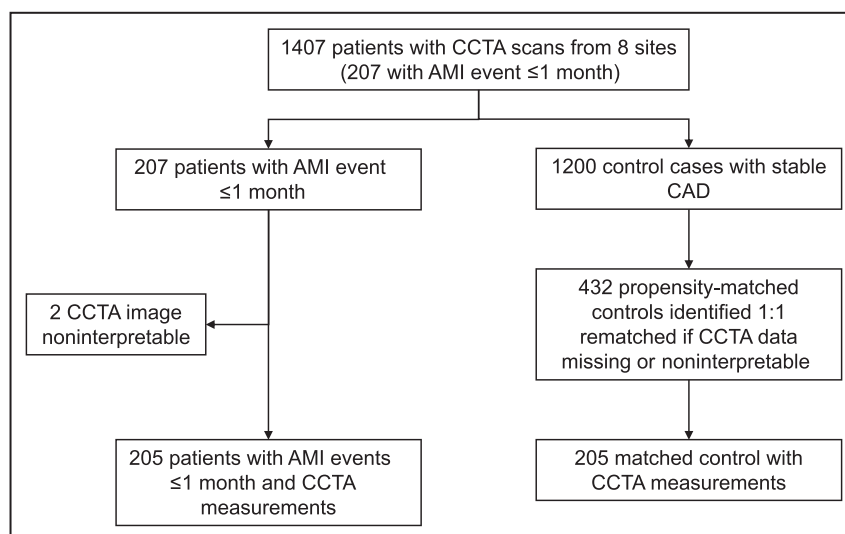


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram for the study.

AMI indicates acute myocardial infarction; CAD, coronary artery disease; and CCTA, coronary computed tomography angiography.

study was approved by the Domain Specific Review Board and Northern A Health and Disability Ethics Committee. Clinical research coordinators at each site prospectively collected patients' clinical backgrounds at recruitment. Except for 2 excluded cases with uninterpretable CCTA images, these patients with recent AMI were propensity-matched 1:1 to patients with only stable CAD. The patients with stable CAD were from a retrospective database of the APOLLO (AI Driven National Platform for CT Coronary Angiography for Clinical and Industrial Applications) registry, which was a multicenter registry of 1200 cases with suspected or known CAD who had undergone CCTA between 2007 and 2017 in Singapore. All patients with stable CAD had no history of prior CAD, AMI events, or coronary revascularization (percutaneous coronary intervention and coronary artery bypass grafting) before CCTA. Each site obtained approval from the local institutional review board or ethics board and submitted study identification-coded data stripped of protected health information for CCTA analysis. Written informed consent was obtained from all participants.

CCTA Analysis

CCTA scans were performed using computed tomography scanners of ≥ 256 -detector rows in accordance with Society of Cardiovascular Computed Tomography (SCCT) guidelines (contrast dosage 72.45 ± 23.20 , 355 [86.59%] prospective gating, tube voltage 110 to 120 kVp, tube current 175.80 ± 138.66 mAs, dose length product 203.82 ± 176.84 mGy*cm).¹⁴ The CardioVascular Systems Imaging and Artificial Intelligence (CVS.AI)

research core of the National Heart Center Singapore (NHCS) analyzed all CCTA scans masked to clinical results and case status. Three independent, experienced readers with >3 years of experience at the CVS.AI research core performed standardized measurements using semiautomated analysis software (QAngioCT Research Edition version 3.2.0.13, Medis Medical Imaging Systems) with appropriate manual correction.¹⁵ One author had full access to all of the data in the study and took responsibility for its integrity and the data analysis.

Quantitative CCTA analysis was performed for each segment of the 18-segment SCCT model with a diameter ≥ 1.5 mm to measure vessel length and volume. For each lesion, measurements were performed of plaque length, plaque volume (PV), percent atheroma volume, minimal lumen area and diameter, diameter stenosis (DS), vessel remodeling index, and plaque composition using predefined Hounsfield unit criteria (necrotic core [NC], -30 to 30 HU, fibrofatty: 30 to 130 HU, fibrous: 131 to 350 HU, and calcification: ≥ 350 HU) (Figure 2).^{11,14,16} Cut points of $\geq 50\%$ and $\geq 70\%$ %DS were used for obstructive CAD. High-risk plaque (HRP) was defined as the presence within a coronary lesion of ≥ 2 high-risk plaque features, which include positive remodeling, low attenuation plaque (LAP), and spotty calcification (SC).^{2,17} To adjust for variations in patients' coronary anatomy size and the number of stented vessels excluded from analysis, the count of HRPs and high-risk features were normalized to total vessel length (in decimeters). We also assessed the mean attenuation of peri-lesion PVAT, which is defined as volumes located within a radial distance from the vessel

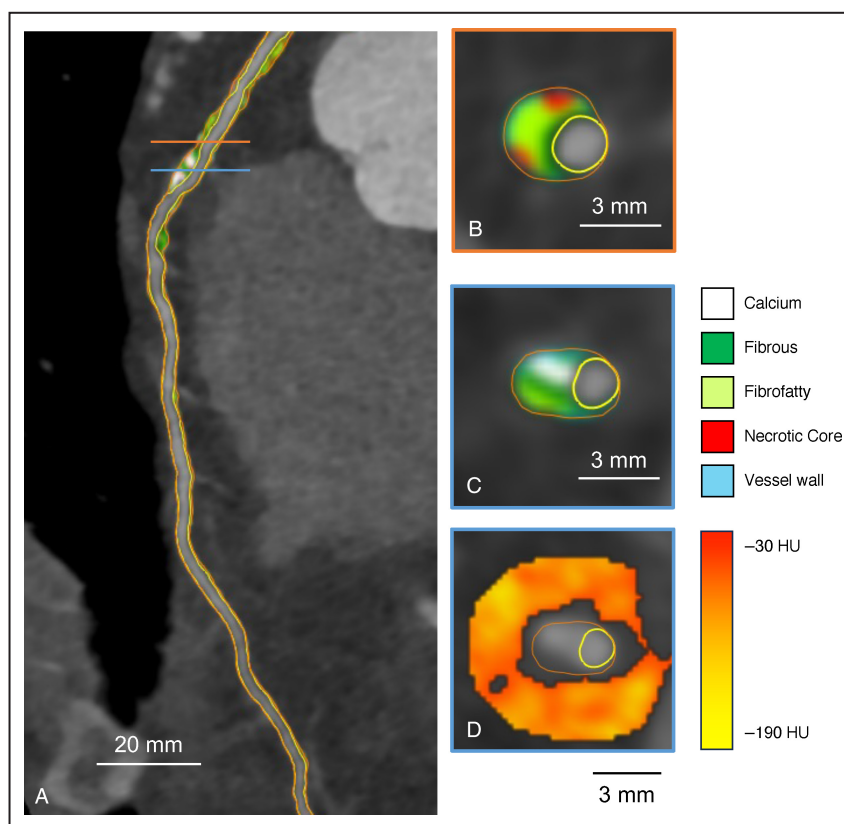


Figure 2. Visual representation of coronary computed tomography angiography plaque quantification.

(A) Longitudinal section of a coronary vessel with color-coded tissue composition (red: necrotic core, yellow: fibrofatty, green: fibrous, white: calcium); (B) a necrotic core-containing cross-section of a coronary plaque with color-coded tissue composition (at the orange bar level of [A]); (C) a calcium-containing cross-section of a coronary plaque with color-coded tissue composition (at the blue bar level of [A]); (D) cross-section of the perivascular adipose tissue around a coronary plaque with color-coded attenuation (at the blue bar level of [A]).

wall, equal in thickness to the segment's average diameter, and exhibiting attenuation values between -190 and -30 HU.^{3,11,18,19} Normal vessel wall content was excluded from the analysis.

In patients post-AMI, coronary vessels containing stents were excluded from the analysis, including culprit and nonculprit vessels stented during the primary percutaneous coronary intervention, to avoid the imaging analysis's potential confounding effects introduced by high-density stents. Lesion-based measurements were summarized at the patient level. The reliability of these measurements was confirmed by interobserver and intraobserver intraclass correlation coefficients (all >0.85) and coefficient of variation (all $<20\%$).

Statistical Analysis

Patients post-AMI were 1:1 propensity-matched to patients with only stable CAD (a priori-determined

propensity factors included age, male sex, hypertension, hyperlipidemia, diabetes, family history of premature CAD, and smoking status) using 1:1 nearest neighbor matching without replacement via R package MatchIt.^{20,21} After matching, absolute standardized mean differences were calculated for each covariate to assess the balance between the two groups.

Continuous variables are expressed as mean $\pm$ SD or median (interquartile range [IQR]), as appropriate. Categorical variables are presented as counts and percentages. Differences between categorical variables were analyzed using Fisher exact or χ^2 test as appropriate, and those between continuous variables using Student t test or Wilcoxon signed-rank test.

To account for residual imbalances after matching, including variables not included in the propensity score model (eg, body mass index [BMI] and lipid control medication), we utilized multiple linear and logistic regression models, adjusting for age, sex, smoking

history, hypertension, diabetes, hyperlipidemia, family history of CAD, BMI, and lipid control medication usage. These models were used to compare per-patient characteristics between cohorts. To compare per-lesion characteristics and peri-lesion PVAT attenuation, multiple linear mixed-effects models with random effects accounting for intraindividual clustering were utilized. Fitted models were reported with 95% CIs for linear estimates and as odds ratios (ORs) with 95% CIs for logistic estimates. The margins function in STATA was used to calculate estimated statistics, averaging over all covariates. Sensitivity analyses for countries of origin, ethnicities, and BMI were performed to assess the robustness of our findings.

Statistical significance was determined by a 2-tailed *P* value of <0.05. All analyses were performed with STATA version 17.0 (StataCorp) and R version 4.1.2 (R Foundation for Statistical Computing).

RESULTS

Patient Characteristics

The study cohort comprised 205 post-AMI cases and 205 propensity-matched patients with stable CAD. A total of 291 stent-containing vessels were excluded, including 205 culprit and 86 nonculprit vessels. The average age of the post-AMI cohort was 59.77±9.24 years (92.20% men), and the average age of the stable CAD cohort was 60.52±10.04 years (90.24% men) (Table 1). The post-AMI cohort comprised 62.44% ST-segment-elevation myocardial infarction cases and 37.56% non-ST-segment-elevation myocardial infarction cases. Patients post-AMI and those with stable CAD were well matched by propensity score: 0.426±0.182 versus 0.396±0.182 (*P*=0.105) (Table 1). Propensity score-matched patients post-AMI and patients with stable CAD had similar risk factors (hypertension, hyperlipidemia, diabetes,

Table 1. Clinical Characteristics of Patients Post-AMI and Patients With Stable CAD

Variables	Post-AMI (n=205)	Stable CAD (n=205)	<i>P</i> value	Absolute SMD*
	n (%) or mean±SD	n (%) or mean±SD		
Age, y	59.77±9.24	60.52±10.04	0.431	0.081
Men, %	189 (92.20)	185 (90.24)	0.485	0.073
Risk factors				
Hypertension, %	94 (45.85)	102 (49.76)	0.429	0.078
Hyperlipidemia, %	102 (49.76)	119 (58.05)	0.092	0.166
Lipid control medication, %	101 (49.27)	124 (60.49)	0.022	
Diabetes, %	42 (20.49)	38 (18.54)	0.618	0.048
Smoking (current, %)	48 (23.41)	53 (25.85)	0.816	0.023
Premature family history of CAD, %	49 (23.90)	47 (22.93)	0.567	0.058
Propensity score	0.426±0.182	0.396±0.182	0.105	0.182
Ethnicity			<0.05	
Not known	6 (2.93)	3 (1.46)		
Chinese	94 (45.85)	157 (76.59)		
Indian	29 (14.15)	19 (9.27)		
Malay	18 (8.78)	8 (3.90)		
White	54 (26.34)	2 (0.98)		
Other†	4 (1.95)	16 (7.80)		
Body mass index, kg/m ²	27.31±4.51	25.77±5.22	0.001	
Worst stenosis severity, %			0.234	
Normal (0%)	0 (0.00)	0 (0.00)		
1%–49% stenosis	100 (48.78)	87 (42.44)		
≥50% stenosis	105 (51.22)	118 (57.56)		
No. of vessels with >50% stenosis, %			0.795	
1 vessel	42 (20.49)	42 (20.49)		
2 vessels	25 (12.20)	30 (14.63)		
≥3 vessels	38 (18.54)	46 (22.44)		

AMI indicates acute myocardial infarction; CAD, coronary artery disease; and SMD, standardized mean difference.

*For parameters entered propensity score matching.

†Post-AMI cohort: The group categorized as "Other" includes Boyanese, Javanese, Sri Lankan, and Punjabi. CAD cohort: The group categorized as "Other" includes Bangladeshi, Filipino, and Eurasian.

family history of premature CAD, and smoking status), but patients post-AMI had higher BMI (27.31 ± 4.51 versus 25.77 ± 5.22 kg/m², $P=0.001$) (Table 1).

Plaque Composition and Quantification

After excluding culprit lesions, patients post-AMI still presented with more lesions than patients with stable CAD (11.68 ± 7.55 versus 9.39 ± 7.11 , $P=0.001$). There was no significant difference in the number of patients post-AMI and patients with stable CAD, with the worst lesion stenosis being $\geq 50\%$ (105 patients [51.22%] versus 118 patients [57.56%], $P=0.234$) (Table 1). The per-patient average %DS, calculated by averaging the DS of all lesions in each patient, was $<50\%$ for both the patients post-AMI and the patients with stable CAD ($26.43 \pm 8.55\%$ versus $28.9 \pm 10.29\%$, $P=0.008$).

However, patients post-AMI exhibited increased atherosclerotic plaque diffusiveness ($29.65 \pm 12.31\%$ versus $22.96 \pm 14.47\%$, $P<0.001$) (Table 2).

In univariable analysis, patients post-AMI did not show significant differences from patients with stable CAD in total PV (674.21 ± 496.12 versus 785.71 ± 849.61 mm³, $P=0.105$) and noncalcified PV (383.35 ± 313.23 versus 378.63 ± 426.25 mm³; $P=0.899$) (Figure 3A and 3C). However, patients post-AMI had lower calcified (48.19 mm³ [IQR, 16.22–139.02 mm³] versus 94.76 mm³ [IQR, 25.26–274.75 mm³]; $P=0.001$) (Figure 3B) and fibrous (229.82 ± 191.03 versus 286.35 ± 328.18 mm³; $P=0.034$) (Figure S1A) volumes than patients with stable CAD. These findings remained consistent after normalization to total PV (Figure 4, Figure S2, Table 2).

Multiple linear regression analysis revealed that increased age, male sex, and a history of hypertension

Table 2. Univariable Comparison of CCTA Findings

Atherosclerotic feature	Post-AMI (n=205)	Stable CAD (n=205)	P value
No. of total lesions	11.68±6.76	9.39±7.11	<0.001
%DS of lesions	26.43±8.55	28.9±10.29	<0.001
No. of lesions with %DS $\geq 50\%$	1 (0–2)	1 (0–2)	0.154
No. of lesions with %DS $\geq 70\%$	0 (0–0)	0 (0–0)	0.877
Area stenosis, %	42.71±12.13	46.4±14.59	<0.001
Minimum luminal area, mm ²	4.04±1.76	4.69±2.52	<0.001
Minimum luminal diameter, mm	1.88±0.47	1.96±0.57	0.110
Total PV, mm ³	674.21±496.12	785.71±849.61	0.105
Calcified, mm ³	48.19 (16.22–139.02)	94.76 (25.26–274.75)	0.001
Fibrous, mm ³	229.82±191.03	286.35±328.18	0.034
Fibrofatty, mm ³	132.6±126.57	83.88±120.43	<0.001
NC, mm ³	11.34 (2.99–26.69)	1.61 (0.12–8.25)	<0.001
Fibrofatty+NC, mm ³	153.52±149.54	92.28±134.02	<0.001
Noncalcified, mm ³	383.35±313.23	378.63±426.25	0.899
Composition by % PV			
% Calcified	21.67±19.48	31.51±19.83	<0.001
% Fibrous	47.59±13.67	53.6±14.78	<0.001
% Fibrofatty	26.1±13.94	13.36±12.60	<0.001
% NC	4.09±4.32	1.17±1.76	<0.001
% Fibrofatty+NC	30.19±17.31	14.53±14.02	<0.001
% Noncalcified volume	77.79±19.36	68.13±19.76	<0.001
Percent atheroma volume, %	24.96±11.48	19.58±13.65	<0.001
Max cross-sectional plaque burden, %	64.06±8.98	65.06±12.46	0.350
Diffuseness, %	29.65±12.31	22.96±14.47	<0.001
Adverse plaque characteristics			
High-risk plaque present	3.39±2.51	2.45±2.38	<0.001
Low attenuation plaque present	6.80±4.21	4.55±4.22	<0.001
Positive remodeling present	2.68±2.02	2.11±2.00	<0.001
Spotty calcification present	3.09±2.74	2.90±2.74	0.494
Peri-lesion PVAT mean attenuation, HU	−75.31±11.27	−78.13±10.59	<0.001

Values are number (percentage), mean±SD, or median (interquartile range). AMI indicates acute myocardial infarction; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; DS, diameter stenosis; HU, NC, necrotic core; PV, plaque volume; and PVAT, perivascular adipose tissue.

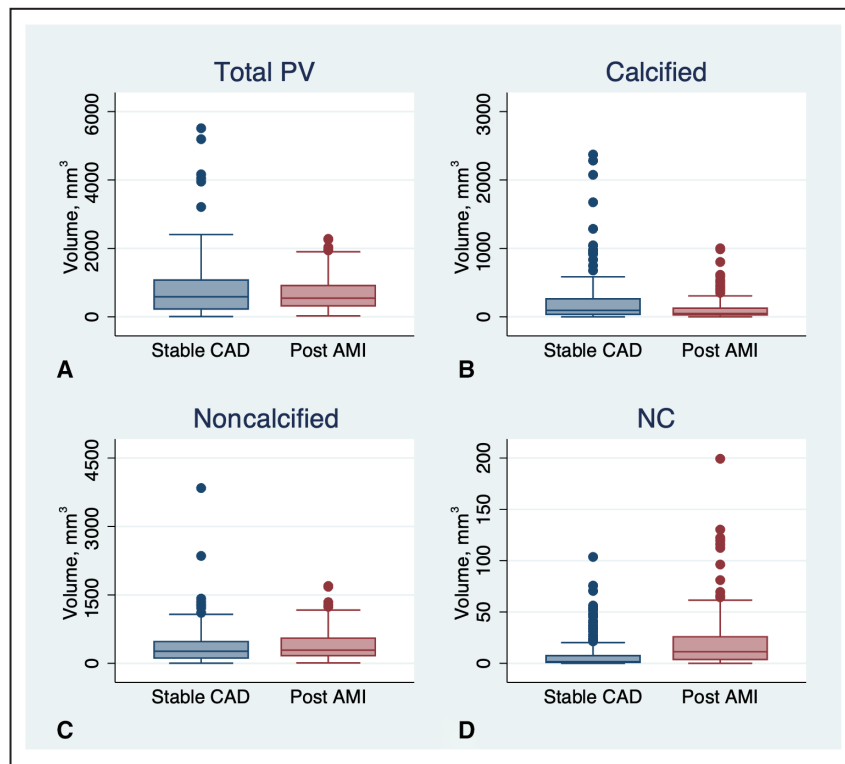


Figure 3. Total plaque volume (PV) and total volume of each tissue type for patients post-acute myocardial infarction (AMI; excluding culprit lesions) and patients with stable coronary artery disease (CAD).

(A) Total PV; (B) volume of calcified content; (C) volume of noncalcified content; and (D) volume of necrotic core (NC) content.

were associated with greater total PV ($P<0.05$ for all). In addition, the increase in age was related to a drop in the noncalcified PV (NCPV) ratio, while current smokers exhibited a higher NCPV ratio, NC volume ratio, and fibrofatty volume ratio ($P<0.05$ for all).

In the per-patient multivariable analysis, patients post-AMI exhibited lower total PV compared with patients with stable CAD (estimate, -174.29 [95% CI, -305.69 to -42.88], $P=0.009$) (Table 3). After adjusting for risk factors, patients with recent AMI demonstrated an increased NCPV ratio by 0.088 (estimate, 0.089 [95% CI, 0.053 – 0.125]) (Figure 5B) owing to increased fibrofatty (estimate, 0.115 [95% CI, 0.090 – 0.140]) and NC (estimate, 0.026 [95% CI, 0.019 – 0.032], $P<0.001$ for all) (Figure 5C, Table 3) volume ratios. Moreover, patients post-AMI had lower fibrous PV ratios (estimate, -0.052 [95% CI, -0.079 to -0.025], $P<0.001$) (Table 3).

In per-lesion multivariable analysis, patients post-AMI exhibited smaller PVs than lesions in patients with stable CAD by 25.85 mm^3 (estimate, -25.85 [95% CI, -34.90 to -16.81], $P<0.001$). Mirroring the per-patient analysis, lesions in patients post-AMI were associated with a higher NCPV ratio (estimate, 0.068 [95% CI, 0.034 – 0.102]), elevated fibrofatty (estimate, 0.090 [95% CI, 0.067 – 0.114]), and increased

NC (estimate, 0.016 [95% CI, 0.011 – 0.022], $P<0.001$ for all) volume ratios.

High-Risk Plaques Analysis

In univariable analysis, lesions in patients post-AMI contained a significantly higher number of HRPs than those in patients with stable CAD (3.39 ± 2.51 versus 2.45 ± 2.38 ; $P<0.001$). In addition, these lesions demonstrated a higher prevalence of both LAP and positive remodeling (both $P<0.05$) (Table 2). The prevalence of spotty calcification was comparable between patients post-AMI and patients with stable CAD (3.09 ± 2.74 versus 2.90 ± 2.74 , $P=0.494$) (Table 2).

In multivariable analyses of vessel-length normalized counts of HRPs and high-risk features, hyperlipidemia and family history of CAD were associated with increased normalized positive remodeling counts. Patients post-AMI incorporated 0.417 more HRPs per decimeter than those in patients with stable CAD (estimate, 0.417 [95% CI, 0.298 – 0.536]). In addition, patients post-AMI exhibited higher normalized counts of each of the high-risk features compared with patients with stable CAD, including LAP (estimate, 0.882 [95% CI, 0.706 – 1.057]), positive

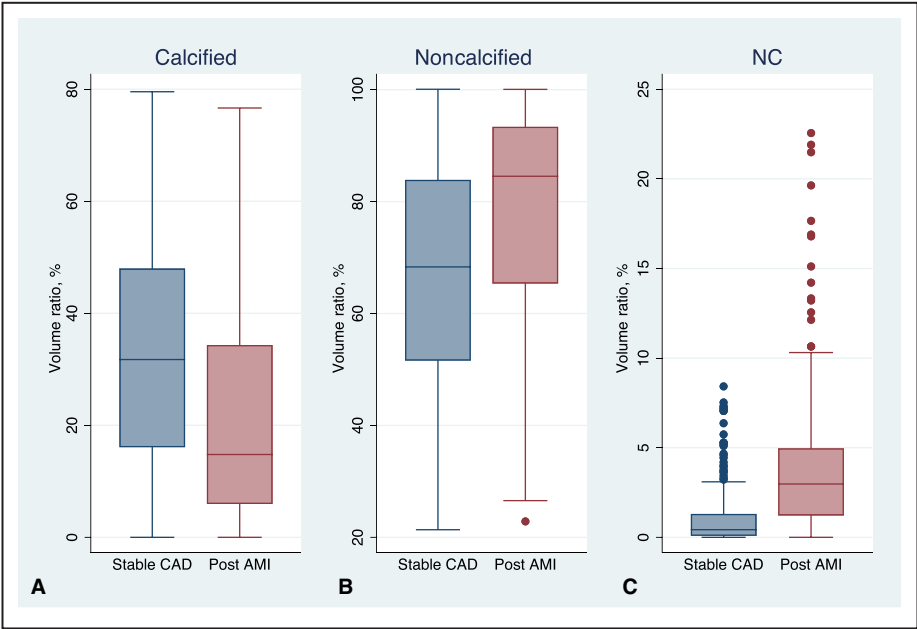


Figure 4. The volume ratio of each tissue type for patients post-acute myocardial infarction (AMI; excluding culprit lesions) and patients with stable coronary artery disease (CAD) after normalized to total plaque volume. (A) Calcified content; (B) noncalcified content; (C) necrotic core (NC) content.

remodeling (estimate, 0.368 [95% CI, 0.269–0.467]), and spotty calcification (estimate, 0.209 [95% CI, 0.078–0.34], $P<0.05$ for all) (Figure 6, Table 3). In the per-lesion analysis, multivariable logistic regression models revealed that the status of post-AMI only contributed to an increased odds for LAP (OR,

1.269 [95% CI, 1.115–1.444], $P<0.001$) but not for other HRP features.

PVAT Analysis

The univariable analysis demonstrated that patients post-AMI have higher peri-lesion PVAT mean attenuation than lesions of patients with stable CAD (-75.31 ± 11.27 HU versus -78.13 ± 10.59 HU, $P<0.001$) (Table 2). Mixed-effect multivariable linear models revealed that the peri-lesion PVAT mean attenuation in patients post-AMI was higher than that in patients with stable CAD by 3.968HU (estimate, 3.968 [95% CI, 2.556–5.379], $P<0.001$) after adjusting for covariates (Figure 7). In addition, peri-lesion PVAT mean attenuation was not significantly associated with corresponding PV. Although peri-lesion PVAT mean attenuation was positively associated with the noncalcified volume ratio of corresponding plaques (estimate, 4.098 [95% CI, 2.747–5.449], $P<0.001$), PVAT attenuation was not associated with fibrofatty and necrotic core volume ratios.

Sensitivity Analysis for the Country of Origin and Ethnicity

We performed sensitivity analyses to address the potential influence of country of origin and ethnicity on lesion characteristics. First, we compared the lesional characteristics between patients post-AMI from Singapore and New Zealand. Singapore patients post-AMI had

Table 3. Multivariable Regression Coefficients of the Post-AMI Group

Outcome	Estimate	SE	P value	95% CI
PV				
Total PV*	−174.29	66.84	0.009	−305.69 to −42.88
Normalized tissue composition†				
NCPV	0.089	0.019	<0.001	0.053–0.125
Fibrous	−0.052	0.014	<0.001	−0.079 to −0.025
NC+fibrofatty	0.141	0.015	<0.001	0.111–0.171
Fibrofatty	0.115	0.013	<0.001	0.140
NC	0.026	0.003	<0.001	0.019–0.032
Normalized HRP feature count, dm ^{−1}				
HRP, n	0.417	0.060	<0.001	0.298–0.536
PR, n	0.368	0.050	<0.001	0.269–0.467
NC, n	0.882	0.089	<0.001	0.706–1.057
SC, n	0.209	0.067	0.002	0.078–0.340

HRP indicates high-risk plaque; NC, necrotic core; NCPV, noncalcified plaque volume; PR, positive remodeling; and SC, spotty calcification. *Lesions in the culprit vessels of patients with post-acute myocardial infarction (AMI) were excluded. †Volume of each tissue type was normalized to total plaque volume (PV).

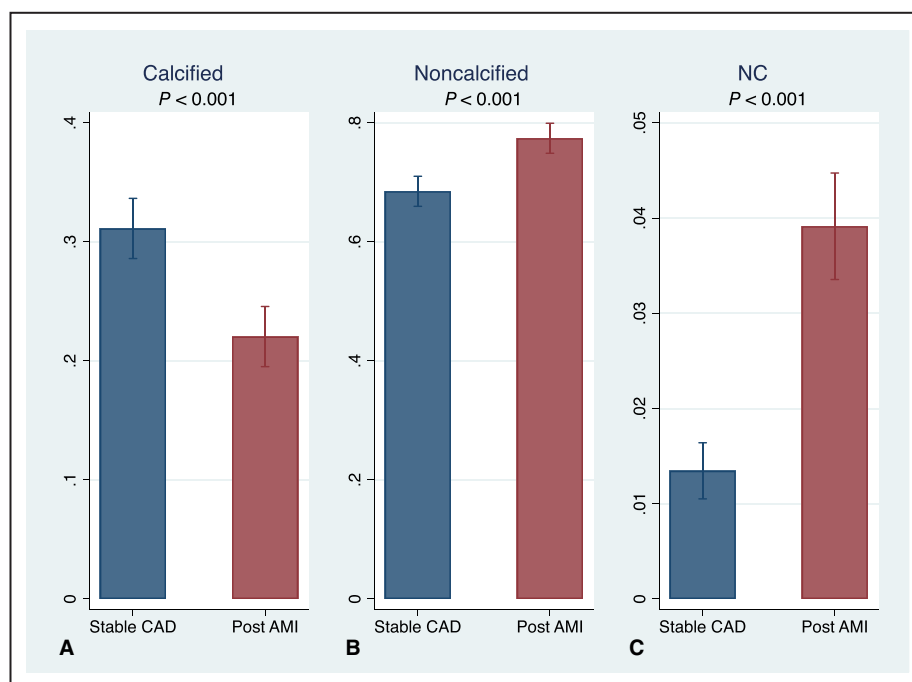


Figure 5. The regression model predicted volume ratio of each tissue type for patients with post-acute myocardial infarction (AMI; excluding culprit lesions) and patients with stable coronary artery disease (CAD) after averaging covariates.

(A) Calcified content; (B) noncalcified content; and (C) necrotic core (NC) content.

a higher lesion count than New Zealand patients ($P=0.029$), but there was no difference in total PV and percent atheroma volume (Table S1). Although univariable analysis indicated higher noncalcified plaque content in New Zealand patients post-AMI (Table S1), this difference was insignificant in multivariable analysis. The 2 cohorts had no significant differences in other inflammation-indicating plaque contents. Notably, New Zealand patients post-AMI had a lower number of HRP than Singapore patients ($P<0.05$), primarily due to a lower prevalence of LAP ($P<0.01$). The 2 cohorts had no difference in peri-lesion PVAT mean attenuation.

Next, we compared patients post-AMI and patients with stable CAD from Singapore. The main study conclusions remained consistent: patients post-AMI had more lesions than patients with stable CAD ($P=0.024$) but similar total PV and percent atheroma volume (Table S1). Patients post-AMI exhibited higher noncalcified plaque content and increased necrotic core and fibrofatty content, indicative of inflammation. Patients post-AMI also had a higher prevalence of HRP and higher peri-lesion PVAT mean attenuation. A specific subgroup analysis of patients of Chinese ethnicity recruited from Singapore was also conducted to address potential ethnic and site influences on clinical outcomes. Most conclusions for the comparison between PV, tissue composition, HRP prevalence, and per-lesion PVAT attenuation was concurred with the

previous analyses, except that there were no significant differences in the count of lesions between Chinese patients post-AMI and patients with stable CAD ($P=0.060$) (Table S1).

Sensitivity Analysis for BMI

To evaluate the influence of BMI, a sensitivity analysis was performed by incorporating BMI in the propensity score model (Table S2). The primary findings of the study remained consistent in the BMI-matched cohorts: (1) patients post-AMI exhibited more lesions but lower total PV than patients with stable CAD; (2) there was no significant difference in noncalcified PV, but patients post-AMI had a higher percentage of noncalcified content after normalizing to total PV; (3) patients post-AMI have higher low-attenuation fibrofatty and NC content volume and lower calcified and fibrous volume, with these trends remaining consistent after normalizing to total PV; and (4) patients post-AMI also have higher counts of HRPs and higher per-lesion PVAT mean attenuation (Table S3).

These analyses underscore the importance of considering geographical, ethnic, and BMI differences when assessing lesion characteristics and inflammatory markers in patients post-AMI and patients with stable CAD, ensuring the robustness of our findings across varied demographics.

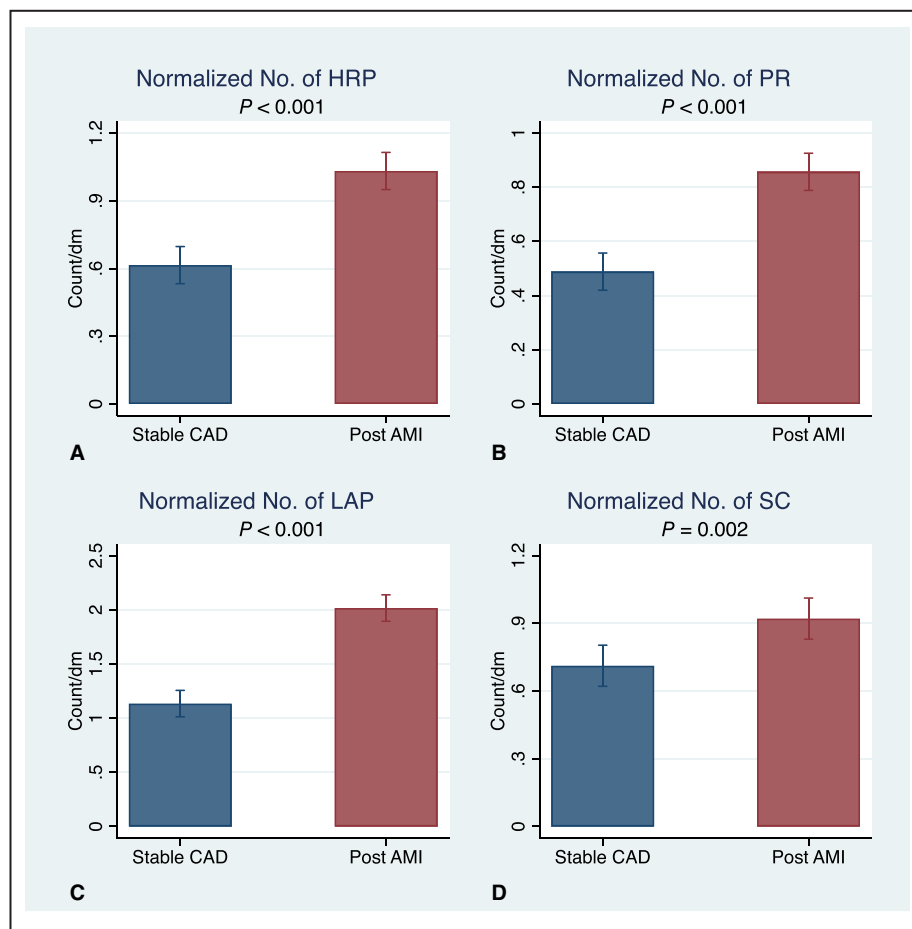


Figure 6. The regression model predicted per-patient high-risk plaques (HRPs) and high-risk feature counts after normalized to vessel length.

AMI indicates acute myocardial infarction; CAD, coronary artery disease; LAP, low attenuation plaques; PR, positive remodeling; and SC, spotty calcification.

DISCUSSION

In a multiethnic Asian-Pacific cohort, we assessed residual inflammation by comparing CCTA-based biomarkers in nonculprit lesions between patients with stable CAD and those post-AMI. Although patients post-AMI exhibited lower total PV than patients with stable CAD, their lesions had a notably elevated NCPV ratio, predominantly due to an increased fibrofatty and necrotic core volume ratio, alongside higher HRP prevalence and higher peri-lesion PVAT mean attenuation, suggesting intensified inflammation. Most of these findings were also preserved in the subgroup analysis of patients of Chinese ethnicity. To the best of our knowledge, this is the first study to simultaneously compare PV, HRPs, and PVAT to assess post-AMI residual inflammatory risk.

Our results concur with prior CCTA and invasive studies reporting that patients with acute coronary syndromes had higher NCPV²² and higher lipid content than patients without acute coronary

syndromes.^{23,24} Accumulation of lipid-laden macrophage foam cells and smooth muscle cells forms the lipid-rich necrotic core and fibrofatty tissue, which, along with enhanced collagen degradation by intensified inflammatory cell activity, signifies a persistent inflammatory state and elevated plaque rupture risk that may be masked by plaque burden quantification alone.^{25–27} Meanwhile, compared with patients who have CAD, patients post-AMI also include a higher HRP prevalence, which is another indicator of plaque inflammation and future adverse cardiovascular event risk.^{12,17,28} Previous studies such as ICONIC (Incident Coronary Syndromes Identified by Computed Tomography) and SCOT-HEART (Scottish Computed Tomography of the Heart) have confirmed that quantitative low-attenuation PVs and qualitative high-risk features are associated with increased MI risks.^{17,29} Yet, it is worth noting that despite these inflammation markers, both stable CAD and nonculprit lesions of patients post-AMI presented an all-lesion mean DS <50%. This underscores the need for comprehensive

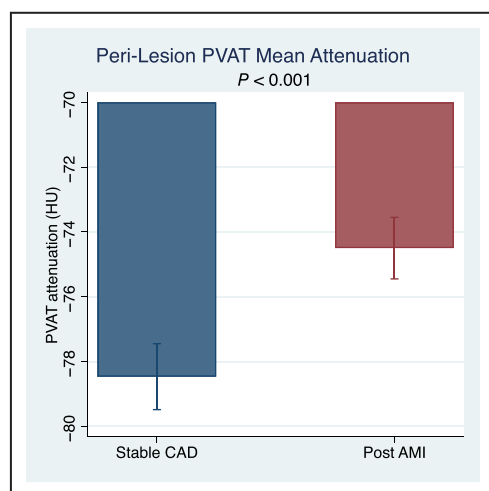


Figure 7. The regression model predicted peri-lesion perivascular adipose tissue (PVAT) mean attenuation.

AMI indicates acute myocardial infarction; and CAD, coronary artery disease.

plaque assessment, rather than merely focusing on coronary stenosis, for effective post-AMI clinical evaluation and decision-making.

In addition, our study observed a notable increase in PVAT mean attenuation for patients post-AMI relative to patients with stable CAD. PVAT mean attenuation has been identified as an independent prognostic risk factor for adverse cardiovascular events, providing added value beyond plaque characteristics.^{4,18,30,31} Furthermore, PVAT mean attenuation serves as a crucial confirmatory factor that complements plaque analysis in identifying coronary lesion inflammation. The attenuation threshold for noncalcified tissue plaque composition may vary across studies and is sometimes not easily reproducible because of variations in vendor, user, and imaging parameters, such as tube voltage and current, making the additional confirmation provided by PVAT particularly useful.^{32–35} This measure indicates vascular inflammation, which is linked to plaque advancement and adverse cardiovascular outcomes.^{3,4,11,18,28,30,31} As an active paracrine tissue, PVAT plays a distinct role in vascular inflammation. It was shown that inflamed vessel walls release cytokines and cause a shift in the PVAT toward smaller, less lipid-rich adipocytes, detectable as increased computed tomography attenuation.³⁰ Furthermore, our investigation uniquely extended to encompass peri-lesion PVAT across all nonculprit lesions, diverging from previous studies predominantly focusing on the PVAT surrounding proximal right coronary arteries.^{18,19} This comprehensive approach serves to reduce selection bias and provides a more holistic view of the inflammatory status across the coronary tree, emphasizing the significance of nonculprit

lesion characteristics in post-AMI residual inflammation and risk stratification.

Our study augments existing literature by examining the characteristics of nonculprit lesions, providing a comprehensive analysis of the inflammatory status of patients post-AMI. Unlike prior research that primarily centered on culprit lesions of hemodynamic significance or employed invasive methods with restricted combined intracoronary and extracoronary analysis capability,^{36,37} our study harnessed noninvasive CCTA, allowing for a thorough examination of the entire coronary tree following AMI. Our findings distinctly indicate that inflammation indicating plaque and PVAT characteristics extend beyond culprit lesions, highlighting the importance of a comprehensive assessment of the coronary trees in patients following AMI and underscoring the overlooked residual inflammatory risk. The importance of addressing nonflow-limiting high-risk plaques was also underscored in the recent PREVENT (Preventive Percutaneous Coronary Intervention Versus Optimal Medical Therapy Alone for the Treatment of Vulnerable Atherosclerotic Coronary Plaques) trial, which demonstrated the benefits of preventive percutaneous coronary intervention in treating vulnerable plaques to prevent major adverse cardiac events.³⁸ This aligns with our findings emphasizing the necessity of identifying and managing residual inflammation and high-risk plaque features in nonculprit lesions to improve long-term outcomes. Such insights advocate for a broadened perspective in post-AMI patient assessments, moving beyond the current practices that primarily target culprit lesions and paving the way for more in-depth investigations. The combination of plaque characteristics and PVAT attenuation offers a dual approach to better understand and manage post-AMI residual inflammation.

Moreover, our findings resonate with recent clinical trials such as CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study), which explored the benefit of atherosclerosis-targeting anti-inflammatory agents and revealed insights into new territories of post-AMI management beyond guideline-driven aggressive risk factor modification.^{39,40} The detailed inflammation mapping offered by CCTA suggested its utility beyond diagnosis, hinting at its potential for personalized anti-inflammatory treatment strategies. By identifying territory-specific inflammation, our study emphasizes the necessity for a more nuanced approach to post-AMI anti-inflammatory management. This underlines the importance of continued research to explore CCTA's full potential in guiding the application of novel anti-inflammatory treatments and refining risk assessment protocols for patients post-AMI.

Despite the benefit, integrating comprehensive CCTA analysis into daily workflows for post-AMI patient assessment is challenging because of

its labor-intensive nature. Artificial intelligence (AI) emerges as a potential solution to streamline this process. AI promises to enhance efficiency by automating the analysis of coronary stenosis and atherosclerotic plaque characteristics, thus addressing the increasing demand for CCTA amidst a shortage of expert readers.^{41,42} However, while AI's diagnostic accuracy shows promise, it requires further validation, particularly in detecting nonobstructive CAD and high-risk plaque features.⁴¹ Embracing AI in CCTA workflows could transform post-AMI care, making detailed evaluations more feasible in routine practice, provided these technologies are thoroughly vetted and appropriately integrated to complement clinical judgment.

LIMITATIONS

Our study has some limitations. First, the observational design and multicenter recruitment may have introduced the potential for unmeasured confounding factors, referral bias, and variations in cohort demographics, especially ethnicity composition. Second, while CCTA offers valuable noninvasive insights, it has limitations in quantifying smaller plaques and analyzing areas adjacent to high-density materials, leading to the exclusion of both culprit and nonculprit stented vessels, potentially underestimating the overall inflammatory state in patients post-AMI. Third, the study population predominantly consisted of male participants, which may limit the generalizability of our findings to the broader population. Although women were approached in equal proportion for consent, a large majority opted out of the post-AMI arm because of personal preferences. Last, the lack of detailed medication information, specifically the types and dosages of lipid-control and antiplatelet medications, constrains our ability to fully understand the influence of pharmacotherapy on patients' CCTA characteristics.

CONCLUSIONS

In this CCTA-based study, patients post-AMI showed increased noncalcified plaque burden due to a higher fibrofatty and necrotic core volume ratio, higher high-risk plaque prevalence, and increased per-lesion PVAT attenuation, indicating a persistent inflammatory process compared with that in patients with stable CAD. This suggests the potential value of thorough CCTA assessment in understanding post-AMI pathophysiology and guiding therapeutic strategies. However, it also underscores the need for prospective studies to evaluate the necessity and impact of CCTA assessments in posttreatment AMI patient care.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Tables S1–S3

Figures S1–S2

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