

RESEARCH ARTICLE

Age-related Pancoronary Characteristics in Patients with ST-segment Elevation Myocardial Infarction

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Abstract

Background: Age-related vulnerable characteristics of pancoronary plaques in patients with ST-segment elevation myocardial infarction (STEMI) have not been systemically evaluated by optical coherence tomography (OCT). Therefore, we sought to explore the discrepancies in pancoronary characteristics between younger and older patients with STEMI through OCT.

Methods: This retrospective single-center study included 588 patients who had STEMI and underwent three-vessel OCT through emergency percutaneous coronary intervention between October 2016 and September 2018. With a median age of 56 years as a cutoff, the patients were divided into a younger group (≤ 56 years, $n = 298$) and an older group (> 56 years, $n = 290$).

Results: A total of 795 non-culprit plaques were found in 298 of the younger patients, whereas 858 non-culprit plaques were identified in 290 of the older patients. Fewer high-risk OCT plaques (15.8% vs. 23.1%; $P = 0.025$), as well as other structures (cholesterol crystals, $P = 0.001$; microchannels, $P = 0.032$; calcifications, $P < 0.001$; spotty calcifications, $P < 0.001$; large calcifications, $P < 0.001$; and thrombi, $P = 0.001$) were identified in younger patients than older patients, at the patient level. In addition, pancoronary vulnerability in younger patients was independently predicted by culprit plaque rupture {CLIMA-defined high-risk plaques (odds ratio [OR]: 3.179; 95% CI: 1.501 to 6.733; $P = 0.003$), non-culprit rupture (OR: 3.802; 95% CI: 1.604 to 9.014; $P = 0.002$), non-culprit thin-cap fibroatheroma (OR: 3.536; 95% CI: 2.051 to 6.094; $P < 0.001$)}, hypertension (OR: 1.920; 95% CI: 1.099 to 3.355; $P = 0.022$), and total cholesterol (OR: 1.094; 95% CI: 1.002 to 1.195; $P = 0.045$). In older patients with STEMI, the predictor was male sex (OR: 3.031; 95% CI: 1.352 to 6.795; $P = 0.007$).

Conclusions: Among patients with STEMI, younger patients had limited vulnerable plaque characteristics, and pancoronary vulnerability was associated with culprit plaque rupture, hypertension, and total cholesterol. In contrast, older patients had greater pancoronary vulnerability with the single predictor of male sex, thus suggesting that traditional risk factors have limited applicability in predicting pancoronary vulnerability in older patients.

Keywords: optical coherence tomography; ST-segment elevation myocardial infarction; non-culprit lesion; age; pancoronary plaque characteristics

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Introduction

Age differences in plaque morphology in patients with coronary artery disease have been verified from pathology and imaging studies [1–3]. Pathological studies have revealed a higher prevalence of plaque erosion among younger patients,

particularly women [1, 4]. However, those studies were limited to postmortem analysis of patients with coronary events. Intravascular ultrasound (IVUS) studies have shown that younger patients, compared with older patients, have fewer necrotic cores and calcium, with a lower plaque burden in non-culprit lesions [3]. Several *in vivo* optical coherence tomography (OCT) studies have also reported consistent results [2]. Younger patients with ST-segment elevation myocardial infarction (STEMI) show more plaque erosion and fewer unstable plaque features in culprit lesions with unknown morphological characteristics than non-culprit lesions, according to OCT [2]. Moreover, the CLIMA study, using OCT, has identified high-risk plaque (HRP) characteristics that are independent predictors of major adverse cardiovascular events (MACEs) [5]. The current study was aimed at investigating the differences in pancoronary plaque vulnerability and non-culprit plaque features in younger versus older patients with STEMI, and determining the predictors of pancoronary plaque vulnerability in these patient groups through three-vessel OCT analysis.

Methods

Study Population

Between October 2016 and September 2018, a series of 675 patients with STEMI whose emergency treatment included OCT imaging of all three major epicardial coronary arteries were identified in the database of the Cardiovascular Department of the 2nd Affiliated Hospital of Harbin Medical University (Harbin, China). STEMI was defined as continuous chest pain that lasted > 30 minutes, arrival at the hospital within 12 hours after the onset of symptoms, ST-segment elevation > 0.1 mV in more than two contiguous leads or new left bundle-branch block on the 12-lead electrocardiogram, and elevated cardiac markers (creatinine kinase-MB or troponin T/I) [6]. Some patients were excluded because of in-stent restenosis or thrombosis (n = 13), pre-dilatation (n = 3), a very short analyzable segment, or suboptimal image quality (n = 71). Finally, 588 patients with STEMI were enrolled and included in the current analysis, among whom the median age (56 years) was

selected as the cutoff value to define the younger group (≤ 56 years, n = 298) and older group (> 56 years, n = 290). A total of 795 non-culprit plaques were identified in the younger group, and 858 non-culprit plaques were observed in the older group (Figure 1). The relevant definitions and diagnostic criteria are presented in the supplementary material online. The Ethics Committee of the 2nd Affiliated Hospital of Harbin Medical University approved this study, which complied with the Declaration of Helsinki. All patients in this study provided signed informed consent.

Coronary Angiography Analysis

A quantitative coronary angiography (QCA) analysis system (CAAS 7.2, Pie Medical Imaging BV, Maastricht, the Netherlands) was used to analyze the coronary angiography images and was operated by two experienced investigators blinded to the patients' clinical presentation. Coronary flow was assessed by classification of thrombolytic flow grading in myocardial infarction. The parameters of QCA, including reference vessel diameter (RVD), minimal lumen diameter (MLD), diameter of stenosis (DS), and lesion length, were measured at the end of cardiac diastole after calibration [7]. The average diameter of the proximal and distal reference diameters was denoted the RVD. The DS was defined as $(RVD - MLD)/RVD \times 100\%$. Each lesion was evaluated angiographically, with matching of OCT images by fiducial side branches.

OCT Image Acquisition and Analysis

The three-vessel OCT images were digitally stored and analyzed with the C7-XR/ILUMIEN OCT system (Abbott Vascular, Santa Clara, CA, USA) by two independent researchers (T.W. and M.C.) who were blinded to patients' information. Any disagreements were resolved by a consensus reading from a third independent investigator (J.Z.). Before OCT imaging was performed, no specified criteria were predefined, and the images were acquired on the basis of the operator's judgment. The culprit lesion underwent intervention and treatment after OCT scanning. OCT scanning in the non-culprit lesions was performed after the culprit lesion was

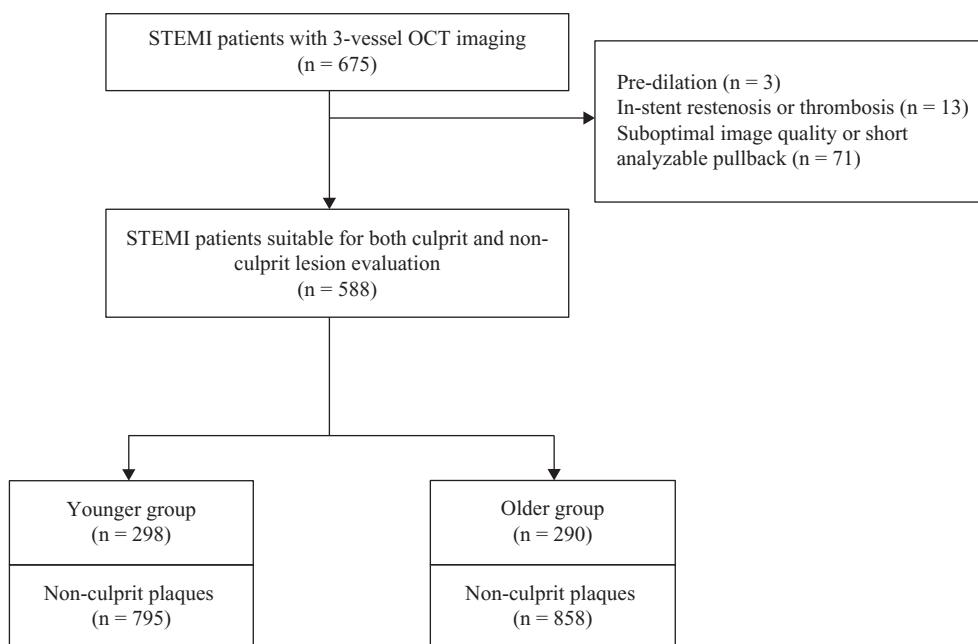


Figure 1 Study Flowchart.

treated. For each patient enrolled in our study, single or multiple pullbacks were performed in each vessel. Imaging of the long vessel segment was conducted to evaluate the entire vessel with multiple pullbacks, which matched and overlapped.

A culprit lesion was considered a lesion with recent plaque disruption or the most severe stenosis, including significant thrombus on OCT, determined from angiographic findings, electrocardiographic changes, and/or left ventricular wall motion abnormalities [6]. A non-culprit lesion was considered a lesion with at least three successive cross-sectional plaques of 1 mm [8]. Plaque rupture (PR) was identified as the appearance of a discontinuous fibrous cap with cavity formation inside the plaque [6, 9]. When PR was observed in the non-culprit plaque, it was designated non-culprit PR. Lipids were identified by signal-poor regions with poorly defined or diffuse borders, and the lipid length and arc were measured. Fibroatheromas were identified as plaques with the presence of a lipid pool $>90^\circ$ with no lateral delineation [6, 9]. Fibrous cap thickness (FCT) was measured three times in lipid-rich plaques (LRPs) at the thinnest part. Macrophage accumulation was defined as the presence of strongly backscattering focal areas inside the fibrous cap [9]. The smallest lumen area within the range of the plaque was defined as the minimum lumen area (MLA).

We further classified non-culprit plaques according to their lesion morphology. Thin-cap fibroatheroma (TCFA) was fibroatheroma with a minimum FCT $\leq 65 \mu\text{m}$, whereas thick-cap fibroatheroma (ThCFA) had an FCT $> 65 \mu\text{m}$. A fibrous plaque was represented by a homogeneous OCT signal with high backscatter, and was defined as any plaque not conforming to the definition of either fibroatheroma or fibrocalcific plaque. A fibrocalcific plaque was defined as a plaque with calcification $>90^\circ$ [9, 10].

According to the CLIMA study, plaques with four simultaneously occurring vulnerable features (FCT $< 75 \mu\text{m}$, maximum lipid arc $>180^\circ$, macrophage accumulation, and MLA $<3.5 \text{ mm}^2$) were considered HRP. Pancoronary vulnerability was defined as the presence of at least one of three vulnerable characteristics at non-culprit lesions: 1) CLIMA-defined HRPs, 2) TCFA, and 3) PR [5]. Excellent intraobserver and interobserver consensus was observed in the recognition of CLIMA-defined HRPs (κ , 0.94 and 0.89, respectively), non-culprit PR (κ , 0.93 and 0.90, respectively), and non-culprit TCFA (κ , 0.92 and 0.89, respectively). Other definitions of, and criteria for, OCT analysis in the present study are presented in the supplemental data. The total analyzed OCT pullback length was $199.4 \pm 32.7 \text{ mm}$ ($86.5 \pm 21.3 \text{ mm}$ in the right coronary artery [RCA], $66.2 \pm 23.8 \text{ mm}$ in the left anterior

descending artery [LAD], and 43.4 ± 13.1 mm in the left circumflex artery [LCX]), and was comparable between younger patients and older patients (202.1 ± 33.9 mm vs. 195.7 ± 36.0 mm; $P = 0.39$).

Statistical Analysis

Continuous variables are presented as median (interquartile range [IQR]) or mean \pm standard deviation (SD). The Kolmogorov-Smirnov test was used to determine continuous data distribution. Continuous data were compared with the Mann-Whitney U test or independent samples Student's t -test, as appropriate. Categorical data are presented as counts (proportions) and were compared with the chi-squared test or with Fisher's exact test. Intraobserver and interobserver differences were quantified with the κ coefficient of agreement for pancoronary vulnerability identification. Non-culprit lesion features between groups (≤ 56 years and > 56 years) were compared with generalized estimating equations to account for potential cluster effects of multiple plaques in a patient. Patients were divided into quartiles in the secondary analysis according to age (≤ 48 years, 49–56 years, 57–63 years, and > 63 years). Comparisons of variables among the four groups were performed with the Kruskal-Wallis test. Logistic regression analysis was used to identify the relationships among pancoronary vulnerability, plaque morphology, and traditional risk factors when the variables showed $P < 0.1$ in the univariate analysis. A two-sided P value < 0.05 was considered to indicate significant differences. All analyses were performed in SPSS version 23.0 software (IBM, Armonk, New York).

Results

Patients and Clinical Characteristics

A total of 1653 non-culprit plaques (795 in the younger group and 858 in the older group) were analyzed in 588 patients with STEMI (Figure 1). The clinical characteristics and laboratory data for younger and older patients with STEMI are shown in Table 1. The younger patients, compared with the older patients, were more frequently male ($P < 0.001$) and current smokers ($P < 0.001$), and had a lower incidence of hypertension ($P = 0.001$).

Furthermore, younger patients, compared with older patients, had a higher incidence of dyslipidemia ($P = 0.012$), and elevated triglyceride (TG) ($P = 0.001$) and hemoglobin ($P < 0.001$) levels, but a lower incidence of chronic kidney disease ($P = 0.006$), and lower levels of hs-CRP ($P = 0.047$) and HbA1c ($P = 0.027$). Other risk factors, laboratory data, and previous history of MI or PCI were comparable between groups.

Angiographic Characteristics

The angiographic characteristics of non-culprit plaques are shown in Table 2. There was no significant difference in pancoronary distribution of non-culprit plaques between the two groups. The QCA data showed a larger MLD ($P = 0.043$) and less severe DS ($P = 0.033$) for non-culprit plaques in younger patients than older patients.

OCT Findings for Non-Culprit Plaques

In plaque-level analysis, younger patients, compared with older patients, had a lower prevalence of non-culprit fibrocalcific plaques ($P < 0.001$) and a higher incidence of non-culprit fibrous plaques ($P < 0.001$). The proportions of ThCFAs and TCFAs in the non-culprit region were comparable between groups (Figure 2). Calcification accumulation was markedly lower in the younger group than the older group, as evidenced by a lower prevalence of total calcification ($P = 0.005$) and large calcification ($P < 0.001$), a shorter calcification length ($P < 0.001$), and a smaller mean calcification arc ($P = 0.006$) and calcium index ($P < 0.001$). Notably, more LRPs and fewer plaques with a maximum lipid arc $> 180^\circ$ were observed in the younger group than in the older group (Figure 3A and B).

Patient-level analysis (Table 3) indicated fewer non-culprit plaques per patient in the younger group than the older group ($P = 0.042$). At least one CLIMA-defined HRP was observed in 15.8% of younger patients but in 23.1% of older patients in the non-culprit region ($P = 0.025$). The same tendency was also observed when the individual characteristics of HRPs were analyzed, except for $FCT < 75$ μm . Slight calcification accumulation (calcification, large calcification, spotty calcification, and pancoronary calcium index) and lower incidence rates of

Table 1 Baseline Clinical Characteristics among Patients of Different Ages.*

Variables	Age ≤56 years (n = 298)	Age >56 years (n = 290)	P value
Male	268 (89.9)	183 (63.1)	<0.001
Age (years)	47.3 ± 6.5	64.7 ± 6.3	<0.001
Risk factors			
Diabetes mellitus	44 (14.8)	43 (14.8)	0.983
Hypertension	97 (32.6)	135 (46.6)	0.001
Dyslipidemia	182/282 (64.5)	148/274 (54.0)	0.012
Smoking			<0.001
Current smoker	183 (61.4)	126 (43.4)	
Former smoker	16 (5.4)	28 (9.7)	
Non-smoker	99 (33.2)	136 (46.9)	
CKD	12 (4.0)	28 (9.7)	0.006
Laboratory data			
TC (mg/dL)	185.9 ± 41.7	183.9 ± 39.0	0.571
Triglycerides (mg/dL)	145.8 (90.9–209.0)	121.3 (85.5–165.0)	0.001
LDL-C (mg/dL)	114.2 ± 35.9	114.8 ± 32.2	0.834
HDL-C (mg/dL)	48.9 ± 11.5	50.0 ± 12.7	0.264
TC/HDL ratio	3.9 ± 1.5	3.8 ± 1.4	0.114
HbA1c (%)	5.7 (5.4–6.2)	5.7 (5.5–6.3)	0.027
Hemoglobin (g/L)	151.9 ± 20.3	141.0 ± 20.2	<0.001
hs-CRP (mg/L)	3.9 (1.7–8.8)	4.8 (2.0–11.1)	0.047
TnI max	65.2 (27.4–120.3)	60.0 (24.9–142.6)	0.892
CKMB max	9.8 (1.8–93.4)	13.8 (2.7–71.1)	0.646
Previous history			
Previous MI	8 (2.7)	8 (2.8)	0.956
Previous PCI	4 (1.3)	8 (2.8)	0.225

*Values shown are n (%), mean ± SD, or median (25th–75th percentiles).

Abbreviations: CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; TC, total cholesterol.

Table 2 Angiographic Findings of Non-Culprit Plaques among Patients of Different Ages.*

Variables	Age ≤56 years (n = 298)	Age >56 years (n = 290)	P value
Non-culprit plaques	n = 795	n = 858	
Location			
LAD	260 (32.7)	262 (30.5)	0.322
RCA	321 (40.4)	341 (39.7)	
LCX	214 (26.9)	255 (29.7)	
QCA data			
RVD (mm)	3.0 ± 0.6	2.9 ± 0.6	0.134
MLD (mm)	2.0 ± 0.7	1.9 ± 0.6	0.043
DS (%)	33.5 ± 13.0	35.4 ± 12.9	0.033
Lesion length (mm)	12.9 ± 5.4	12.8 ± 5.4	0.316

*Values are presented as n (%), mean ± SD, or median (25th–75th percentile).

Abbreviations: DS, diameter stenosis; LAD, left anterior descending artery; LCX, left circumflex artery; MLD, minimal lumen diameter; QCA, quantitative coronary angiography analysis; RCA, right coronary artery; RVD, reference vessel diameter; SD, standard deviation; TIMI, thrombolysis in myocardial infarction.

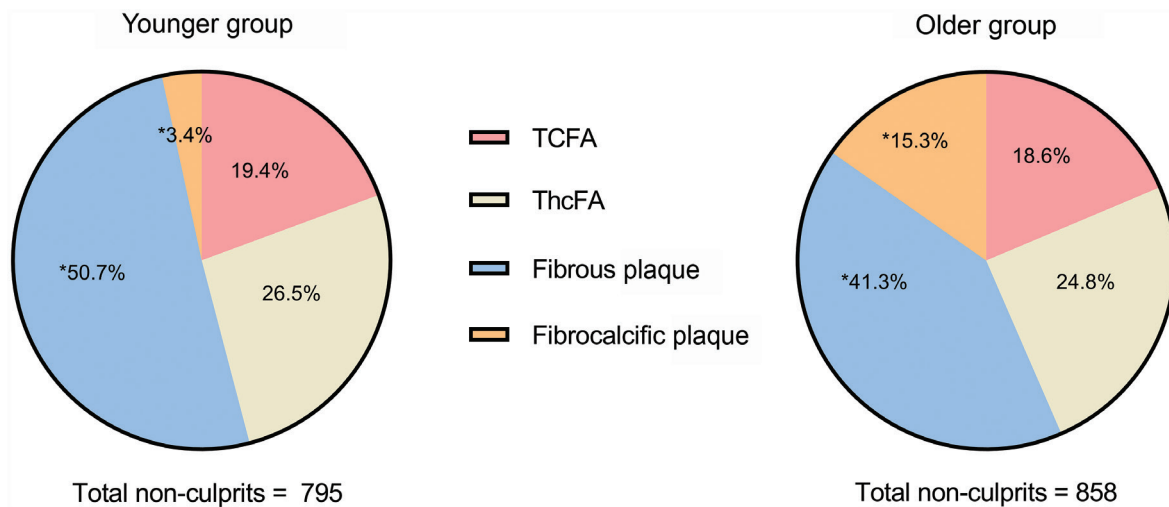


Figure 2 Younger Patients with STEMI had Fewer Fibrocalcific Plaques but more Non-Culprit Fibrous Plaques. No differences were observed in the percentages of non-culprit ThCFAs and non-culprit TCFA between groups. *means the data which is significantly different between the two groups.

other vulnerable characteristics (cholesterol crystals, microchannels, and thrombi) were observed in younger patients than older patients. Furthermore, in the subgroup analysis, the number of non-culprit CLIMA HRP, along with several non-culprit vulnerable characteristics (macrophages, cholesterol crystals, calcification, spotty calcification, and large calcification), increased with age from younger to older patients (Supplementary Table S1).

Patient-Level Univariate and Multivariate Analysis

In the multivariate analysis, in patients ≤ 56 years with STEMI, culprit PR was an independent predictor of CLIMA-defined HRP (odds ratio [OR]: 3.179; 95% CI: 1.501 to 6.733; $P = 0.003$). Meanwhile, culprit PR was also predictive of non-culprit rupture (OR: 3.802; 95% CI: 1.604 to 9.014; $P = 0.002$) and non-culprit TCFA (OR: 3.536; 95% CI: 2.051 to 6.094; $P < 0.001$). Hypertension emerged as the other predictor of non-culprit TCFA (OR: 1.920; 95% CI: 1.099 to 3.355; $P = 0.022$). In addition, the level of total cholesterol (TC) (OR: 1.094; 95% CI: 1.002 to 1.195; $P = 0.045$) was predictive of non-culprit rupture. For patients > 56 years of age, male sex was the sole predictor of non-culprit rupture (OR: 3.031; 95% CI: 1.352 to 6.795; $P = 0.007$), independently of other coronary risk factor profiles (Figure 4, Supplementary Tables S2–S7).

Discussion

This study's age-related three-vessel OCT findings in a relatively large observational cohort of 588 patients with STEMI provide an overall understanding of non-culprit plaques in the pancoronary tree. The principal findings were as follows: 1) Younger patients with STEMI had fewer pancoronary vulnerable features than older patients. 2) Younger patients had a lower incidence of pancoronary vulnerability than older patients, when pancoronary vulnerability was defined by the existence of at least one CLIMA-defined HRP, TCFA, or rupture in the non-culprit region. 3) Culprit PR, hypertension, and TC were independent predictors of pancoronary vulnerability in younger patients, whereas the sole predictor in older patients was male sex.

Pancoronary Vulnerable Characteristics in Younger and Older Patients with STEMI

Previous studies have demonstrated that culprit plaque features in OCT studies and non-culprit plaque characteristics in IVUS studies differ with age [2, 3]. However, the effect of age on plaque composition and vulnerable components in the entire coronary tree, as detected by OCT, had not been revealed. The data from this large study enabled us to perform the first investigation of differences in non-culprit plaque features among younger and older individuals.

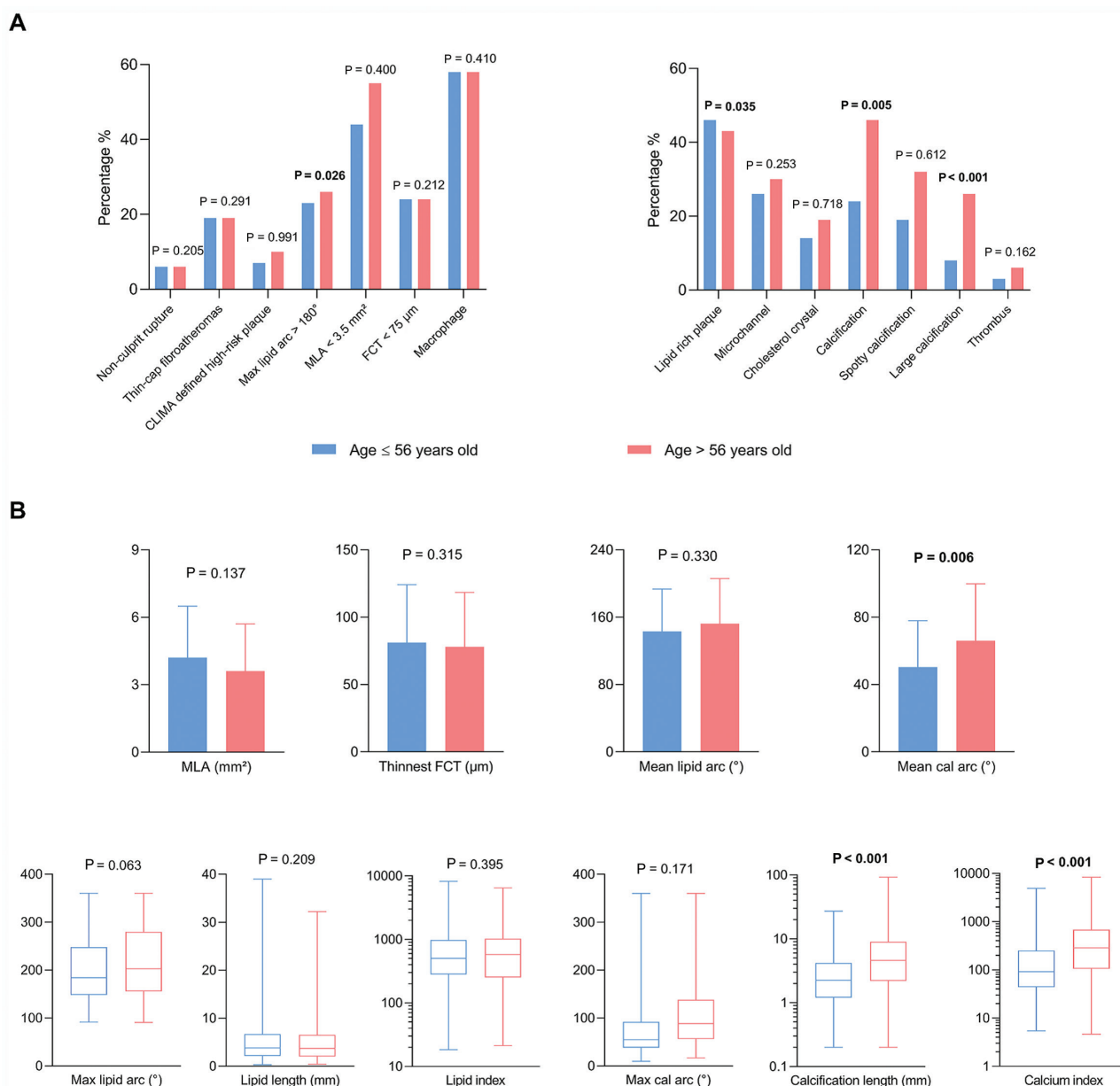


Figure 3 Qualitative and quantitative OCT data analysis of pancoronary characteristics between younger and older patients. A. Qualitative analysis of non-culprit lesions indicated a higher percentage of maximum lipid arc >180 (°), LRP, calcification, and extensive calcification in older patients. B. Quantitative OCT results indicated a larger mean calcification arc, longer calcification length, and more extensive calcium index in older than younger patients.

Macrophages have been demonstrated to play a critical role in plaque instability by releasing proteolytic enzymes and other proinflammatory mediators [11]. The presence of cholesterol crystals also increases the inflammatory response of macrophages and neutrophils in plaques, and causes mechanical damage to fibrous caps [12]. The present research showed that macrophages and cholesterol crystals were less frequent in the coronary tree in younger patients, thereby suggesting greater pancoronary stability than that in older patients.

Recently, an IVUS study has found that fibrous tissue is associated with plaque stability [13]; moreover, in our study, fibrous tissue was more frequently present in non-culprit plaques in the younger group. Our analysis showed different age-related pancoronary vulnerable features in entire coronary trees in patients with STEMI, thus supporting that age has regulatory effects on the genesis and progression of atherosclerosis.

Prior studies have reported that younger patients with STEMI are more likely to have plaque erosion,

Table 3 Patient-Level OCT Analysis of Non-Culprit Plaques in Patients with STEMI of Different Ages.*

Variables	Age ≤56 years (n = 298)	Age >56 years (n = 290)	P value
Non-culprit plaques	n = 795	n = 858	
Average non-culprits	2.7 ± 1.8	3.0 ± 1.7	0.042
Number of non-culprit plaques			
≥1 LRP	190 (63.8)	199 (68.6)	0.213
Pancoronary lipid index	921.6 (408.8–1925.2)	1082.2 (540.2–2080.7)	0.396
≥1 plaque with calcium deposition	121 (40.6)	199 (68.6)	<0.001
Pancoronary calcium index	124.1 (53.0–391.0)	695.9 (207.0–1398.8)	<0.001
High-risk OCT features			
MLA <3.5 (mm ²)	187 (62.8)	228 (78.6)	<0.001
FCT <75 (μm)	126 (42.3)	142 (49.0)	0.104
Maximum lipid arc >180 (°)	123 (41.3)	152 (52.4)	0.007
Macrophages	200 (67.1)	225 (77.6)	0.005
Other features			
Cholesterol crystals	80 (26.8)	117 (40.3)	0.001
Microchannels	134 (45.0)	156 (53.8)	0.032
Calcifications	121 (40.6)	199 (68.6)	<0.001
Spotty calcifications	108 (36.2)	170 (58.6)	<0.001
Large calcifications	59 (19.8)	148 (51.0)	<0.001
Thrombi	19 (6.4)	43 (14.8)	0.001
Pancoronary vulnerability			
High-risk plaques	47 (15.8)	67 (23.1)	0.025
Non-culprit plaque rupture	38 (12.8)	44 (15.2)	0.397
Non-culprit TCFA	105 (35.2)	116 (40.0)	0.233

*Values are presented as n (%), mean ± SD, or median (25th–75th percentile).

Abbreviations: FCT, fibrous-cap thickness; LRP, lipid rich plaque; MLA, minimal lumen area; OCT, optical coherence tomography; SD, standard deviation; TCFA, thin-cap fibroatheroma. In patient-based analysis, patients with more than one LRP were considered to have “≥1 LRP,” and the pancoronary (three-vessel) lipid index for each patient was calculated by summation of the lipid index of every non-culprit LRP. Patients with more than one plaque with calcium deposition were considered to have “≥1 plaque with calcium deposition,” and the pancoronary (three-vessel) calcium index for each patient was calculated by summation of the calcium index of every non-culprit plaque.

whereas older patients are more likely to present with PR; therefore, the pathophysiology of STEMI development may differ between younger and older patients². In young patients, acute coronary syndrome might be caused by underlying hypercoagulability or fibrinolytic dysfunction, instead of PR rich in lipid components [14]. In contrast, smoking is more common among younger than older patients and plays an essential role in the fibrinolytic process [15]. In the present study, although younger patients with STEMI presented with more severe dyslipidemia and higher TG levels, these lipid components did not result in greater plaque burden and coronary stenosis in younger patients, thus potentially partly explaining the findings of

the above study. Among the risk factors that were more prevalent among younger than older patients in the current study, smoking and dyslipidemia are potentially modifiable. Consequently, more aggressive smoking cessation and lipid-lowering therapy may be more meaningful in younger patients.

Age-Related Differences in Cardiovascular Clinical Outcomes

The aging process causes changes in the cardiovascular system, thus accelerating atherosclerosis [16]. Previous studies have suggested that younger patients have better long-term survival than older patients, on the basis of lower mortality and MACE

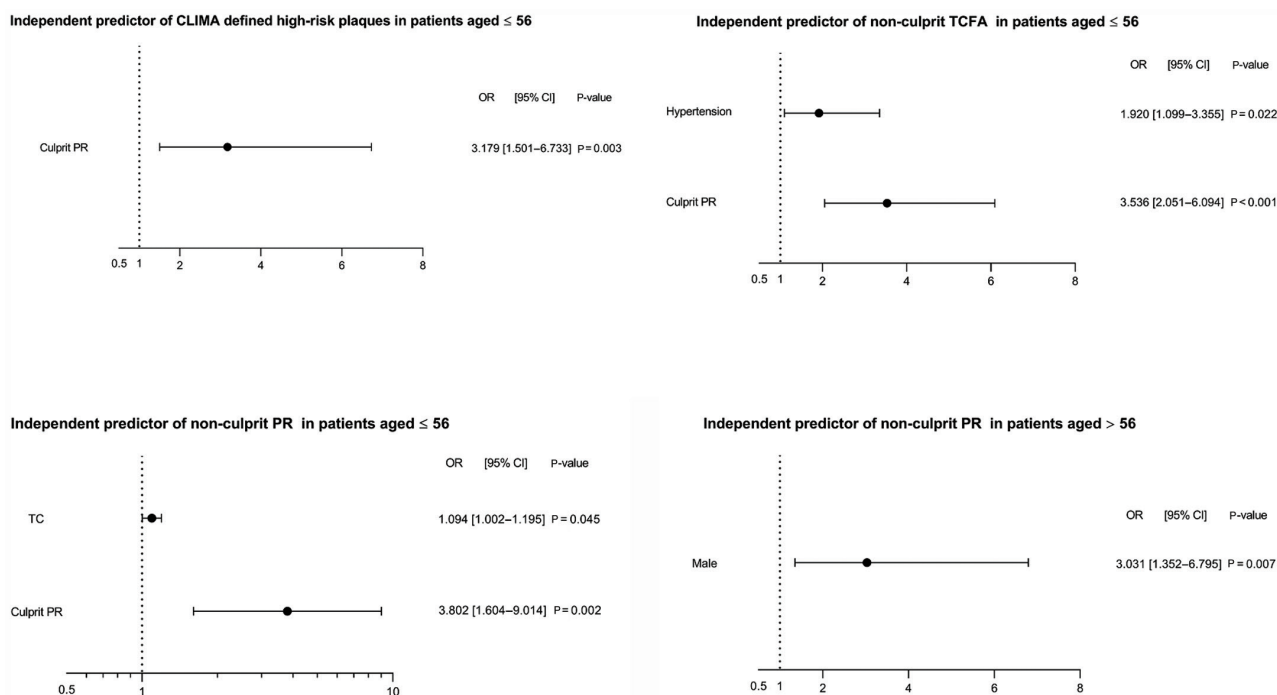


Figure 4 In Multivariate Analysis, Culprit PR Appeared to be an Independent Predictor of CLIMA-defined HRPs, Non-Culprit Rupture, and Non-Culprit TCFA, in Younger Patients with STEMI.

Hypertension was considered a predictor of non-culprit TCFA, whereas TC level predicted non-culprit rupture in younger patients with STEMI. In contrast, in older patients, male sex was a predictor of non-culprit rupture.

incidence rates [17, 18]. Although the definition of younger or older patients in the studies above was inconsistent with that in our research, the results did indicate better prognosis in younger patients. In the PROSPECT study [19], nearly half of the recurrent MACEs were associated with non-culprit lesions within 3 years, and the features of non-culprit lesions could predict the possibility of MACE to some extent. The present study may help explain these findings.

CLIMA-defined HRPs have been demonstrated to be associated with a higher incidence of MACEs among patients with STEMI [5]. In our study, younger patients with STEMI showed fewer CLIMA-defined HRPs, thus indicating less pancoronary vulnerability than that in older patients. In addition, multiple studies have consistently indicated that calcification is a reliable, reproducible, and independent indicator of future cardiovascular events [20, 21]. In agreement with findings from a previous *in vivo* study [3], we observed that non-culprit plaque calcification was less common in younger than older patients, at both the plaque and patient levels. We extended this result by demonstrating that the proportion of calcified plaques

increased with age. On the basis of the current observations, the age-related recurrence rate of MACEs might be explained by pancoronary vulnerability and calcification in non-culprit vessels.

Predictors of Pancoronary Vulnerability in Patients of Different Ages with STEMI

A recent OCT study has reported that non-culprit lesions exhibit more vulnerable characteristics in patients with STEMI with culprit PR than those with culprit PE, thus indicating a more advanced atherosclerosis process [22]. The present study further revealed that pancoronary vulnerability was predictable by culprit PR in younger patients, in contrast to older patients.

Patients with hypertension have been found to have more HRPs than those without in a coronary CT angiography study [23], thus indicating that concurrent hypertension has more vulnerable plaque features in patients with coronary heart disease than those without suffering from hypertension. We further demonstrated that hypertension is a predictor of non-culprit TCFA (indicating pancoronary vulnerability) in younger patients with STEMI in our

OCT study. The potential mechanism underlying the effect of hypertension on pancoronary vulnerability based on age remains to be further explored.

Although higher blood lipid levels did not evolve into an increased pancoronary lipid burden in younger patients with STEMI, TC was observed to be a predictor of non-culprit PR (indicating pancoronary vulnerability) in the present study. Patients with hypercholesterolemia have been found to show elevated plaque inflammation, as defined by the presence of macrophages [24]. TC may increase pancoronary vulnerability by promoting the inflammatory response. Aggressive lipid-lowering therapy appeared to be significant to delay the progression of pancoronary instability for younger patients with STEMI.

Male sex was the sole predictor of pancoronary vulnerability (non-culprit PR) for older patients in the current study. In a previous IVUS study, atherosclerotic manifestations in non-culprit plaque composition have been reported to differ between men and women [25]. Non-culprit lesions in men are characterized by a larger necrotic core volume, denser calcium volume, and more fibrous and fibrofatty tissue than observed in women [25]. Calcified plaques have been associated with greater clinical stability and a smaller necrotic core area [26]. Variations in non-culprit plaque features between women and men may be potential mechanisms linking male sex to the presence of non-culprit PR. We expected to observe sex-specific differences in younger patients, because estrogen has been proposed to retard plaque development, stabilize existing plaques, and prevent PR in women [27]. However, we observed that older patients, rather than younger patients, showed

sex-specific differences. The estrogen levels would have diminished in most postmenopausal women. Therefore, the long-term effects of estrogen's protective effect still cannot be ignored in the postmenopausal stage. Moreover, in a previous study, the higher prevalence of a family history of ischemic heart disease among younger women has indicated their greater tendency toward developing coronary atherosclerosis [28], and is likely to suggest higher pancoronary vulnerability, which might counteract the protective effect of estrogen on coronary arteries in some younger female patients. Therefore, the factors described above may partly explain why sex predictors were not present in younger patients with STEMI.

Study Limitations

Some issues must be considered in interpreting our results. First, because our observational cohort study was retrospective, consequently selection bias could not be avoided. Second, the patients in the current study were selected from a single center. Third, three-vessel OCT imaging may not be accurate under certain circumstances, such as complex lesions or patients in unstable condition. Fourth, portions of the distal or ostial vessels were not included in OCT imaging pullbacks, although we had already detected all plaques of the three vessels in patients with STEMI. Fifth, the identification of OCT-defined macrophages according to pathological results is not entirely accurate. Sixth, we could not evaluate vessel remodeling and plaque burden because of the limited OCT penetration depth.

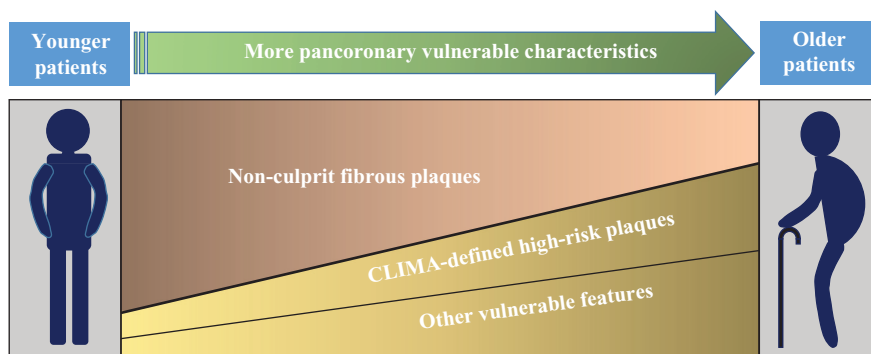


Figure 5 Fibrous Plaques Accounted for a Larger Proportion of Non-Culprit Plaque Morphologies in Younger than Older Patients with STEMI.

CLIMA-defined HRP were less commonly observed in younger than older patients, and had less vulnerable features, thus indicating limited pancoronary vulnerability.

Finally, although we found a relationship between pancoronary vulnerability and age in patients with STEMI, the effects of this relationship on clinical outcomes remain to be studied.

Conclusion

Among patients with STEMI, younger patients had limited vulnerable plaque characteristics, and the pancoronary vulnerability in younger patients was predicted by the presence of culprit PR, hypertension, and TC. In contrast, older patients had more pancoronary vulnerability, and the sole predictor was male sex, thus suggesting limited applicability of traditional risk factors to predict pancoronary vulnerability in older patients (Figure 5).

Data Availability Statement

The data are available from the corresponding author on reasonable request.

Ethics Statement

The studies involving human participants were reviewed and approved by The Ethics Committee of the 2nd Affiliated Hospital of Harbin Medical University (Harbin, China). The patients/participants provided written informed consent to participate in this study.

Author Contributions

The first three authors have contributed equally to this work and share the first authorship.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

Supplementary Materials

Supplementary materials for this paper are available at the following link: https://cvia-journal.org/wp-content/uploads/2023/11/Supplemental_Material.pdf

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