Original Article

The influence between plaque rupture and non-plaque rupture on clinical outcomes in patients with ST-segment elevation myocardial infarction after primary percutaneous coronary intervention: a prospective cohort study

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Background: Coronary atherosclerosis can lead to acute clinical events upon atherosclerotic plaque rupture (PR) or erosion and arterial thrombus formation. Identifying the effect of distinct plaque characteristics on clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) is critical for clinical therapy. Our goal was to ascertain the correlation between clinical outcome, long-term prognosis, and morphological plaque characteristics in STEMI.

Methods: The data used in this prospective cohort research came from a prior multicenter prospective cohort study (ChiCTR1800019923). One hundred and thirteen consecutive STEMI patients were involved in our cohort study. Patients with STEMI who received primary percutaneous coronary intervention (pPCI) within 24 hours of symptom onset were included in the study and divided into two groups according to plaque characteristics derived from intravascular ultrasound (IVUS): a PR group and a non-PR group. The primary outcome was the incidence of no reflow or slow flow, the secondary outcome was major adverse cardiac events (MACEs) at 1-year follow-up.

Results: This study enrolled 113 consecutive patients with STEMI [mean age 56 (range, 49–65.5) years; males 90.27%]. Of the 113 patients, PR was found in 93 (82.3%), while non-PR was found in 20 (17.7%). The PR group had a higher rates of plaque eccentricity index (64.28%±22.69% *vs.* 60.08%±15.54%; P=0.045), higher rates of lipid pool-like images (62.37% *vs.* 30.00%; P=0.008), and higher rates of tissue prolapse (22.95% *vs.* 13.33%; P=0.01). Compared with that in the non-PR group, the incidence of no reflow or slow flow was higher in the PR group after pPCI (26.88% *vs.* 5.00%; P=0.04). Multivariable logistic regression showed that PR [odds ratio (OR) =8.188; 95% confidence interval (CI): 1.020–65.734; P=0.048]

was an independent predictor of no reflow or slow flow. Survival analysis revealed no significant differences in MACE incidence between the two groups at 1-year follow-up (7.61% *vs.* 10.00%; P=0.66). Furthermore, 29 patients with PR were treated without stenting, most of them were free of MACEs (27/29). MACE between subgroups of stenting and non-stenting had no significant differences (7.94% *vs.* 6.90%; P=0.86) in the PR group.

Conclusions: In comparison to patients with non-PR, PR were not associated with the risk of recurrent myocardial infarction (MI), revascularization, heart failure, or cardiac death at 1-year follow-up, while associated with an increased incidence of no reflow or slow flow during pPCI. This observation would be considered while risk stratification and dealing with patients who have STEMI. Most patients with PR who were treated without stenting were MACE free. Further research should be conducted to determine whether interventional treatment without stenting is feasible for patients with STEMI and PR.

Keywords: Plaque rupture (PR); intravascular ultrasound (IVUS); ST-segment elevation myocardial infarction (STEMI)

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Introduction

The etiology of ST-segment elevation myocardial infarction (STEMI) is mediated by calcified nodules, plaque erosion, or, more frequently, plaque rupture (PR) (1). PR, as the primary pathophysiological cause of STEMI, is intricately linked to the intrinsic characteristics of each plaque's susceptibility, the external stresses acting upon it (trigger), and internal strain (2). Once primary percutaneous coronary intervention (pPCI) has restored reperfusion in a timely manner which decreased the incidence of complication such as cardiac rupture from ~8% to 0.14–0.96% over the last decades (2), despite the removal of the obstructive coronary thrombus or plaque, up to 40% of patients still have inadequate myocardial perfusion. This may be due to the presence of atherosclerotic plaque with rupture or ultrasound attenuation (3) and can lead to poorer clinical outcomes and unfavorable left ventricular remodeling (4,5). According to recent research, patients with acute coronary syndrome (ACS) may experience worsening coronary flow following percutaneous coronary intervention (PCI) due to atherosclerotic plaque with rupture (6,7).

However, the direct link between distinct plaque pathologies of coronary culprit lesions and the long-term prognosis in patients with STEMI has not yet been clarified in a few studies, and few reports have been conducted on Chinese patients with STEMI. Niccoli *et al.* pointed out when PR is identified by optical coherence tomography (OCT) as the culprit lesion in patients with ACS, their prognosis is poorer than that of those with intact fibrous cap (8). However, Hu *et al.* indicated that adverse cardiac event rates between PR and plaque erosion after pPCI were similar during the 1-year follow-up, and a greater incidence of no reflow or delayed flow was linked to plaque rupture (9). Both the object of observation included a portion of

Highlight box

Key findings

- Differences in plaque morphology did not increase the individual risk of recurrent myocardial infarction (MI), revascularization, heart failure, or cardiac death at 1-year follow-up, while plaque rupture (PR) was associated with an increased incidence of no reflow or slow flow during primary percutaneous coronary intervention (pPCI). Interventional treatment without stenting may feasible for patients with ST-segment elevation MI and PR.

What is known and what is new?

- It is well known that plaque rupture or erosion is the primary cause of acute MI.
- Our study reveals that PR is associated with a higher risk of no reflow or slow flow in the infarct-related coronary artery during pPCI but not increase risk of recurrent MI, revascularization, heart failure, or cardiac death.

What is the implication, and what should change now?

- Plaque morphology could aid in the assessment of the infarct-related coronary artery reperfusion flow during pPCI but may not be an indicator of prognosis.
- Interventional treatment without stenting is feasible for patients with ST-segment elevation MI and PR.

patients diagnosed as acute non-ST elevation myocardial infarction or unstable angina in these studies. Hence, the nature of the relationship between plaque characteristics and clinical outcomes of STEMI remains unclear, and further investigation is warranted to clarify this association in a wider range of individuals. To identify whether the presence of PR worsens clinical outcomes in STEMI patients, we aimed to investigate the influence of different kinds of plaque detected by intravascular ultrasound (IVUS) in coronary culprit lesions on coronary flow and 1-year clinical outcomes in patients with STEMI after pPCI. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1482/rc).

Methods

Population and study design

In this prospective cohort study, a series of patients with STEMI were enrolled from the Guangdong Provincial People's Hospital Zhuhai Hospital (Zhuhai Golden Bay Center Hospital) between August 2018 and April 2021. The inclusion criteria for patients were as follows: age range of 18 to 80 years, diagnosis of acute STEMI (moderate or severe chest pain lasting for more than 30 minutes, electrocardiography showing ST-segment elevation, troponin I/T level increased to above the 99th percentile of the general population at a participating site laboratory), a time from symptom onset of 24 hours, and stable hemodynamic status at admission. Meanwhile, the exclusion criteria were as follows: clinical instability [acute heart failure (AHF), prolonged ventricular fibrillation, cardiogenic shock]; severe valvular heart disease and cardiomyopathy; and a history of coronary artery bypass grafting (CABG), active hemorrhaging, multi-organ failure, cancer; or other disorders with a 1-year survival rate. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital, Guangzhou, China [No. GDREC2018346H (R2)]. Informed consent was taken from all the patients.

Study protocol

Oral medication including 300 mg of aspirin, 180 mg of ticagrelor, or 300 mg of clopidogrel and intravenous injection with heparin (100 IU/kg) were administered to all patients immediately after a diagnosis of STEMI in order to sustain a 250- to 300-second activated clotting time during the emergency catheterization procedure. pPCI was performed according to international guidelines (10). A frame rate of 30 frames per second was used during the coronary angiography procedure. The use of manual thrombus aspiration and intracoronary and/or intravenous injection of glycoprotein IIb/IIIa receptor inhibitor (GPI) in patients with high thrombus burden was completely dependent on the treating cardiologist's judgement. Percutaneous transluminal coronary angioplasty was performed with a 2-mm diameter balloon at 2- to 4-ATM inflation pressure if necessary. Imaging processing of the coronary artery culprit lesion was carried out via IVUS after the antegrade coronary flow was once again present and before stent implantation.

After preinterventional IVUS, PCI was carried out according to a standard approach. The choice of PCI strategy in including stent implantation and use of postdilatation balloon was left to the independent discretion of the PCI cardiologist.

Angiographic analysis

The analysis of quantitative coronary angiography (QCA) was performed with an automated and accurate edge detection system (Stenosis Analysis, GE Healthcare, Chicago, IL, USA) by two independent operators blinded to the clinical staff and IVUS findings. Coronary blood flow angiography was evaluated based on the thrombolysis in myocardial infarction (TIMI) flow grade and the TIMI myocardial perfusion grade (TMPG) at baseline, during processing and at the end stage of PCI. The term "angiographic no reflow or slow flow" is used to describe a decrease in TIMI flow grade or TMPG ≤2 degrees after pPCI with no mechanical obstruction being detected (11,12).

IVUS examination

IVUS examination was completed with an IVUS imaging system (Boston Scientific Corporation, Watertown, WA, USA) with a diameter of 3.6 F and a frequency of 40 MHz and with a mechanically rotating catheter with a withdrawal speed of 0.5 mm/s. After intracoronary injection of 200 g of nitroglycerin, all, the IVUS imaging processing system was immediately connected to the ultrasonic image analyzer to acquire the short-axis perspectives of two-dimensional IVUS images of the target plaque distally to proximally. The

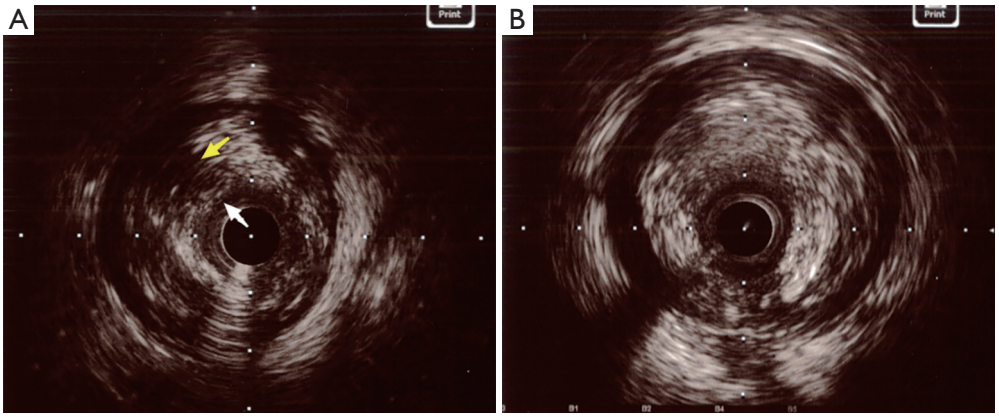

Figure 1 An example of IVUS imaging showing PR and non-PR. (A) IVUS of PR showing the presence of plaque with fibrous-cap disruption (white arrow) and cavity (yellow arrow). (B) The IVUS of non-PR showing the presence of plaque without fibrous-cap disruption and cavity. IVUS, intravascular ultrasound; PR, plaque rupture.

automated transducer was then pulled back automatically with a constant speed of 0.5 mm/s to the coronary aorto-ostial junction after the IVUS catheter had been advanced past the lesion. For offline analysis, DVD recordings of IVUS pictures were obtained.

Grayscale IVUS was subjected to geometric and quantitative analysis by two independent observers in accordance with the guidelines from the international IVUS clinical consensus (13). The culprit lesion was located at the minimum lumen cross-sectional area (CSA). One of the more normal-appearing segments within 10 mm of the anteroposterior boundary of the lesion location served as the reference segment proximal and distally. At the site of culprit lesion and anteroposterior reference segments, we measured the areas of the external elastic membrane (EEM) and lumen CSA (mm^2) using a planimetry software (Boston Scientific Image Viewer, Boston Scientific Corporation). The total area of plaque and media (PM) was defined as the area of the EEM less the lumen CSA. The plaque burden = the PM/the EEM CSA. Plaque eccentricity = (the maximum diameter of the PM thickness – the minimum diameter of PM thickness in the CSA segments)/the maximum diameter of the PM thickness. The remodeling index = the lesion site of EEM CSA/the mean value of the reference-segment EEM CSA. Positive remodeling was considered to be a remodeling index score greater than 1.05, while negative remodeling was considered to be a remodeling index score less than 0.95.

Visual analysis was used to determine the composition of the targeted plaque at the coronary culprit lesion (13). A cavity within the plaque that was connected tightly with the vascular lumen of an overlaying remaining fibrous cap fragment was considered to be IVUS PR (14), as shown in *Figure 1*. A hypoechoic plaque with profound ultrasonic attenuation but no calcification or very thick fibrous plaque was considered to be attenuated plaque.

Clinical laboratory and cardiac enzyme analyses

Blood samples were obtained from patients during the period of admission. The peak values of creatine kinase-MB (CK-MB) were derived from blood samples gathered at 4-hour intervals after PCI.

Measurement of coronary physiology

After successful pPCI, offline computation of Murray law-based quantitative flow ratio (μQFR) was conducted using AngioPlus Core software version 2 (Pulse Medical, Shanghai, China) by two independent and experienced analysts with official certification for μQFR analysis who were blinded to the study purposes. The detailed method for single-view μQFR computation has been described elsewhere (15), and the steps were performed automatically by the software. An example is presented in *Figure 2*.

Echocardiography

After pPCI, the Vivid E9 computer and digital imaging apparatus (GE HealthCare) was used to perform two-dimensional echocardiography. Left ventricular end diastolic volume (LVEDV) and left ventricular end systolic

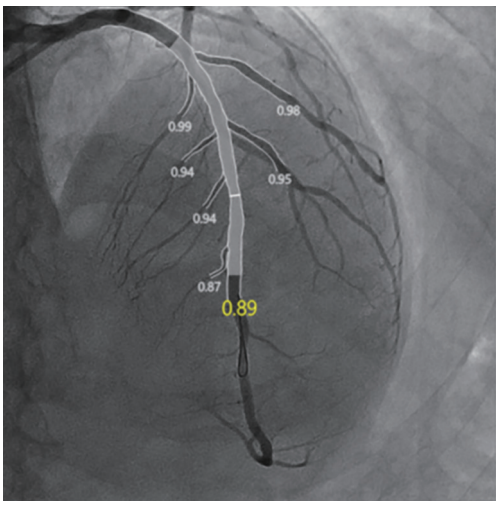

Figure 2 An example of QFR analysis. Angiograph of a single-view of culprit lesion with the μQFR being 0.89. QFR, quantitative flow ratio; μQFR, Murray law-based quantitative flow ratio.

volume (LVESV) were calculated using the biplane Simpson method. The following formula was used to calculate the left ventricular ejection fraction (LVEF; %): LVEF = (LVEDV – LVESV)/LVEDV × 100%.

Outcome definitions and clinical follow-up

In this study, the primary outcome was no reflow or slow flow and the secondary outcome was major adverse cardiac events (MACEs), which included myocardial infarction (MI), target vessel revascularization (TVR), AHF, and cardiac death. Persistent severe chest pain for at least 30 minutes with ischemia correlated with electrocardiographic alterations and elevated troponin I/T levels in the >99th percentile of the normal population were considered to indicate recurrent MI. TVR was classified as a repeated PCI or CABG of the target vessel for any one of the conditions: (I) the presence of myocardial ischemia-related signs and symptoms or positive stress tests accompanied by a diameter stenosis of more than 50% as determined by QCA or (II) a diameter stenosis of more than 70% as per QCA without the presence of ischemic-related clinical signs and symptoms or positive stress tests. AHF was defined as the sudden development of heart failure symptoms and/or signs necessitating consultation with the emergency department, hospital admission, or potential admission to the intensive care unit (ICU). Cardiac death was considered to be death as a result of a cardiac condition, for instance, MI, arrhythmia, heart failure, or unforeseen demise. All patients were treated with two kinds of antiplatelet drugs, statins, and other medications for STEMI for at least 1 year. The electronic medical records kept at the hospital were used to access the in-hospital information regarding the clinical baseline characteristics, procedural specifics, the primary and secondary outcome. Following patient discharge, a follow-up visit was completed by phone or in-person return visits at 1, 6, and 12 months after the operation. Any MACEs that occurred were also noted.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) for normally distributed data. The Mann-Whitney test or independent samples *t*-test was used to examine between-group differences. Counts (proportions) are used to describe categorical data, which were compared using the χ^2 test or Fisher exact test if the anticipated cell value was 5. Referring to the same type of studies (9,16), the incidence of the primary endpoint event in the experimental group and the control group was 17.7% and 4.8%, the odds ratio (OR) value was 15.73, the level of unilateral significance was 0.025, the clinically acceptable non-margin of error was 20%, and the efficacy of the test was 70%, respectively. Considering the shedding rate of 3%, the total sample size was 105 cases, with at least 83 cases in the experimental group and 20 cases in the control group. Multivariate logistic regression analysis with the generalized estimating equation model was used to examine the association between factors and the reduced restoration of hemodynamics. To forecast the course of illness and evaluate survival, Kaplan-Meier survival curves were generated, and the log-rank test was used for comparison. All tests were two-sided. The threshold for statistical significance was fixed at P<0.05. SPSS version 24 (IBM Corp., Armonk, NY, USA) was used to conduct all analyses.

Results

Baseline characteristic

Among the total of 147 patients with ACS who underwent pPCI and were monitored by IVUS and μQFR at Guangdong Provincial People's Hospital Zhuhai Hospital from August 2018 to April 2021, 23 were excluded due to not having STEMI, and 11 were excluded due to meeting at least one of the exclusion criteria. Finally, 113 patients

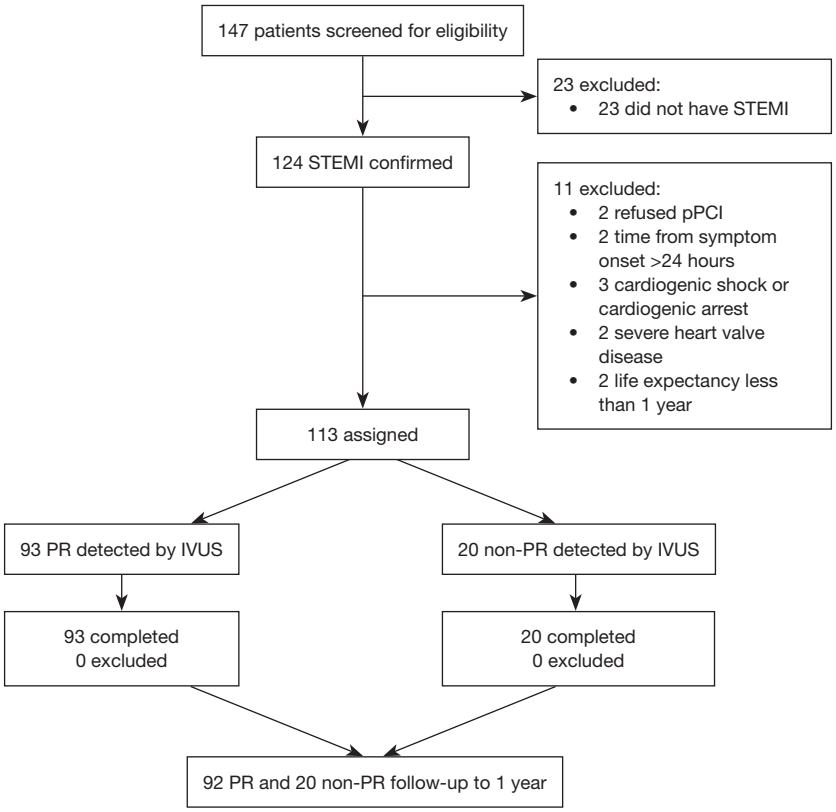

Figure 3 Flowchart of patient recruitment in the study. One hundred and twelve (92 PR and 20 non-PR) finished the follow-up, and one of PR was lost during follow-up of the 113 patients enrolled. STEMI, ST-segment elevation myocardial infarction; pPCI, primary percutaneous coronary intervention; PR, plaque rupture; IVUS, intravascular ultrasound.

with STEMI were enrolled in the study, as shown in *Figure 3*. About 90.3% of the patients were male, with an average age of 56 (range, 49–65.5) years. The average time from symptom onset to balloon dilatation (O to B) was 277.18±222.4 minutes, and that from door to balloon dilatation (D to B) was 60.2±18.14 minutes. PR was observed in 93 of the 113 (82.3%) patients with STEMI. *Table 1* shows a list of the clinical baseline characteristics and data of the groups with PR and those without PR. We could not find a significant difference between the two groups in terms of age, sex, coronary risk factors, anamnesis, or Killip rating. In the laboratory findings, there were also no significant differences in the laboratory records related to blood lipids, hemoglobin, brain natriuretic peptide (BNP), or high-sensitivity C-reactive protein (hs-CRP) before pPCI or the peak levels of CK-MB after pPCI; however, the creatinine level was observed to be higher in the non-PR group than in the PR group (P<0.05). Moreover, the echocardiography data, including LVEF and LVEDD, after pPCI were comparable between the two groups.

Angiographic findings and procedural characteristics

The data from pPCI and statistical evaluation of the coronary angiography are provided in *Table 2*. There was no significant difference between the two groups in the distribution of the culprit arteries. The PR group had the same incidence of multivessel disease as the non-PR group. No significant differences between the groups were found in the time of O to B, time of D to B, strategy, the percentage of individuals with stenting, or the mean number of stents in pPCI. Of the 93 patients in the PR group, 29 patients were treated without stent implantation, while of the 20 patients in the non-PR group, 3 were treated in this manner (31.18% *vs.* 15.5%; P=0.23). Intra-aortic balloon pump (IABP), thrombus aspiration, and the injection of GPI were conducted in 6 (5.31%), 17 (15.04%), and 60 (53.1%) patients, respectively, and there were no significance

Table 1 Baseline characteristics

Characteristics	PR (n=93)	Non-PR (n=20)	P value
Age, years	56.73±12.13	61.30±14.02	0.44
Male	84 (90.32)	18 (90.00)	0.97
Weight, kg	68.37±10.57	68.35±8.96	0.34
BMI, kg/m^2	25.02±3.28	25.46±3.19	0.65
Hypertension	46 (49.46)	9 (45.00)	0.72
Diabetes mellitus	16 (17.20)	2 (10.00)	0.74
Current smoker	71 (76.34)	16 (80.00)	0.25
Prior MI	5 (5.38)	1 (5.00)	0.71
Family history of CAD	3 (3.23)	1 (5.00)	0.55
History of peripheral artery	1 (1.08)	0	0.64
Class of Killip			0.58
I	85	19	
II	2	0	
III	2	1	
IV	4	0	
TG, mg/dL	1.90±1.69	1.63±1.07	0.59
TC, mg/dL	5.00±1.24	5.01±1.12	0.93
LDL-C, mg/dL	3.37±0.96	3.33±1.18	0.40
HDL-C, mg/dL	1.06±0.25	1.15±0.27	0.37
Creatinine, μmol/L	84.69±32.96	125.65±153.74	0.01
HGB, g/L	144.86±15.69	141.9±21.33	0.09
The peak value of CKMB, U/L	230.46±204.57	304.07±258.95	0.21
The peak value of BNP, pg/mL	224.10±440.01	302.50±638.54	0.39
LVEF, %	51.45±8.80	49.40±10.11	0.25
LVEDD, cm	4.91±0.49	4.99±0.59	0.28
hs-CRP, μg/mL	10.68±26.23	10.93±21.68	0.90

Data are expressed as mean ± SD, number (percentage), or number. PR, plaque rupture; BMI, body mass index; MI, myocardial infarction; CAD, coronary artery disease; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HGB, hemoglobin; CKMB, creatine kinase MB; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation.

differences between the two groups in this regard. Neither the thrombus scores, TIMI, or TMPG before pPCI nor the thrombus scores after pretreatment showed any discernible change. The TIMI and TMPG of coronary flow post-PCI were restored to normal in 99.16% and 88.5% of the patients with STEMI, respectively. As shown in *Figure 4*, the incidence of no reflow or slow flow of the acute infarct-related coronary artery was significantly different between the two groups for all processes of pPCI (26.88% *vs.* 5.00%; P=0.04).

Preintervention IVUS findings

The quantitative and morphological IVUS findings before

Table 2 Data for pPCI and quantitative coronary analysis

Variables	PR (n=93)	Non-PR (n=20)	P value
Culprit vessel			
LAD	43 (46.24)	9 (45.00)	0.70
LCX	9 (9.68)	2 (10.00)	0.45
RCA	41 (44.09)	9 (45.00)	0.31
No. of diseased vessels			0.37
Single	43 (46.24)	12 (60.00)	
Double	27 (29.03)	2 (10.00)	
Multivessel	23 (24.73)	6 (30.00)	
O to B, min	272.41±218.27	299.10±245.29	0.64
D to B, min	60.23±17.96	60.10±19.44	0.67
Strategy			0.63
Immediate stent	61 (65.59)	15 (75.00)	
Deferring stent	32 (34.41)	5 (25.00)	
No. of patients with stenting	64 (68.82)	17 (85.00)	0.18
No. of stents	0.76±0.58	0.85±0.37	0.41
IABP	5 (5.38)	1 (5.00)	0.95
Thrombus aspiration	13 (13.98)	4 (20.00)	0.49
GPI	47 (50.54)	13 (65.00)	0.24
Thrombus score of CAG			0.49
0	0	0	
1	8 (8.6)	0	
2	7 (7.53)	2 (10.00)	
3	9 (9.68)	3 (15.00)	
4	7 (7.53)	3 (15.00)	
5	62 (66.67)	12 (60.00)	
TIMI of CAG			0.61
0	52 (55.91)	11 (55.00)	
1	7 (7.53)	1 (5.00)	
2	6 (6.45)	3 (15.00)	
3	28 (30.11)	5 (25.00)	
TMPG of CAG			0.57
0	44 (47.31)	9 (45.00)	
1	14 (15.05)	3 (15.00)	
2	7 (7.53)	0	
3	28 (30.11)	8 (40.00)	

Table 2 *(continued)*

Table 2 *(continued)*

Variables	PR (n=93)	Non-PR (n=20)	P value
Thrombus score of CAG after pretreatment			0.57
0	39 (41.94)	7 (35.00)	
1	32 (34.41)	5 (25.00)	
2	14 (15.05)	4 (20.00)	
3	7 (7.53)	3 (15.00)	
4	1 (1.08)	1 (5.00)	
5	0	0	

Data are presented as mean ± SD or number (percentage). pPCI, primary percutaneous coronary intervention; PR, plaque rupture; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; O to B, onset to balloon dilatation; D to B, door to balloon dilatation; IABP, intra-aortic balloon pump; GPI, glycoprotein IIb/IIIa receptor inhibitor; CAG, coronary arteriography; TIMI, thrombolysis in myocardial infarction; TMPG, TIMI myocardial perfusion grading; SD, standard deviation.

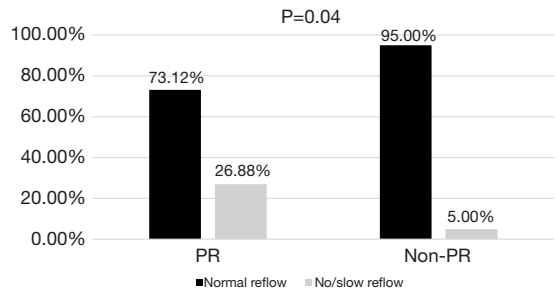

Figure 4 Incidence of no reflow or slow flow during pPCI in the two groups. PR, plaque rupture; pPCI, primary percutaneous coronary intervention.

and after pPCI are summarized in *Tables 3*,*4*. PR occurred in 93 patients (82.3%). The frequency of lipid pool-like images in the culprit lesions was noticeably higher in the PR group than in the non-PR group (62.37% *vs.* 30.00%; P=0.008). The incidence of ultrasound attenuation, positive or negative remodeling, and the presence of calcium were comparable between the two groups. Neither EEM CSA nor lumen CSA of the anteroposterior reference site was significantly different between the PR group and the non-PR group. The non-PR group had a lower index of plaque eccentricity than did the PR group (64.28%±22.69% *vs.* 60.08%±15.54%; P=0.045). Lesion length, minimum lumen diameter, minimum lumen area, plaque load, and the remodeling index of the lesion site did not significantly differ between the two groups. The PR group had a higher rate of tissue prolapse than did the non-PR group (22.95% *vs.* 13.33%; P=0.01). However, the stent minimum lumen diameter, stent length, minimum stent area (MSA), and stent expansion, were similar between the two groups. Additionally, there was no discernible difference in terms of stent malapposition in lesion location between the two groups.

µQFR findings after intervention

The quantitative flow ratio (QFR) values measured in the two groups, including µQFR and blood velocity, are summarized in *Table 5*. There was no discernible change in the valvular µQFR or blood velocity between the two groups.

Predictors of decreased restoration of hemodynamics

In the multivariable logistic regression analysis of decreased restoration of hemodynamics, PR [OR =8.188; 95% confidence interval (CI): 1.020–65.734; P=0.048] was the independent predictor of no reflow or slow flow, as shown in *Table 6*.

Clinical outcome at follow-up

The clinical outcomes of patients between two groups at 1-year follow-up are displayed in *Table 7*. Of the 113 patients enrolled, 112 (99.12%) finished the follow-up, and 108 (96.43%) were followed up to 1 year. Overall, the incidence rate of MACEs was 8.04%, with the incidence rate of nonfatal MI, TVR, AHF, and cardiac death being 0.89%, 0%, 4.46%, and 2.68%, respectively. The incidence of MACEs was similar among PR patients and non-PR

Table 3 Quantitative and morphological IVUS data before pPCI

Variables	PR (n=93)	Non-PR (n=20)	P value
Reference vessel diameter, mm	3.63±0.84	3.60±0.76	0.80
EEM CSA at the proximal reference site, mm^2	17.17±5.45	19.39±5.39	0.97
EEM CSA at the distal reference site, mm^2	13.52±5.03	14.95±5.66	0.36
Lumen CSA at the proximal reference site, mm^2	10.50±4.56	12.17±5.34	0.24
Lumen CSA at the distal reference site, mm^2	8.30±3.91	9.92±5.23	0.25
Lesion length, mm	21.35±10.83	25.11±10.54	0.11
MLD, mm	1.84±0.47	1.80±0.43	0.89
Lesion EEM at the minimum lumen site, mm^2	15.22±5.89	16.18±4.22	0.74
MLA, mm^2	3.68±2.67	3.17±1.30	0.73
Plaque area, mm^2	12.36±4.47	13.15±3.87	0.22
Plaque burden, %	78.38±6.93	79.70±7.42	0.19
Remodeling index	1.03±0.21	0.96±0.20	0.19
Plaque eccentricity index, %	64.28±22.69	60.08±15.54	0.045
Calcified nodule	7 (7.53)	4 (20.00)	0.09
Superficial calcium	51 (54.84)	7 (35)	0.11
Deep calcium	12 (12.90)	4 (20.00)	0.41
Attenuated plaque	65 (69.89)	12 (60.00)	0.39
Lipid pool-like image	58 (62.37)	6 (30.00)	0.008
Negative remodel	36 (38.71)	11 (55.00)	0.18
Positive remodel	39 (41.94)	6 (30.00)	0.32

Data are presented as mean ± SD or number (percentage). IVUS, intravascular ultrasound; pPCI, primary percutaneous coronary intervention; PR, plaque rupture; EEM, external elastic membrane; CSA, cross-sectional area; MLD, minimum luminal diameter; MLA, minimum luminal area; SD, standard deviation.

Table 4 Quantitative and morphological IVUS data after pPCI

Variables	PR (n=61)	Non-PR (n=15)	P value
Minimum stent diameter, mm	2.73±0.54	2.68±0.46	0.72
Stent length, mm	27.41±9.42	27.53±6.79	0.80
MSA, mm^2	6.74±2.37	6.59±2.19	0.84
Stent expansion ratio, %	0.82±0.15	0.79±0.12	0.47
Stent malapposition	10 (16.39)	4 (26.67)	0.36
Tissue prolapse	14 (22.95)	2 (13.33)	0.01

Data are presented as mean ± SD or number (percentage). IVUS, intravascular ultrasound; pPCI, primary percutaneous coronary intervention; PR, plaque rupture; MSA, minimum stent area; SD, standard deviation.

Table 5 QFR findings after pPCI

Variables	PR (n=93)	Non-PR (n=20)	P value
μQFR	0.913±0.10	0.909±0.06	0.47
Blood velocity	15.81±5.61	17.75±7.2	0.32

Data are presented as mean ± SD. QFR, quantitative flow ratio; pPCI, primary percutaneous coronary intervention; PR, plaque rupture; μQFR, Murray law-based quantitative flow ratio; SD, standard deviation.

Table 6 Predictors of no reflow or slow flow in multivariate analysis

Variables	Multivariable analysis		
	P value	OR	OR (95% CI)
O to B	0.88	1.000	0.998–1.002
Diabetes	0.34	0.511	0.129–2.020
PR	0.048	8.188	1.020–65.734
Plaque burden	0.29	1.039	0.969–1.114
LVEF	0.49	0.982	0.932–1.034

OR, odds ratio; CI, confidence interval; O to B, onset to balloon dilatation; PR, plaque rupture; LVEF, left ventricular ejection fraction.

Table 7 Clinical outcomes at 1-year follow-up between group of PR and non-PR

Variables	Overall (n=112)	PR (n=92)	Non-PR (n=20)	P value
MI	1 (0.89)	1 (1.09)	0	0.82
TVR	0	0	0	–
AHF	5 (4.46)	3 (3.26)	2 (10.00)	0.21
Cardiac death	3 (2.68)	3 (3.26)	0	0.55
MACE	9 (8.04)	7 (7.61)	2 (10.00)	0.66

Data are presented as number (percentage). Comparisons of the events between two groups were performed using the Fisher exact test. PR, plaque rupture; MI, myocardial infarction; TVR, target vessel revascularization; AHF, acute heart failure; MACE, major adverse cardiovascular events.

patients (7.61% *vs.* 10.00%; P=0.66). There were also no significant differences in MI, TVR, AHF, and cardiac death incidence rates between the two groups. However, the PR group demonstrated a proportionally greater rate of cardiac mortality as compared to the non-PR group (3.26% *vs.* 0%; P=0.55). In the PR group, the clinical outcomes between subgroups of stenting and non-stenting at 1-year follow-up had no significant differences, neither MACEs nor MI, TVR, AHF, or cardiac death, as displayed in *Table 8*. Finally, Kaplan-Meier analysis revealed that the MACE-free survival rate in patients with STEMI between the two groups was similar (P=0.75; *Figure 5*).

Discussion

Large-scale prospective investigations of coronary atherosclerosis dependent on intravascular imaging have demonstrated that invasive evaluation of coronary plaque morphology can identify lesions with high-risk characteristics of plaque, which may result adverse events. Anatomical features of coronary arteries can be characterized by the well-established, high-resolution, intravascular imaging modality IVUS with an accuracy that is comparable to histological investigation (17). In our study, of the 113 patients with STEMI who received the IVUS

Table 8 Clinical outcomes at 1-year follow-up between subgroups of stent and non-stent

Variables	PR (n=92)	Stenting (n=63)	Non-stenting (n=29)	P value
MI	1 (1.09)	1 (1.59)	0	0.50
TVR	0	0	0	–
AHF	3 (3.26)	1 (1.59)	2 (6.90)	0.19
Cardiac death	3 (3.26)	3 (4.76)	0	0.23
MACE	7 (7.61)	5 (7.94)	2 (6.90)	0.86

Data are presented as number (percentage). Comparisons of the events between the two subgroups were performed using the Fisher exact test. PR, plaque rupture; MI, myocardial infarction; TVR, target vessel revascularization; AHF, acute heart failure; MACE, major adverse cardiovascular events.

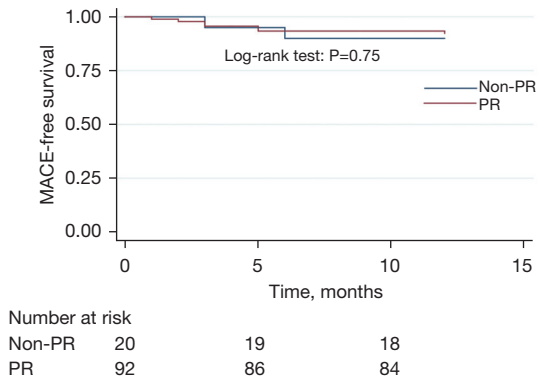

Figure 5 MACE-free survival Kaplan-Meier curves according to the presence or absence of PR. The curves were compared with the log-rank test. PR, plaque rupture; MACE, major adverse cardiovascular event.

evaluation before stenting, 82.3% experienced PR, which is similar to that in a previous report on STEMI (18). PR is a common pathogenic mechanism of STEMI. Although plaque erosion and calcified nodules are also contributing factors, their incidence is lower than that of PR (18).

In previous pathological studies, patients with PR exhibited culprit site characteristics that were distinct from those of patients without PR. These patients had a greater number of thrombi and were more likely to have lipidic atherosclerotic plaques with thin-cap fibroatheromas (TCFAs) at the culprit site of coronary artery (19,20). Additionally, it has been found that PR lesions are characterized by more positive remodeling and greater plaque burden, whereas no vascular remodeling is frequently observed in non-PR lesions (21). According to recent research, PR and attenuated plaques can occur at the same sites (22). Both of plaque features suggest that PR was more vulnerable. PR and susceptible atherosclerosis may have been highly correlated compared with non-PR.

In our study, the necrotic core and lipid pool-like images were more likely to be viewed in ruptured culprit plaques than in nonruptured plaques, which is in line with a previous study (23). However, we did not find patients with STEMI and PR had more severe stenosis than did those without PR at the location of the culprit lesions. Moreover, there were no significant differences in the measurement and analysis of plaque morphology, for instance, the lumen diameter, minimum luminal area (MLA), plaque area, plaque burden, remodeling index, or ultrasonic attenuation, between the two groups, but the minimum lumen diameter, MLA, remodeling index, and incidence rate of ultrasonic attenuation were relatively larger in the PR group, which might be a consequence of the small sample size. With more patients included, the difference in the above observations between the two groups may be even greater.

The current treatment for STEMI includes pPCI and stenting, regardless of what the underlying pathologies are. The morphology of the culprit plaques is not routinely assessed. Previous research has reported that patients with STEMI caused by plaque erosion might be stabilized with antiplatelet medication without stent implantation (24,25), but no studies have examined PR in this regard. In our study, a relatively large number of patients who had moderate stenosis opted for a delayed stenting strategy due to the high thrombotic burden. Ultimately, 32 patients were treated with antithrombotic therapy without stenting, and most of them were in the PR group (29/32). The proportion of patients with stenting was lower in PR group than in non-PR group, but this did not represent a statistical difference. Remarkably, except for two patients who experienced AHF, the STEMI patients with PR who received conservative treatment without stenting (n=27) did not experience MACEs during the 1-year follow-up. In

contrast, one patient experienced recurrent MI and three case of cardiac death occurred among the other 63 patients who were treated with stenting in the PR group. It has been suggested that no stenting is feasible in pPCI for patients with STEMI (26), and individualized and interventional therapy strategies for STEMI induced by PR need more studies to be formulated.

Previous studies have shown that PR may cause repeated local thrombosis and distal embolization, directly impacting the coronary microcirculation due to highly thrombogenic substrates being released. Higuma *et al.* (27) reported that compared to non-PR, PR is linked to poorer myocardial perfusion after PCI. Highly thrombogenic substrates, such as tissue factor and lipid, are released from the lipid pool without TCAFs when occurred with PR. These substances might cause distant embolization and repeated local thrombosis, which would disrupt the coronary microcirculation (28).

These findings indicate that the presence of PR might be associated with worse coronary flow. In our study, the MLA, thrombus burden, and coronary flow during pPCI was similar between the two groups, but the incidence rate of no reflow or slow flow in the PR group was greater than that in the non-PR group after pPCI. This might be related to the observation by Vergallo *et al.* (29) that the presence of multiple TCFA and lipid pools is more common in patients with PR, thus predisposing them to plaque development and ongoing instability.

The most common causes of STEMI are PR and plaque erosion. However, little research on how these two different diseases affect individuals with STEMI clinically has been conducted. There is some evidence from pathology and *in vivo* investigations suggesting that in addition to clinical characteristics, underlying plaque morphology may be able to predict the short- and long-term outcomes of stent implantation (30,31). Niccoli *et al.* (8) indicated that patients with PR have a poorer clinical prognosis than those with plaque erosion after a 3-year follow-up. However, Hu *et al.* (9), in a study adopting intravascular OCT in a 1-year follow-up, found no evidence of distinct clinical outcomes associated with plaque characteristics.

In our study, the patients with PR had the same prognosis to those who did not have PR after PCI, which is in contrast to the findings of some of the other investigations (32). The MACEs comprised recurrent MI, AHF, and cardiac death. The distinct prognoses encountered in our study may be explained as follows: first, the plaque morphology of the lesions, such as the plaque area and burden, EEM, and lumen CSA in the PR group was the same as that in the non-PR group, which might have decreased the incidence of recurrent MI and TVR. Second, compared to that in the patients with PR, the peak value of BNP in those without PR was nonsignificantly higher, which could be a result of the increased rate of AHF and the more serious state of the illness in patients with non-PR. This may in turn explain why the clinical outcome of patients without PR was not superior to those with PR. Finally, the inflammatory mechanisms of PR are characterized by increased hs-CRP levels, which may be due to plaque destabilization (33). Despite receiving standard treatment for ACS, patients with PR and elevated levels of CRP may still be at a severe risk of adverse cardiovascular events due to systemic inflammation (34). However, the hs-CRP level did not differ between the two groups in our study, which implies that the patients with PR might have had a less severe inflammatory response and better stabilization than do typical patients with PR. Nevertheless, hs-CRP is not the only biomarker indicating inflammation and several medications given for ACS can affect hs-CRP levels, e.g., statins (35) or angiotensin converting enzyme inhibitors (ACEIs) & angiotensin receptor blockers (ARBs) (36). In other words, the severity of systemic inflammation may still have been different between the two groups despite the similar hs-CRP values observed.

The following limitations should be taken into consideration when interpreting our results. First, the sample size in our study was small, yet this cohort is special by virtue of the diversity of the data that was gathered. Second, we employed a prospective, a single-center design, and additional prospective studies are required to investigate and elucidate the mechanisms of the interaction between the morphology of atherosclerotic plaques and clinical outcome. Third, our data were exclusively acquired using a 40-MHz IVUS transducer, and thus extending our findings to other forms of intracavitary imaging of coronary arteries should be done with caution. Moreover, it must be recognized that high backscattering in the presence of "red" thrombi makes lumen boundary identification difficult, complicating the estimation of the atherosclerotic plaque burden and increasing the possibility that the real incidence of PR is underestimated.

Conclusions

When treating patients with STEMI, the presence of PR as assessed by preinterventional IVUS is associated

with a higher risk of no reflow or slow flow in the infarct-related coronary artery. In our study, different kinds of plaque morphology were not associated with the respective risk of MI, revascularization, heart failure, or cardiac death in 1-year follow-up. The characterization of plaque morphology could be meaningful for the assessment of the infarct-related coronary artery reperfusion flow during pPCI but not for prognosis. Moreover, a portion of patients with STEMI caused by PR managed without stenting remained free of MACEs for 1-year of follow-up. Interventional treatment without stenting may be an alternative option for patients with STEMI caused by PR.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital, Guangzhou, China [No. GDREC2018346H (R2)]. Informed consent was taken from all the patients.

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