

TNF- α is a Novel Biomarker for Predicting Plaque Rupture in Patients with ST-Segment Elevation Myocardial Infarction

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Background and Aims: Patients with plaque rupture (PR) present with different cardiovascular risks, clinical strategies, and outcomes from those with plaque erosion (PE). However, there are lack of noninvasive biomarkers to distinguish PE from PR.

Methods: A prospective analysis of 382 patients with ST-segment elevation myocardial infarction (STEMI) was conducted. Of these patients, 262 and 120 presented with PR and PE, respectively. An additional 83 patients diagnosed with stable angina pectoris were enrolled as control group. Peripheral blood monocytes were collected pre-percutaneous coronary intervention and used to evaluate the mRNA expression of *IL-4*, *IL-10*, *IL-1 β* , and *TNF- α* in all patients.

Results: STEMI patients had higher *IL-4*, *IL-10*, *IL-1 β* , and *TNF- α* expression than the control patients. The mRNA levels of *IL-4*, *IL-1 β* , and *TNF- α* were significantly higher in PR patients than PE; however, no significant difference was observed in *IL-10* between PE and PR. The areas under the receiver-operating characteristic curves for *IL-4*, *IL-1 β* , and *TNF- α* for PR versus PE were 0.685, 0.747, and 0.895, respectively. At the cut-off value of 2.52, *TNF- α* demonstrated a sensitivity of 70.61% and specificity of 93.33% for discriminating PR from PE patients. When added to the model of established clinical risk factors, *TNF- α* significantly improved the predictive accuracy of PR. Multivariable logistic regression analysis indicated that *TNF- α* mRNA level was independently associated with PR (odds ratio, 3.09; 95% confidence interval, 2.29–4.16; $p < 0.001$).

Conclusion: The inflammatory response of peripheral blood mononuclear cells in patients with PR was higher than that in patients with PE. *TNF- α* may be a potential biomarker for predicting PR that could facilitate risk stratification and management in STEMI patients.

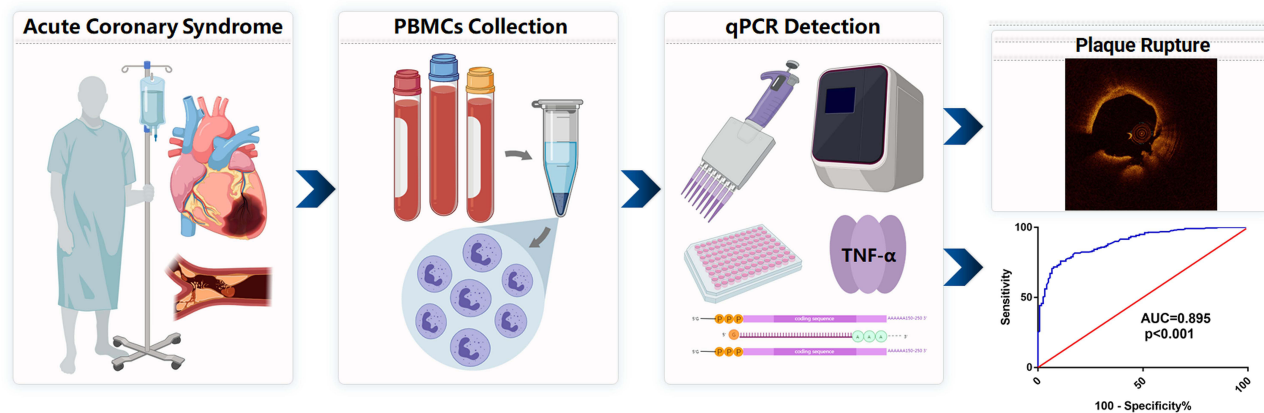
Keywords: acute coronary syndrome, plaque rupture, plaque erosion, inflammation, *TNF- α*

Introduction

Acute coronary syndrome (ACS) results from the sudden thrombotic occlusion of the coronary artery and is one of the most important cardiovascular diseases in humans. ACS can be divided into three common subtypes based on the pathological mechanism: plaque rupture (PR), plaque erosion (PE), and calcified nodules (CN).¹ Our previous studies indicated that PR is the most common subtype of ACS, and accounts for approximately two-thirds of ACS cases, whereas PE has been found in approximately one-third of ACS cases.² Current guidelines for the management of ACS generally recommend early percutaneous coronary intervention (PCI) and stent implantation to achieve reperfusion and revascularization.¹ However, evidence from our group and Sugiyama's group demonstrate that antithrombotic therapy, instead of stent implantation, may be safe and effective for some patients with PE. Furthermore, it was reported that the risk of major adverse cardiac events and complications was higher in patients with PR than in patients with PE.^{3–6} Thus, it is important to differentiate between PE and PR to establish a personalized treatment strategy and improve the prognosis of patients with ACS.

Serum biomarkers for predicting PE and PR have received considerable attention. Several studies have reported that serum levels of trimethylamine N-oxide (TMAO), myeloperoxidase (MPO), and microRNA-3667-3p are associated with

Graphical Abstract



plaque morphology and could be used as biomarkers for predicting PE or PR in patients with ACS.^{7–10} However, either the patient population in each study was too small to be conclusive or the results were unsatisfactory. Therefore, large sample size population trials and more accurate markers are needed to identify biomarkers for PR.

Autopsy and OCT studies demonstrate that culprit lesions from PR express a higher inflammatory response than those from PE.^{11,12} Nonetheless, the association between inflammatory factors and culprit lesion morphology in patients with ACS has not yet been investigated. Interleukin-4 (IL-4) and IL-10, and IL-1 β and tumor necrosis factor- α (TNF- α) constitute two classic pairs of anti- and pro-inflammatory factors, respectively. Here, we first explored the *IL-4*, *IL-10*, *IL-1 β* , and *TNF- α* mRNA expression in the monocytes from peripheral blood samples using quantitative RT-PCR and then analyzed the relationship between mRNA expression and plaque morphology as determined using OCT in patients with ST-segment elevation myocardial infarction (STEMI).

Materials and Methods

Study Population and Design

The study flow chart was shown in [Supplemental Figure 1](#). Between August 2014 and April 2016, 466 STEMI patients underwent OCT examination were included in the study, 84 patients were excluded, and 382 patients were included in the final analysis. In addition, according to ESC guidelines (13), 83 patients diagnosed with stable angina pectoris served as controls group at same time. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study was approved by the Harbin Medical University ethics committee, all the patients provided written informed consent. We prospectively enrolled 466 STEMI patients (EROSION study, ClinicalTrials.gov ID: NCT02041650) who underwent OCT examination in the Second Hospital of Harbin Medical University. The definition of STEMI and identification of the culprit lesion were described previously.⁵ STEMI was defined as typical chest pain, ST-segment-elevation >0.1 mV in at least 2 contiguous leads or new left bundle-branch block on the 18-lead ECG, and cardiac troponin values with at least one value above the upper reference. The patients with cardiac shock, congestive heart failure, end-stage renal disease, and coronary artery bypass graft were excluded.⁷ According to OCT image of culprit lesion, the patients were divided into PE and PR.

Optical Coherence Tomography Image Acquisition and Analysis

C7-XR OCT intravascular imaging system (OCT C7 Dragonfly, St. Jude Medical, St Paul, MN, USA) was used in this study. According to our previous study, OCT-erosion was identified by the presence of attached thrombus overlying an intact and visualized plaque, while OCT-rupture was identified by disruption of fibrous cap and cavity formation in the

plaque.² The typical image of PE and PR were shown in [Supplemental Figure 2](#). All OCT images were analysis by 3 independent investigators blinded to the other data.

PCR Analysis

The blood samples were collected pre-PCI, and monocytes were separated by monocyte separation medium kit according to manufacturer's instructions (Solarbio, China). And add 500ul trizol (Thermo Scientific, USA) into the monocytes for RNA extraction, the RNA concentration was evaluated by BioSpec-nano (SHIMADZU, Japan). The RNA quality which out of the range (OD260/280,1.6–2.2; OD260/230, 1.6–2.2) was excluded, and Reverse transcription kit (Roche, Switzerland) was used to reverse RNA to cDNA. The PCRs were amplified for 40 cycles (95°C for 10 seconds, 61°C for 30 seconds) on a 96-well CFX96 Real-Time System (BIO-RAD, Canada). mRNA analyzed for proinflammatory factor (*IL-1 β* and *TNF- α*), and anti-inflammatory factor (*IL-4*, and *IL-10*). The sequences were designed in Universal Probe Library Assay Design Center and were shown in [Supplemental Table 1](#). According to previous studies for the calculation of expression fold change, through the calculation of threshold cycle value (CT) value of each sample, the quantitative results are obtained according to $2^{-\Delta\Delta CT}$ methods. β -actin was regarded as the internal parameter.^{13,14}

Statistical Analysis

Continuous data are presented as mean \pm SD or median (interquartile range). The student *t* test or the Mann–Whitney *U*-test were used for statistical comparisons in two groups. Categorical variables are presented as count (percent), comparisons between groups were made with the χ^2 or Fisher exact test. Hemoglobin and platelet count were transformed to binary variables based on above-median or below-median cut off values. A logistic regression model was used to evaluate the association between plaque classification and mRNA of *TNF- α* and was adjusted for all other baseline characteristics with $p < 0.10$ on univariable analysis. Receiver-operating characteristic curve (ROC) was performed to evaluate the diagnostic accuracy in the detection of plaque characteristics for candidate mRNAs.

Results

Patient Characteristics and OCT Findings

Of the 466 STEMI patients who underwent OCT examination and were thus included in this study, 63 were excluded because of in-stent thrombosis ($n = 13$), neoatherosclerosis ($n = 10$), massive thrombus ($n = 24$), and poor imaging quality ($n = 16$). The remaining 403 patients were suitable for plaque morphology evaluation. Plaque morphology evaluation revealed that 262 of these patients had PR, and 120 had PE. The baseline data for the 382 STEMI patients and 89 control patients are summarized in [Table 1](#) and [Supplemental Table 2](#). The mean age in the PE cohort was 51.7 years; 75.8% of participants were males, 73.3% were current smokers, 9.2% had diabetes mellitus, and 16.7% had hypertension. Patients with PR were more likely to be older. Diabetes mellitus ($p < 0.001$) and hypertension ($p < 0.001$) were more frequent in patients with PR. The percentage of current smokers in the PR group was significantly lower than that in the PE group (42.4% versus 73.3%, $p < 0.001$). Additionally, there were no significant differences in the history of previous myocardial infarction, previous stroke, or sex between the two groups. Clinical laboratory examinations revealed that the PE group had a higher white blood cell count ($p < 0.001$), hemoglobin concentration ($p < 0.001$), and platelet count ($p < 0.001$), as well as higher blood lipid levels than the PR group. However, there was no significant difference in high-sensitivity C-reactive protein (hs-CRP) ($p = 0.083$) and creatinine ($p = 0.088$) levels between these two groups. In addition, preoperative medication was recorded. There was no significant difference in preoperative use of statins, angiotensin converting enzyme inhibitor (ACEI), double antiplatelet therapy (DAPT), angiotensin receptor blocker (ARB), calcium channel blocker (CCB) in PE and PR patients. The OCT findings are summarized in [Supplemental Table 3](#). The results revealed that the length of the eroded plaques was significantly shorter than that of ruptured plaques (19.3 ± 6.5 mm versus 21.4 ± 6.8 mm, $p = 0.003$). Furthermore, the prevalence of lipid-rich plaques was higher in patients with plaque rupture ($p < 0.001$). In addition, thin cap fibroatheroma (TCFA), calcification, macrophages, and microchannels were all significantly less prevalent in the PE group when compared to the PR group. The minimal lumen area (MLA) was significantly larger in the eroded plaques than in the ruptured plaques ($p < 0.001$).

Table 1 Baseline Characteristics of PR and PE

	All(n=382)	PR(n=262)	PE(n=120)	p-value
Age, y	55.0±11.0	56.5±10.5	51.7±11.2	<0.001
Men, (%)	284(74.3)	193(73.7)	91(75.8)	0.652
Diabetes mellitus, (%)	88(23.0)	77(29.4)	11(9.2)	<0.001
Hypertension, (%)	159(41.6)	139(53.1)	20(16.7)	<0.001
Previous MI, (%)	7(1.8)	5(1.9)	2(1.7)	0.117
Previous stroke, (%)	23(6.0)	16(6.1)	7(5.8)	0.917
Current smoker, (%)	199(52.1)	111(42.4)	88(73.3)	<0.001
Former smoker, (%)	34(8.9)	25(9.5)	9(7.5)	
Non-smoker, (%)	147(38.5)	126(48.1)	23(19.2)	
WBC, 10 ⁹ /L	11.4±5.4	10.3±4.8	13.7±6.0	<0.001
Hemoglobin, g/L	14.2±1.9	13.9±1.9	14.8±1.8	<0.001
Platelet, 10 ⁹ /L	240.7±65.9	234.3±55.0	254.6±83.6	0.003
Creatinine, umol/L	77.2±22.7	78.24±24.4	74.9±18.2	0.088
Triglyceride, mg/dL	121.4 (90.7–157.4)	126.4 (97.4–170.9)	110.7 (83.3–132.8)	<0.001
TC, mg/dL	169.8±52.3	181.7±47.6	143.5±52.9	<0.001
LDL-C, mg/dL	107.7±39.3	99.8±51.9	100.0±52.1	0.004
HDL-C, mg/dL	47.8±12.1	47.7±10.3	48.2±15.5	0.357
hs-CRP, mg/L	5.3(2.5–10.5)	6.3(2.8–10.5)	4.0(1.9–11.0)	0.083
Pre-medicate				
DAPT	382(100.0)	262(100.0)	120(100.0)	
Statins	357(93.5)	245(93.5)	112(93.3)	0.474
Beta-blockers	213(55.8)	149(56.9)	64(53.3)	0.417
CCB	26(6.8)	16(6.1)	10(8.3)	0.211
ACEI or ARB	236(61.7)	161(61.5)	75(65.2)	0.405

Note: Values are presented as n (%), mean ± SD or median (25th–75th percentiles).

Abbreviations: MI, myocardial infarction; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol; PE, plaque erosion; PR, plaque rupture; ACEI, angiotensin converting enzyme inhibitor; DAPT, double antiplatelet therapy; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

The Inflammatory Response in PR and PE Patients

We compared the mRNA expression profile for both anti-inflammatory factors (*IL-4* and *IL-10*) and pro-inflammatory factors (*IL-1β* and *TNF-α*) in the monocytes from both PE and PR patients. Patients with STEMI exhibited increased expression for *IL-4* (4.17-fold change, $p < 0.001$), *IL-10* (2.59-fold change, $p = 0.036$), *IL-1β* (3.43-fold change, $p < 0.001$), and *TNF-α* (4.49-fold change, $p < 0.001$) compared to the controls ([Supplemental Figure 3](#)). In addition, patients with PR showed higher expression of *IL-4* (3.35-fold change, $p < 0.001$), *IL-1β* (1.61-fold change, $p = 0.012$), and *TNF-α* (4.51-fold change, $p < 0.001$) than patients with PE ([Figure 1](#)). However, no significant difference was observed in *IL-10* mRNA levels between these groups ($P = 0.625$). Additionally, a heat map of the inflammatory factors is shown in [Supplemental Figure 4](#).

Diagnostic and Predictive Value of *IL-4*, *IL-10*, and *TNF-α* in Distinguishing PR from PE

Given the significant differences in the mRNA expression of *IL-4*, *IL-10* and *TNF-α* between the PE and PR groups, we performed ROC curve analysis to evaluate the diagnostic value of *IL-4*, *IL-10* and *TNF-α* in differentiating between PE and PR. The area under the ROC curve (AUC) for *IL-4*, *IL-10* and *TNF-α* for PR versus PE was 0.685 (95% CI, 0.631–0.739, $p < 0.001$), 0.747 (95% CI, 0.686–0.809, $p < 0.001$), and 0.895 (95% CI, 0.864–0.927, $p < 0.001$), respectively ([Supplemental Figure 5](#)). Furthermore, we found that *TNF-α* achieved a maximum sensitivity of 70.61% and specificity of 93.33% for PR when using a cutoff value of 2.52 (mRNA fold change) ([Supplemental Table 4](#)). Furthermore, we determined the extra predictive value of *TNF-α* as a risk factor for PR by completing several evaluations using the previously established risk factor model (all variables with $p < 0.10$ in the univariate logistic regression). It was revealed that the AUC was significantly increased when *TNF-α* was added to the classical clinical risks for PR (0.85 versus 0.95).

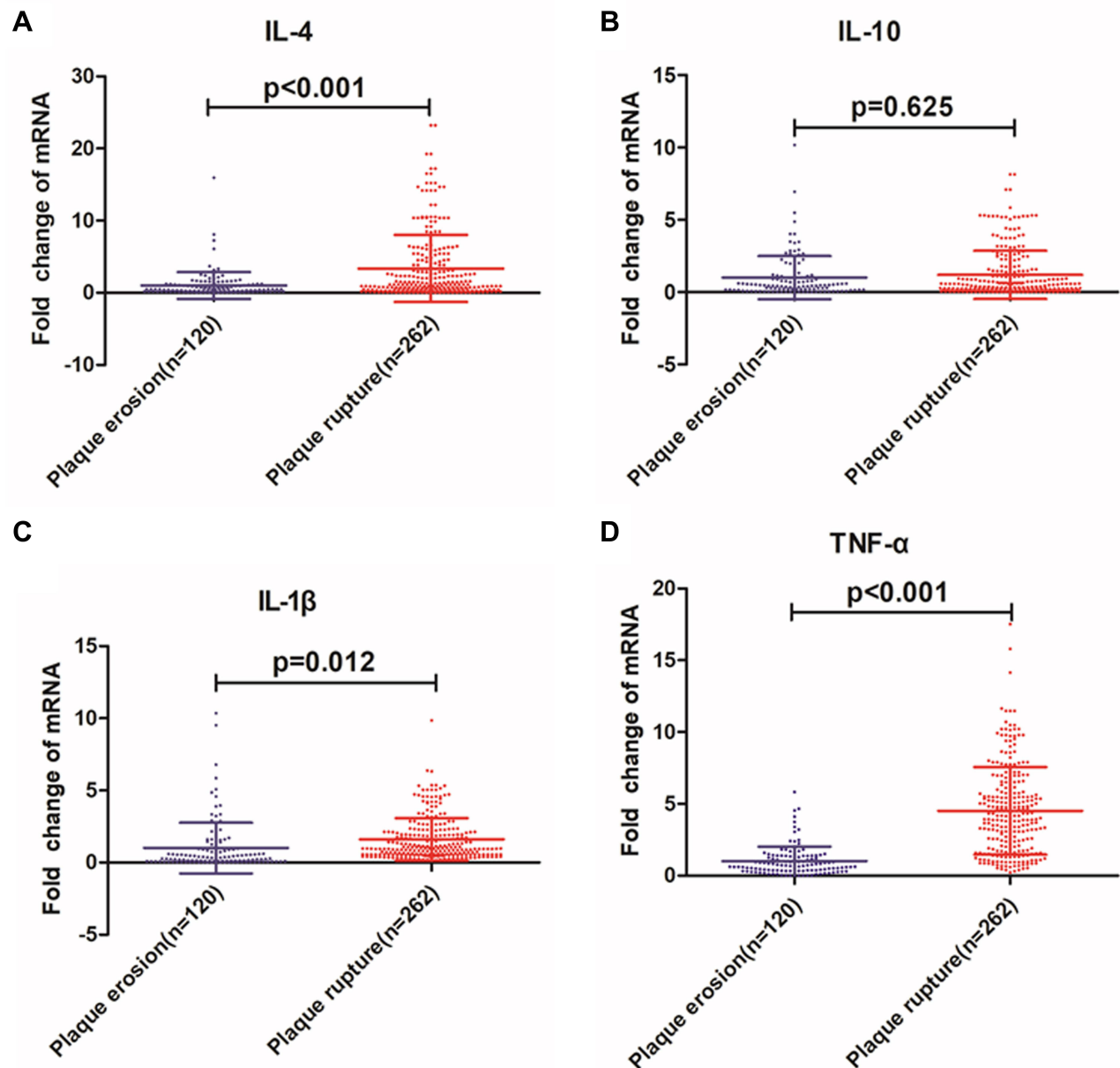


Figure 1 Comparison of IL-4, IL-10, IL-1 β and TNF- α mRNA levels between patients with PR and those with PE. (A) IL-4 mRNA level in PE and PR (fold change). (B) IL-10 mRNA level in PE and PR (fold change). (C) IL-1 β mRNA level in PE and PR (fold change). (D) TNF- α mRNA level in PE and PR (fold change). The data shown as mean \pm SD.

(Figure 2). Multivariable logistic regression demonstrated that the mRNA levels of *TNF- α* were independently correlated with PR (Table 2). Subgroup analysis (Figure 3) showed that the associations between *TNF- α* and PR were generally consistent across common clinical risk factors (age, sex, smoking status, diabetes, and dyslipidemia). In addition, *IL-4* also showed a correlation with PR (Supplemental Table 5). To better understand the predictive power of *TNF- α* for PR, we divided our 382 STEMI patients into two groups based on their median *TNF- α* level, the incidence of PR risk factors (hypertension, diabetes mellitus, and dyslipidemia), and unique OCT features (TCFA and lipid-rich plaque) were compared between the two groups. The results (Supplemental Table 6) revealed that there was a higher proportion of patients with hypertension and diabetes in the high-*TNF- α* group than in the low-*TNF- α* group, and that patients with high *TNF- α* levels had worse lipid levels. As for OCT features, we found that, comparing to the low-*TNF- α* group, the high-*TNF- α* group had a higher proportion of TCFA, calcification and lipid-rich plaques, smaller MLA, and thinner fiber cap thickness, which is more similar to PR.

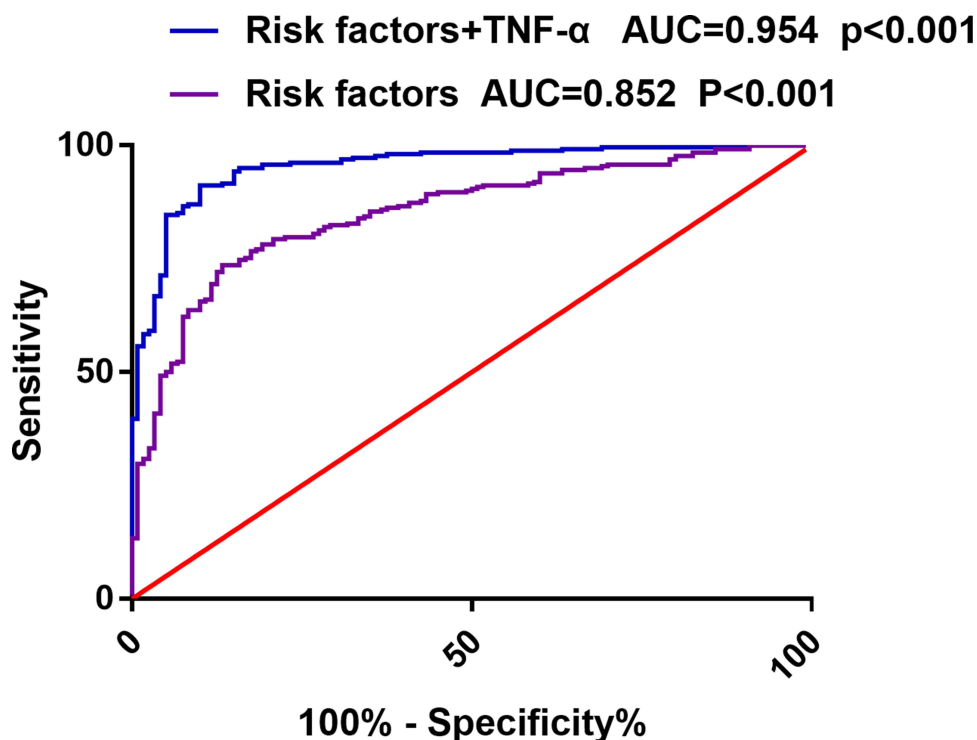


Figure 2 ROC curve for models of established cardiovascular risk factors with or without the incorporation of TNF- α level.

Discussion

The major findings of this study are as follows: (1) STEMI patients presented with increased *IL-4*, *IL-10*, *IL-1 β* , and *TNF- α* mRNA levels in their blood monocytes than stable angina pectoris patients. Furthermore, PR patients expressed higher levels of *IL-4*, *IL-1 β* , and *TNF- α* mRNA than PE patients, while there were no significant differences in *IL-10* expression between these two groups. (2) STEMI patients with higher *TNF- α* expression (fold change >2.55) presented with more vulnerable plaque characteristics (larger mean lipid arc, thinner fibrous cap thickness, and more frequent TCFA and calcification), smaller MLA, and longer lipid length compared to those with lower *TNF- α* expression. (3) Elevated blood monocyte *TNF- α* mRNA levels independently correlated with PR and increased the diagnostic accuracy for PR when added to models of established clinical risk factors. (4) The AUC for *IL-4*, *IL-1 β* , and *TNF- α*

Table 2 Logistic Regression Analysis of PR

Variables	Unadjusted			Adjusted		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.04	1.02 to 1.07	<0.001	1.01	0.98 to 1.05	0.525
Diabetes mellitus	4.12	2.10 to 8.10	<0.001	3.76	1.39 to 10.16	0.009
Hypertension	5.03	2.97 to 8.49	<0.001	4.93	2.25 to 10.80	<0.001
Non-current smoker	3.74	2.33 to 6.00	<0.001	5.26	2.46 to 11.26	<0.001
Hemoglobin < 140g/L	2.38	1.49 to 3.79	<0.001	1.84	0.86 to 3.96	0.119
Platelet < 270	1.68	1.05 to 2.71	0.032	1.68	0.72 to 3.92	0.229
Renal dysfunction	0.89	0.57 to 1.40	0.615			
WBC	0.86	0.82 to 0.91	<0.001	0.92	0.84 to 0.99	0.032
hs-CRP	1.04	0.99 to 1.08	0.098	1.08	1.00 to 1.17	0.057
Dyslipidemia	2.42	1.55 to 3.76	<0.001	2.08	1.01 to 4.29	0.047
TNF- α	2.92	2.27 to 3.76	<0.001	3.09	2.29 to 4.16	<0.001

Note: Hemoglobin and platelet count were transformed to binary variables based on above-median or below-median cut off values.

Abbreviations: WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; CI, confidence interval; PR, plaque rupture.

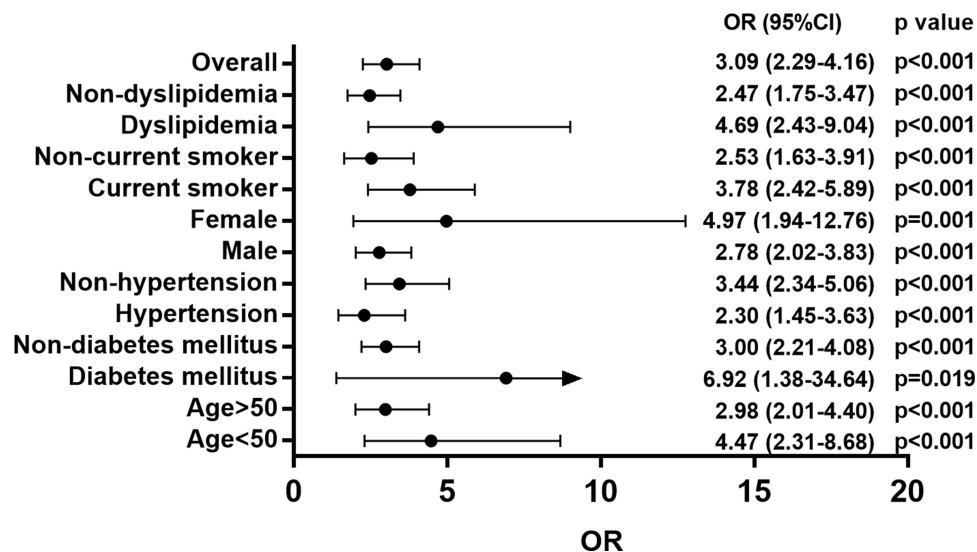


Figure 3 Subgroup analysis of $TNF-\alpha$ for predicting PR across common clinical risk factors.

for PR versus PE was 0.685, 0.747, and 0.895, respectively, indicating that $TNF-\alpha$ mRNA in blood monocytes could be a potential biomarker for the discrimination of PR versus PE.

$TNF-\alpha$ as a Biomarker for PR

PR and PE are considered to be the two most important pathologic mechanisms of ACS, accounting for two-thirds and one-third of ACS cases, respectively.² There is growing evidence suggesting that the risk of cardiovascular events is significantly higher in patients with PR than in those with PE.¹⁵ In addition, the optimal clinical management strategy for patients with PE may differ from that for patients with PR.¹ To date, OCT is the only imaging method that can differentiate between PE and PR in vivo. Therefore, noninvasive differentiation between PE and PR is of great clinical significance for optimizing the treatment strategy and risk management of ACS.

Several recent studies have reported that clinical characteristics and laboratory tests can be used to discriminate between PR and PE. Jang and colleagues found that age <68 years, absence of diabetes mellitus, hemoglobin level >15.0 g/dL, and normal renal function are all independent parameters associated with PE.¹⁶ Furthermore, Dai et al reported that active smoking was significantly associated with PE.¹⁷ In this study, we found that patients with PE were younger than patients with PR and that diabetes mellitus, dyslipidemia, and hypertension were more frequent in the PR group than in the PE group. Subsequent multivariable logistic regression analysis demonstrated that diabetes mellitus, dyslipidemia, and hypertension were all independently correlated with PR, consistent with previous studies. However, clinical features and laboratory tests in previous studies had limited predictive power for plaque morphology. Therefore, there is an urgent need for effective and accurate serum biomarkers to distinguish PR from PE.

A previous study found that serum MPO level was associated with PE, and ROC analysis indicated that the AUC was 0.75 for MPO when discriminating between PE and PR.⁸ Another study enrolled 77 patients with PR and 69 patients with PE and collected their sera to evaluate TMAO levels,⁷ the results showed that the TMAO level was higher in PR, and had a good ability to predict PR, with an AUC of 0.89. However, many of these studies had minor shortcomings, including small sample sizes and low prediction ability. Based on previous studies, it was found that there were significant differences in inflammatory responses between PR and PE, especially monocytes and macrophages.¹¹ Recently, an increasing number of studies have shown that the RNA level in monocytes can serve as a potential biomarker to diagnose diseases and predict clinical outcomes.^{13,18} In this study, we analyzed the mRNA expression of *IL-10*, *IL-4*, *IL-1 β* , and *TNF- α* in blood monocytes from 382 STEMI patients (262 patients with PR and 120 patients with PE) and found that the PR group exhibited higher expression of *IL-10*, *IL-4*, *IL-1 β* , and *TNF- α* mRNA than the PE group. It is noteworthy that there is no significant difference in preoperative medication status between PE and PR patients, which to some extent

avoids the impact of statins and DAPT on inflammatory response. Our results also suggest that *TNF- α* mRNA may exhibit superior diagnostic capacity for PR, with an AUC of 0.895. Moreover, multivariate logistic regression analysis indicated that *TNF- α* mRNA levels in monocytes were independently associated with PR (odds ratio [OR], 2.99; 95% confidence interval, 2.25–3.97; $p < 0.0001$). In addition, subgroup analysis demonstrated that the associations between *TNF- α* mRNA and PR were generally consistent across common clinical risk factors. These data suggest that *TNF- α* mRNA is a good predictor of PR, even in specific populations.

Possible Role of *TNF- α* in Ruptured Plaque Progression

Inflammation plays a vital role in the progression of atherosclerotic plaques.¹⁹ Among the many inflammatory factors, IL-4 and IL-10, and IL-1 β and *TNF- α* comprise the two pairs of classic anti- and pro-inflammatory factors, respectively. We found that the mRNA expression of the pro-inflammatory factors *IL-1 β* and *TNF- α* was significantly increased in the PR group when compared to the PE group. Furthermore, in our study, the high-*TNF- α* group showed a higher percentage of TCFA and lipid-rich plaque and larger lipid core than the low-*TNF- α* group in STEMI patients. Lipid-rich plaques, including abundant inflammatory cells, a large necrotic core, and thin fibrous cap plaque, are the main pathological characteristics of ruptured plaques. Previous studies have provided some insights into the involvement of IL-1 β and *TNF- α* in the progression of atherosclerosis. Sustained *TNF- α* activation has been reported in patients with stable angina and ACS when compared to healthy patients.²⁰ Furthermore, IL-1 β and *TNF- α* have been reported to contribute to the adhesion between monocytes and endothelial cells in atherosclerotic plaques.^{21–23} Subsequently, the CANTOS Trials suggested that anti-inflammatory therapy targeting IL-1 β , using canakinumab, led to a significantly lower rate of recurrent cardiovascular events.²⁴ Several additional studies have also shown that *TNF- α* damages endothelial and smooth muscle cells, thereby leading to the formation of necrotic cores in these plaques.²⁵ *TNF- α* inhibitors have also been shown to reduce atherosclerotic plaque progression and improve vascular inflammation.²⁶ These studies indicate that IL-1 β and *TNF- α* are essential for the progression of lipid-rich plaques. Interestingly, we observed that levels of the anti-inflammatory factors *IL-4* and *IL-10* were increased in patients with STEMI; additionally, the level of *IL-4* was increased in PR patients compared to PE patients. This phenomenon has also been observed by other research groups and may be associated with the negative feedback regulation of the body's anti-inflammatory response.^{27,28}

Clinical Significance of *TNF- α* in PR

The current standard of care mandates immediate stenting for STEMI, regardless of the morphologic characteristics of the plaque responsible for it, often described as a “one-size-fits-all” clinical strategy.²⁹ However, it was reported that patients with PE experience delayed vascular healing after drug-eluting stent implantation.³⁰ In addition, anti-thrombotic therapy, instead of stent implantation, is largely safe and effective for many patients with PE.^{3–5} Moreover, criminal plaque morphology is important for the prognosis of ACS patients, as previous studies indicate that patients with PR have a higher risk of major adverse cardiac events and complications than those with PE.¹⁵ Taken together, these data suggest that non-invasive prediction of plaque morphology using serum biomarkers may be an important improvement for the clinical management of these diseases, allowing for personalized treatment strategies and improved prognosis for patients with ACS. Herein, we compared the mRNA levels of *IL-4*, *IL-10*, *IL-1 β* , and *TNF- α* in monocytes from both PE and PR STEMI patients and found that *TNF- α* is independently correlated with PR and has a good diagnostic capacity for this pathobiology. Our results suggest that *TNF- α* in monocytes could not only serve as a biomarker for PR but also provide clinical value for risk stratification and aid in the determination of the optimal treatment strategy for patients with ACS.

Conclusion

The inflammatory response of peripheral blood mononuclear cells in patients with PR was higher than that in patients with PE. *TNF- α* may be a potential biomarker for predicting PR that could facilitate risk stratification and management in STEMI patients.

Data Sharing Statement

All original data are available from the corresponding author.

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Author Contributions

Conception & study design: Bo Yu, and Haibo Jia. Execution & acquisition of data: Xing Luo. Analysis and interpretation: Chen Zhao. Took part in drafting & critically reviewing the article: Shenfang Wang and Xing Luo. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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