The abnormal level and prognostic potency of multiple inflammatory cytokines in PCI-treated STEMI patients

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Abstract
Objective: Inflammatory cytokines modulate atherogenesis and plaque rupture to involve in ST-segment elevation myocardial infarction (STEMI) progression. The present study determined eight inflammatory cytokine levels in 212 percutaneous coronary intervention (PCI)-treated STEMI patients, aiming to comprehensively investigate their potency in estimating major adverse cardiac event (MACE) risk.

Methods: Serum tumor necrosis factor (TNF-α), interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-17A, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1) of 212 PCI-treated STEMI patients and 30 angina pectoris patients were determined using enzyme-linked immunosorbent assay.

Results: TNF-α (52.5 (43.9–62.6) pg/ml versus 46.4 (39.0–59.1) pg/ml, p = 0.031), IL-8 (61.6 (49.6–81.7) pg/ml versus 46.7 (32.5–63.1) pg/ml, p = 0.001), IL-17A (57.4 (45.7–77.3) pg/ml versus 43.2 (34.2–64.6) pg/ml, p = 0.001), and VCAM-1 (593.6 (503.4–811.4) ng/ml versus 493.8 (390.3–653.7) ng/ml, p = 0.004) levels were elevated in STEMI patients compared to angina pectoris patients, while IL-1β (p = 0.069), IL-6 (p = 0.110), IL-10 (p = 0.052), and ICAM-1 (p = 0.069) were of no difference. Moreover, both IL-17A high (vs. low) (p = 0.026) and VCAM-1 high (vs. low) (p = 0.012) were linked with increased cumulative MACE rate. The multivariable Cox’s analysis exhibited that IL-17A high (vs. low) (p = 0.034) and VCAM-1 high (vs. low) (p = 0.014) were independently associated with increased cumulative MACE risk. Additionally, age, diabetes mellitus, C-reactive protein, multivessel disease, stent length, and stent type were also independent factors for cumulative MACE risk.

Conclusion: IL-17A and VCAM-1 high level independently correlate with elevated MACE risk in STEMI patients, implying its potency in identifying patients with poor prognoses.

KEYWORDS
inflammatory cytokine, major adverse cardiac events, percutaneous coronary intervention, prognostic potency, ST-segment elevation myocardial infarction

Abbreviation: AUC, area under the curve; CABG, coronary artery bypass grafting.; Cl, confidence interval; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; cTnI, troponin I; ELISA, enzyme-linked immunosorbent assay; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac event; PCI, percutaneous coronary intervention; ROC, receiver-operating characteristic; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1

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1 | INTRODUCTION

ST-segment elevation myocardial infarction (STEMI), defined as ST-segment elevation in two anatomically contiguous leads, is the most urgent manifestation of coronary artery disease.1,2 Over the past decade, the number of new STEMI cases is increasing in China annually, meanwhile, its mortality is constant.3 Concerning the STEMI treatment, for patients with symptom onset within 12 h, percutaneous coronary intervention (PCI) is the preferred strategy to restore myocardial perfusion as soon as possible.4–6 Unfortunately, the major adverse cardiac event (MACE) frequently occurs after PCI treatment, implying a poor prognosis in STEMI patients.7,8 Hence, it is meaningful to explore reliable biomarkers for monitoring MACE risk in PCI-treated STEMI patients.

Inflammation is non-negligible in STEMI etiology, which is considered an essential process that participates in the initiation and progression of atherosclerotic plaque.9–11 Consequently, some studies notice that the increased level of inflammatory cytokines possesses a certain value in predicting the MACE risk of STEMI patients, including interleukin (IL)-1, IL-6, IL-17, IL-37, etc.12–15 For instance, one study suggests that the high level of IL-6 is correlated with elevated MACE risk in STEMI patients who receive primary PCI treatment.13 Another study shows that the high circulating IL-37 level is a predictor of in-hospital MACE rate in STEMI patients treated with PCI.16 However, the previous studies only focus on a single or a few inflammatory cytokines (no more than three), and comprehensive studies focusing on the prognostic value of plentiful inflammatory cytokines in PCI-treated STEMI patients remain rare.

Therefore, the present study determined eight inflammatory cytokines in 212 PCI-treated STEMI patients, aiming to comprehensively investigate their potency in estimating MACE risk and identify the prognostic indicators for PCI-treated STEMI patients.

2 | METHODS

2.1 | Patients

Two hundred and twelve STEMI patients receiving PCI between April 2018 and February 2021 were enrolled in this prospective study. The enrollment criteria were: (1) presented with STEMI (≥2 mm in two contiguous precordial leads or ≥1 mm in two extremity electrocardiographic leads) within 12 h after symptom onset; (2) older than 18 years old; (3) received PCI for the first time; (4) received peripheral blood (PB) collection immediately after admission. The exclusion criteria were: (1) had contraindications of PCI; (2) had an active hemorrhage or hemorrhagic risk; (3) had a prior history of cardiothoracic surgery; (4) had systemic immune diseases or inflammatory diseases; (5) had cancers or hematologic malignancies. Additionally, a total of 30 angina pectoris patients were also recruited as disease controls. The recruitment criteria were: (1) confirmed as angina pectoris; (2) aged over 18 years old; (3) voluntary for PB sample collection; (4) had cardiothoracic surgery, systemic immune diseases, inflammatory diseases, cancers, or hematologic malignancies. The study was permitted by Ethics Committee. Each patient or family member signed the informed consent.

2.2 | Data collection

Clinical characteristics of STEMI patients were obtained, which contained demographics, underlying diseases, and blood laboratory detections. Besides, disease characteristics and PCI operation information of STEMI patients were also collected, which included symptom-to-balloon time, multivessel disease, culprit lesion, thrombus aspiration, number of implanted stents, type of stent, stent diameter, stent length, and infarct size (recorded as the infarct size at 3rd day after PCI).

2.3 | Sample collection and processing

PB samples were gained from STEMI patients before PCI and from angina pectoris patients after recruitment, then the serum sample was

| TABLE 1 | Clinical characteristics of STEMI patients |
|-------------------------|-------------------------|
| **Items**               | **STEMI patients (N = 212)** |
| **Demographics**        |                          |
| Age (years), mean±SD    | 62.6±10.3               |
| Gender, No. (%)         |                          |
| Female                  | 57 (26.9)               |
| Male                    | 155 (73.1)              |
| BMI (kg/m²), mean±SD    | 24.9±3.1                |
| Current smoker, No. (%) | 80 (37.7)               |
| **Underlying diseases** |                          |
| History of hypertension, No. (%) | 146 (68.9) |
| History of hyperlipidemia, No. (%) | 94 (44.3) |
| History of diabetes mellitus, No. (%) | 49 (23.1) |
| **Blood laboratory detections** |  |
| WBC (10⁹/L), mean±SD    | 10.5±3.7                |
| FBG (mmol/L), median (IQR) | 6.2 (5.4–7.1) |
| Scr (μmol/L), mean±SD   | 87.4±17.1               |
| TG (mmol/L), median (IQR) | 2.6 (1.8–3.1) |
| TC (mmol/L), median (IQR) | 5.4 (4.6–6.4) |
| LDL-C (mmol/L), median (IQR) | 3.9 (3.2–4.7) |
| HDL-C (mmol/L), median (IQR) | 1.1 (1.0–1.3) |
| CRP (mg/L), median (IQR) | 6.6 (4.7–9.0) |
| cTnI (ng/ml), median (IQR) | 6.3 (4.2–7.9) |
| CK-MB (ng/ml), median (IQR) | 53.2 (33.8–75.4) |

Abbreviations: BMI, body mass index; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; cTnI, troponin I; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.
isolated by centrifuge and stored at −80°C. Following that, inflammatory cyto-
kinases were detected in batch by enzyme-linked immunosorbent assay (ELISA) assay using commercial kits (Bio-Technne China Co., Ltd.). The inflammatory cytokines contained tumor necrosis factor (TNF)-α, IL-1β, IL-6, IL-8, IL-10, IL-17A, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1). The kits used in the study were as follows: Human TNF-alpha Quantikine ELISA Kit (No. Cat. DTA00D, sensitivity: 6.23 pg/ml, range: 15.6–1000 pg/ml), Human IL-1 beta/IL-1F2 Quantikine ELISA Kit (No. Cat. DLB50, sensitivity: 1 pg/ml, range: 3.9–250 pg/ml), Human IL-6 Quantikine ELISA Kit (No. Cat. D6050, sensitivity: 0.7 pg/ml, range: 3.1–300 pg/ml), Human IL-8/CXCL8 Quantikine ELISA Kit (No. Cat. D8000C, sensitivity: 7.5 pg/ml, range: 31.2–2000 pg/ml), Human IL-10 Quantikine ELISA Kit (No. Cat. D1000B, sensitivity: 3.9 pg/ml, range: 7.8–500 pg/ml), Human IL-17 Quantikine ELISA Kit (No. Cat. D1700, sensitivity: 15 pg/ml, range: 31.2–2000 pg/ml), Human VCAM-1/CD106 Quantikine ELISA Kit (No. Cat. DVC00, sensitivity: 1.26 ng/ml, range: 6.3–200 ng/ml), Human ICAM-1/CD54 Quantikine ELISA Kit (No. Cat. DCD540, sensitivity: 0.254 ng/ml, range: 1.6–50 ng/ml). The assays were performed in strict accordance with the kit protocols from manufacturers. In the analysis, the inflammatory cyto-
kinases were classified as high and low based on the median values.

2.4 | Follow-up and assessment

Standardized follow-up was carried out for the STEMI patients until February 2022. The median follow-up duration was 15.0 months, with the interquartile range of 9.0–24.0 months and the range of 1.0–39.0 months. During the follow-up, a major adverse cardiac event (MACE) was recorded, which was defined as an occurrence of death for any reason, myocardial infarction, or repeat revascularization. Then, the cumulative MACE rate was calculated.

2.5 | Statistics

Statistical analysis was performed using SPSS V.22.0 (IBM Corp.). Figure plotting was completed using GraphPad Prism V.6.0 (GraphPad Software Inc.). Data were presented as mean with standard deviation (normal distributed continuous variables), median with interquartile range (skewed distributed continuous variables), and count with percentage (categorized variables). Differences of inflammatory cyto-
kinases between STEMI patients and angina pectoris patients were detected by the Mann-Whitney U test. Correlations between cumula-
tive MACE rate and inflammatory cytokines were evaluated by KM curves, and analyzed by log-rank test, Breslow test, or Tarone-Ware test, as appropriate. All parameters were included in univariable and step forward multivariable Cox’s proportional hazard regression model to assess the factors related to cumulative MACE risk, and the con-
tinuous variables were categorized based on the median or the normal values, as appropriate. The predictive ability of IL-17A and VCAM-1 for MACE occurrence risk was plotted using the receiver-operating characteristic (ROC) curve. Association analyses were performed using Spearman’s rank correlation test. \( p < 0.05 \) was considered significant.

### TABLE 2 Disease and operation information of STEMI patients

| Items                                      | STEMI patients (\( N = 212 \)) |
|--------------------------------------------|---------------------------------|
| Symptom-to-balloon time (min), median (IQR) | 180.0 (130.0–270.0)             |
| Multivessel disease, No, (%)               |                                 |
| No                                         | 124 (58.5)                      |
| Yes                                        | 88 (41.5)                       |
| Culprit lesion, No, (%)                    |                                 |
| LAD                                        | 92 (43.4)                       |
| LCX                                        | 44 (20.8)                       |
| RCA                                        | 76 (35.8)                       |
| Thrombus aspiration, No, (%)               |                                 |
| No                                         | 170 (80.2)                      |
| Yes                                        | 42 (19.8)                       |
| Number of implanted stents, No (%)         |                                 |
| 1                                          | 162 (76.4)                      |
| 2                                          | 50 (23.6)                       |
| Type of stent, No (%)                      |                                 |
| Sirolimus-eluting stent                    | 153 (72.2)                      |
| Everolimus-eluting stent                   | 59 (27.8)                       |
| Stent diameter (mm), median (IQR)          | 3.0 (3.0–3.5)                   |
| Stent length (mm), median (IQR)            | 33.0 (23.0–38.0)                |
| Infarct size (%), median (IQR)             | 23.0 (17.3–30.0)                |

Abbreviations: IQR, interquartile range; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction.
RESULTS

3.1 Clinical characteristics of STEMI patients

The entire 212 STEMI patients consisted of 57 (26.9%) females and 155 (73.1%) males, with a mean age of 62.6 ± 10.3 years (Table 1). Concerning blood laboratory detections, the median (interquartile range [IQR]) value of troponin I (cTnI) and creatine kinase-myocardial band (CK-MB) was 6.3 (4.2–7.9) ng/ml and 53.2 (33.8–75.4) ng/ml, accordingly. The specific clinical characteristics of STEMI patients were exhibited in Table 1.

3.2 Disease and operation information of STEMI patients

The median (IQR) value of symptom-to-balloon time was 180.0 (130.0–270.0) min. Besides, 88 (41.5%) patients were assessed with multivessel disease, and the other 124 (58.5%) patients were not. Concerning the stents, 162 (76.4%) patients were implanted with one stent, and the rest 50 (23.6%) patients were implanted with two stents. The median (IQR) values of stent diameter and length were 3.0 (3.0–3.5) mm and 33.0 (23.0–38.0) mm, correspondingly (Table 2).

3.3 Inflammatory cytokine levels in STEMI patients and angina pectoris patients

TNF-α (p = 0.031, Figure 1A), IL-8 (p = 0.001, Figure 1B), IL-17A (p = 0.001, Figure 1C), and VCAM-1 (p = 0.004, Figure 1D) levels were elevated in STEMI patients compared to angina pectoris patients, while IL-1β (p = 0.069, Figure 1E), IL-6 (p = 0.110, Figure 1F), IL-10 (p = 0.052, Figure 1G), and ICAM-1 (p = 0.069, Figure 1H) were not different between STEMI patients and angina pectoris patients.

3.4 Correlation of inflammatory cytokines with infarct size and lipid metabolism in STEMI patients

Subgroup analysis was conducted to investigate the association of inflammatory cytokines with infarct size, which showed that TNF-α (r = 0.248, p < 0.001), IL-1β (r = 0.228, p = 0.001), IL-8 (r = 0.175,
$p = 0.011$, VCAM-1 ($r = 0.175$, $p = 0.010$), and ICAM-1 ($r = 0.203$, $p = 0.003$) were positively associated with infarct size, while IL-10 ($r = -0.201$, $p = 0.003$) was negatively related to infarct size in STEMI patients (Table S1).

Moreover, it was also observed that IL-17A was positively linked with triglyceride (TG) ($r = 0.163$, $p = 0.017$) and low-density lipoprotein cholesterol (LDL-C) ($r = 0.211$, $p = 0.002$); meanwhile, VCAM-1 was positively related to TG ($r = 0.324$, $p < 0.001$), total cholesterol (TC) ($r = 0.176$, $p = 0.010$), and LDL-C ($r = 0.365$, $p < 0.001$) in STEMI patients (Table S2).

### 3.5 Correlation of inflammatory cytokines with cumulative MACE rate in STEMI patients

The cumulative 1-year, 2-year, and 3-year MACE rates in STEMI patients were 6.1%, 11.6%, and 17.4%, correspondingly (Figure 2A). Furthermore, both IL-17A high (vs. low) ($p = 0.026$, Figure 2B) and VCAM-1 high (vs. low) ($p = 0.012$, Figure 2C) were linked with increased cumulative MACE rate; whereas TNF-α high, IL-1β high, IL-6 high, IL-8 high, IL-10 high, and ICAM-1 high were not related to cumulative MACE rate in STEMI patients (all $p > 0.050$, Figure 2D–I).

Additionally, ROC curves were performed to determine the predictive ability of IL-17A and VCAM-1 for MACE occurrence risk, which showed that IL-17A could hardly predict MACE occurrence risk (area under the curve (AUC): 0.616, 95% confidence interval (CI): 0.500–0.733, Figure S1A), while the predictive value of VCAM-1 for MACE occurrence risk was favorable (AUC: 0.736, 95% CI: 0.606–0.866, Figure S1B) in STEMI patients. Moreover, the sensitivity and specificity were 0.750 and 0.589 at the best cutoff point of IL-17A, and they were 0.750 and 0.781 at the best cutoff point of VCAM-1.

### 3.6 Independent factors of cumulative MACE risk in STEMI patients

IL-17A high (vs. low) ($p = 0.034$) and VCAM-1 high (vs. low) ($p = 0.020$) were both related to elevated cumulative MACE risk in STEMI patients. Additionally, history of diabetes mellitus (vs. no) ($p = 0.026$), C-reactive protein (CRP) $\geq 5$ mg/L (vs. <5 mg/L) ($p = 0.012$),
cTnI $\geq$ 4.2 ng/ml (vs. <4.2 ng/ml) ($p = 0.040$), multivessel disease (vs. no) ($p = 0.014$), and stent length $\geq$ 33 mm (vs. <33 mm) ($p = 0.015$) were linked with increased cumulative MACE risk (Table 3).

To further eliminate the potential confounding factors, the multivariable Cox's proportional hazards regression analysis was conducted, which exhibited that IL-17A high (vs. low) ($p = 0.034$), VCAM-1 high (vs. low) ($p = 0.014$), age $\geq$ 65 years (vs. <65 years) ($p = 0.009$), history of diabetes mellitus (vs. no) ($p = 0.003$), CRP $\geq$ 5 mg/L (vs. <5 mg/L) ($p = 0.003$), multivessel disease (vs. no) ($p = 0.009$), and stent length $\geq$ 33 mm (vs. <33 mm) ($p = 0.036$).

### TABLE 3

Univariable Cox's proportional hazards regression analysis for cumulative MACE risk in STEMI patients

| Items                                      | $p$ Value | HR   | 95% CI Lower | 95% CI Upper |
|--------------------------------------------|-----------|------|--------------|--------------|
| TNF-α (high vs. low)                       | 0.160     | 1.934| 0.771        | 4.848        |
| IL-1β (high vs. low)                       | 0.379     | 1.494| 0.610        | 3.656        |
| IL-6 (high vs. low)                        | 0.332     | 1.558| 0.636        | 3.816        |
| IL-8 (high vs. low)                        | 0.131     | 2.092| 0.802        | 5.453        |
| IL-10 (low vs. high)                       | 0.225     | 0.566| 0.226        | 1.420        |
| IL-17A (high vs. low)                      | 0.034     | 2.992| 1.087        | 8.233        |
| VCAM-1 (high vs. low)                      | 0.020     | 3.692| 1.233        | 11.058       |
| ICAM-1 (high vs. low)                      | 0.034     | 2.992| 1.087        | 8.233        |
| Age (≥65 years vs. <65 years)              | 0.034     | 2.992| 1.087        | 8.233        |
| Gender (male vs. female)                   | 0.225     | 1.522| 0.633        | 3.660        |
| History of diabetes mellitus (yes vs. no)  | 0.026     | 2.725| 1.128        | 6.587        |
| WBC (≥10 x 10^9/L vs. <10 x 10^9/L)        | 0.108     | 2.194| 0.842        | 5.714        |
| FBG (≥6.2 mmol/L vs. <6.2 mmol/L)          | 0.248     | 1.720| 0.686        | 4.314        |
| Scr (≥110 μmol/L vs. <110 μmol/L)          | 0.200     | 2.047| 0.684        | 6.127        |
| TG (≥1.7 mmol/L vs. <1.7 mmol/L)           | 0.378     | 1.512| 0.603        | 3.792        |
| TC (≥5.2 mmol/L vs. <5.2 mmol/L)           | 0.113     | 2.035| 0.845        | 4.900        |
| LDL-C (≥3.4 mmol/L vs. <3.4 mmol/L)        | 0.210     | 1.777| 0.723        | 4.365        |
| HDL-C (≥0.94 mmol/L vs. >0.94 mmol/L)      | 0.623     | 0.802| 0.332        | 1.935        |
| CRP (≥5 mg/L vs. <5 mg/L)                  | 0.012     | 3.667| 1.332        | 10.095       |
| cTnI (≥4.2 ng/ml vs. <4.2 ng/ml)           | 0.040     | 2.895| 1.051        | 7.976        |
| CK-MB (≥33.9 ng/ml vs. <33.9 ng/ml)        | 0.357     | 1.524| 0.622        | 3.732        |
| Symptom-to-balloon time (≥130 min vs. <130 min) | 0.195 | 3.781| 0.506        | 28.262       |
| Multivessel disease (yes vs. no)           | 0.014     | 3.305| 1.270        | 8.603        |

The bold values represent the results with statistical significance, whose $p$ value < 0.050.

Abbreviations: BMI, body mass index; CI, confidence interval; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; cTnI, troponin I; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; ICAM, intercellular adhesion molecule; IL, interleukin; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac events; RCA, right coronary artery; Scr, serum creatinine; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; WBC, white blood cell.
were independently associated with increased cumulative MACE risk. Differently, the application of the everolimus-eluting stent (vs. sirolimus-eluting stent) \((p = 0.034)\) was independently related to decreased MACE risk (Table 4).

### 4 | DISCUSSION

Among the complicated etiologies of STEMI, the most widely accepted one is the plaque rupture-caused coronary artery thrombosis.\(^2\) When vascular walls are exposed to a proinflammation environment, the recruitment and accumulation of leukocytes are enhanced, which further promotes endothelial injury and the formation of thrombosis.\(^{17}\) Subsequently, considering the essential role of inflammation in the pathogenesis of STEMI, the previous studies notice the abnormal level of several inflammatory cytokines in STEMI patients.\(^{18–21}\) For instance, one previous study observes that serum TNF-\(\alpha\) and IL-6 are beyond the normal range in STEMI patients who undergo PCI treatment.\(^{20}\) Another study discloses the high level of TNF-\(\alpha\), IL-10, IL-4, and IL-1\(\beta\) in STEMI patients compared with the controls.\(^{19}\) Partially in line with the previous studies, this study displayed that TNF-\(\alpha\), IL-8, IL-17A, and VCAM-1 level was elevated in STEMI patients compared to angina pectoris patients. The possible explanation was listed as follows: TNF-\(\alpha\), IL-8, IL-17A, and VCAM-1 were all proinflammatory cytokines, which accelerate endothelial dysfunction and increased atherosclerotic plaque burden.\(^{12,22}\) Thus, the level of those inflammatory cytokines was elevated in STEMI patients compared with angina pectoris patients.

A few studies have been carried out to explore the correlation of some specific inflammatory cytokines with MACE risk in STEMI patients.\(^{13,15,23–25}\) For example, one previous study indicates that the elevation of IL-6 is correlated with high MACE risk in STEMI patients who undergo PCI therapy.\(^{13}\) Another study finds the important role of VCAM-1 in the occurrence of post-PCI restenosis.\(^{23}\) Nevertheless, the prognostic value of inflammatory cytokines lacks comprehensive study at present. The current study analyzed eight inflammatory cytokines, then found that IL-17A high (vs. low) and VCAM-1 high (vs. low) were independently associated with increased cumulative MACE risk in PCI-treated STEMI patients. The probable reasons were as follows: (1) IL-17A high level at an early stage aggravated the extent of left ventricular remodeling after STEMI, while the latter factor was closely linked with an increased risk of MACE (including heart failure, recurrent myocardial infarction, etc.).\(^{26,27}\) Hence, elevated IL-17A level was independently related to accelerated MACE risk in STEMI patients. (2) Concerning VCAM-1 (also a member of inflammatory cytokine), it mediated the adhesion of vascular endothelial cells and leukocytes, which was closely associated with vascular endothelial injury and further exacerbated atherosclerotic lesions.\(^{28–30}\) Additionally, VCAM-1 contributed to trimethylamine-N-oxide, then enhanced arterial thrombosis and increased the occurrence of post-PCI restenosis.\(^{31–33}\) Combining the above two aspects, VCAM-1 high (vs. low) was independently correlated with elevated MACE risk in PCI-treated STEMI patients. Besides, it is observed that the previous studies notice that IL-6 and TNF-\(\alpha\) could serve as a prognostic indicator in STEMI patients, while their prognostic value lacked statistical significance in this study, which might be explained by that: the previous studies only focused on a single or a few inflammatory cytokines (no more than three) inflammatory cytokines, while this study comprehensively investigated eight inflammatory cytokines, and utilized the multivariable Cox’s proportional hazards regression analysis to eliminate the interinfluence among inflammatory cytokines. Hence, some different findings between this study and the previous study were noticed.

Some limitations existed in this study. Firstly, the determination of inflammatory cytokines at multiple time points after treatment was also necessary for further studies to monitor disease progression. Secondly, the median (IQR) follow-up duration was 15.0 (9.0–24.0) months, ranging from 1.0 to 39.0 months, and the total 3-year MACE rate was 17.4%; hence, the long-term predicting value of inflammatory cytokines for MACE risk deserved further study. Thirdly, patients in this study all received primary PCI, while the inflammatory cytokine level and their prognostic value remained unclear in

**TABLE 4** Multivariable Cox’s proportional hazards regression analysis for cumulative MACE risk in STEMI patients

| Items | \(p\) Value | HR | 95% CI Lower | 95% CI Upper |
|-------|-------------|----|--------------|--------------|
| IL-17A (high vs. low) | 0.034 | 3.127 | 1.091 | 8.965 |
| VCAM-1 (high vs. low) | 0.014 | 4.533 | 1.355 | 15.160 |
| Age (≥65 years vs. <65 years) | 0.003 | 5.762 | 1.787 | 18.581 |
| History of diabetes mellitus (yes vs. no) | 0.009 | 4.605 | 1.460 | 14.528 |
| CRP (≥5 mg/L vs. <5 mg/L) | 0.003 | 7.372 | 1.985 | 27.384 |
| Multivessel disease (yes vs. no) | 0.009 | 4.142 | 1.427 | 12.024 |
| Type of stent (everolimus-eluting stent vs. sirolimus-eluting stent) | 0.034 | 0.276 | 0.084 | 0.906 |
| Stent length (≥33 mm vs. <33 mm) | 0.036 | 4.133 | 1.097 | 15.571 |

The bold values represent the results with statistical significance, whose \(p\) value < 0.050.

Abbreviations: CI, confidence interval; CRP, C-reactive protein; cTnI, troponin I; HR, hazard ratio; IL, interleukin; MACE, major adverse cardiac events; STEMI, ST-segment elevation myocardial infarction; VCAM, vascular cell adhesion molecule.
recurrent patients who underwent PCI retreatment. Fourthly, patients with electrocardiographic changes in left bundle branch block of new onset were not included in this study according to the enrollment criteria, while it could also be regarded as STEMI presentation. Fifthly, the comparison of inflammatory cytokine levels between PCI-treated and coronary artery bypass grafting (CABG)-treated STEMI patients was undetected in this study, which deserved further investigation.

In summary, IL-17A and VCAM-1 high level independently correlate with elevated MACE risk in STEMI patients, which might serve as useful indicators in assistance of STEMI diagnosis and identifying patients with poor prognosis.

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DATA AVAILABILITY STATEMENT
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

CONSENT TO PARTICIPATE
Each patient or family member signed the informed consent.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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