Combination of eosinophil percentage and high-sensitivity C-reactive protein predicts in-hospital major adverse cardiac events in ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention

Liu Ye1 | Hong-mei Bai2 | Dan Jiang1 | Bing He2 | Xue-song Wen2 | Ping Ge1 | Dong-ying Zhang2

1The First Branch, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
2Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Correspondence
Ping Ge, The First Branch, The First Affiliated Hospital of Chongqing Medical University, No. 191 Renmin Road, Yuzhong District, Chongqing, China.
Email: 442216169@qq.com
Dong-ying Zhang, The First Affiliated Hospital of Chongqing Medical University, NO. 1 Youyi Road, Yuzhong District, Chongqing, China.
Email: zhangdongying@cqmu.edu.cn

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Abstract

Background: Eosinophil levels predict prognosis in ST-segment elevation myocardial infarction (STEMI) patients. Both eosinophils and high-sensitivity C-reactive protein (hs-CRP) play a major role in the acute inflammatory response of myocardial infarction. The purpose of this study was to evaluate eosinophil percentage (EOS%) and hs-CRP as prognostic markers for in-hospital adverse events in STEMI patients undergoing primary percutaneous coronary intervention.

Methods: We retrospectively analyzed the clinical data of 518 patients. Major adverse cardiac events (MACEs) were defined as cardiac rupture, cardiac arrest, malignant arrhythmia, and cardiac death. Based on the receiver operating characteristic (ROC) analysis, all patients were regrouped into 3 groups (None, One, and Two) according to cutoff EOS% value (≤0.3%) and hs-CRP value (>11.8 mg/L). Both Cox regression analyses and the KM (Kaplan-Meier) survival curve were used to examine the prognostic role of combined hs-CRP and EOS% in cardiovascular events.

Results: Of the 518 STEMI patients, 50 of them developed MACEs. Patients who developed MACEs had a significantly lower EOS% and higher hs-CRP than patients who remained MACE-free. In the multivariable Cox regression analysis, the highest risk of in-hospital MACEs was constantly observed in patients with a combined low EOS% and elevated hs-CRP. Patients with reduced EOS% and high hs-CRP had significantly higher incidence rates of cardiac rupture ($P = .001$), cardiac arrest ($P = .001$), and malignant arrhythmia ($P < .001$); furthermore, they had the worst cumulative survival compared with the other two groups.

Conclusion: Combined reduced EOS% and elevated hs-CRP were valuable tools for identifying patients at risk of in-hospital MACEs.
INTRODUCTION

Inflammation and thrombosis are the main mechanisms of the acute coronary syndrome (ACS). High-sensitivity C-reactive protein (hs-CRP), a classical marker of systemic inflammation, can predict cardiovascular risk in ACS patients. Eosinophils are an important inflammatory cell and are involved in the acute inflammatory response of myocardial infarction. Numerous thrombotic events were observed in patients with eosinophil-related disorders. Some studies have confirmed that eosinophils infiltrate coronary artery thrombosis. Eosinophils in the peripheral blood were significantly reduced in myocardial infarction, and the fall of eosinophils suggested a significantly increased risk of cardiac events. However, we do not know whether combined EOS% and hs-CRP actually add to the predictive ability of determining the risk of cardiovascular events. The aim of this study was to investigate eosinophils and hs-CRP as prognostic markers for in-hospital Major adverse cardiac events (MACEs) in ST-segment elevation myocardial infarction (STEMI) patients after undergoing percutaneous coronary intervention (PCI).

MATERIALS AND METHODS

2.1 Study population

We retrospectively reviewed the clinical records of 573 consecutive patients with STEMI who underwent PCI within 12 hours from their onset of symptoms at The First Affiliated Hospital of Chongqing Medical University between October 2015 and August 2017. STEMI was defined as a rise and/or fall of cTn values with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of acute myocardial ischemia; new ST-segment elevations in two contiguous leads or new bundle branch blocks or development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; and identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy. Principal exclusion criteria were as follows: previous myocardial infarction and PCI; congenital heart disease; liver cirrhosis; hemodialysis; immunological disease; malignant tumors; pregnancy; the infection caused by various pathogens; chronic inflammatory disease; trauma; and patients given corticosteroid.

Baseline data included sex, age, hypertension, diabetes, chronic kidney disease (CKD), stroke, ischemic duration, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), left ventricular ejection fraction (LVEF), baseline angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), and β-blocker use. Ischemic time refers to the time from symptom onset to admission. SBP, DBP, and HR were measured immediately upon admission. LVEF was assessed using the Simpson method. ACEI/ARB or β-blocker use was defined within 24 hours after hospital admission. Venous blood for blood routine test was collected immediately after admission. Other blood samples were drawn on the first day of admission. The following parameters were measured and analyzed in the study: neutrophil, EOS%, defined as the ratio of the number of eosinophils to the number of white blood cell count (reference range: 0.4%-8.0%), urea, serum creatinine, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), peak creatine kinase (CK)-MB, peak troponin I (TNI), and hs-CRP. The peak TNI and CK-MB levels referred to the maximum value examined during hospitalization. MACEs included cardiac arrest caused by cardiogenic disease, cardiac rupture, malignant arrhythmia, and cardiac death. For patients experiencing more than one MACEs, only the first event was considered in the analysis. Malignant arrhythmia compromised non-sustained ventricular tachycardia (VT) and sustained VT, ventricular fibrillation (VF), and...
complete atrioventricular block, which were documented by ECG or cardiac monitoring.

2.2 | Statistical analysis

Eosinophils and hs-CRP were both analyzed as a continuous variable and as a grouped variable. Continuous variables were represented as mean ± standard deviation (SD) or median (25th, 75th percentile). Categorical variables are expressed as numbers and percentages. The continuous variable between the two groups was checked using an independent sample t test or Mann-Whitney U test as needed. Comparisons between categorical variables were evaluated by using the chi-square test. The receiver operating characteristic (ROC) curve was constructed to determine the cutoff value of EOS% and hs-CRP for predicting in-hospital MACEs. According to the cutoff EOS% levels and hs-CRP levels, patients were divided into 3 groups (None, One, and Two), which were defined as follows: Patients with decreased EOS% (≤0.3%) and elevated hs-CRP (>11.8 mg/L) were assigned to Two group; patients with only one of these biomarker abnormalities were assigned to One group; and patients with neither of these abnormalities were assigned to None group. If the continuous variable conformed to the normal distribution and the variance, it was checked by the ANOVA test; otherwise, it was compared with the Kruskal-Wallis test. Multiple comparisons were adjusted using the chi-square test with Bonferroni correction. Cox regression analyses were used to explore the relationship between the two biomarkers (EOS% and hs-CRP) and in-hospital MACEs. The following variables were contained in the multivariable models based on the unadjusted P < .10 or clinical relevance. A total of four Cox regression adjusted models were constructed. The median for hospitalization days of MACEs free was 7 days, and it was set as the deadline. The Kaplan-Meier method was constructed for the in-hospital adverse events cumulative incidence and compared by using log-rank tests. Analyses were used by SPSS statistical

| Variables                        | MACE-free (n = 468) | MACE (n = 50) | P  |
|----------------------------------|-------------------|--------------|----|
| Male/female                      | 369/99            | 36/14        | .174|
| Age (y)                          | 63 (53-72)        | 66 (60-76)   | .029|
| Hypertension (n, %)              | 242 (51.7)        | 27 (54.0)    | .768|
| Diabetes (n, %)                  | 141 (30.1)        | 19 (38)      | .262|
| CKD (n, %)                       | 20 (4.3)          | 4 (8)        | .275|
| Ischemic time (h)                | 4 (3-7)           | 5 (3-8)      | .077|
| Stroke (n, %)                    | 13 (2.8)          | 2 (4.0)      | .644|
| SBP (mm Hg)                      | 125 (108-145)     | 118 (99-132) | .017|
| DBP (mm Hg)                      | 76 (66-89)        | 74 (62-85)   | .140|
| Heart rate (bpm)                 | 80 (70-93)        | 90 (70-106)  | .035|
| Killip class on admission (class ≥ III) | 51 (10.9%) | 21 (42%)   | .000|
| Neutrophil (×10^9/L)             | 9.09 (7.06-11.4)  | 10.4 (8.08-12.6) | .013|
| EOS%                             | 0.3 (0.1-0.7)     | 0.1 (0.0-0.2) | .000|
| Hs-CRP (mg/L)                    | 5.1 (2.0-10.8)    | 9.2 (4.3-20.0) | .002|
| Urea (mmol/L)                    | 5.7 (4.7-6.8)     | 6.1 (4.8-7.3) | .217|
| Serum creatinine (µmol/L)        | 73 (62-89)        | 92 (71-112)  | .000|
| TC (mmol/L)                      | 4.3 (3.8-5.1)     | 4.4 (3.8-5.2) | .845|
| TG (mmol/L)                      | 1.5 (1.0-2.3)     | 1.5 (1.0-1.9) | .385|
| HDL (mmol/L)                     | 1.1 (0.9-1.3)     | 1.0 (0.9-1.2) | .172|
| LDL (mmol/L)                     | 2.8 (2.2-3.5)     | 2.2 (2.9-3.6) | .412|
| Peak CK-MB (ng/mL)               | 33.7 (10.4-72.3)  | 34.1 (16.7-79.2) | .428|
| Peak troponin I (ng/mL)          | 3.9 (0.7-13.9)    | 6.8 (2.6-20.6) | .123|
| LVEF (%)                         | 57 (52-60)        | 54 (44-60)   | .034|
| β-blocker (n, %)                 | 280 (59.8)        | 22 (44)      | .031|
| ACEI or ARB (n, %)               | 219 (46.8)        | 14 (28)      | .011|

Note: Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor antagonists; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; DBP, diastolic blood pressure; EOS%, eosinophil percentage; HDL, high-density lipoprotein; HS-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

FIGURE 2 The receiver operating characteristic (ROC) curve of the EOS%, high-sensitivity C-reactive protein (hs-CRP), combined biomarker model hs-CRP, and EOS% for predicting in-hospital MACE. The cutoff values were ≤0.3% for EOS% (sensitivity, 94%; specificity, 43%), >11.8 mg/L for hs-CRP (sensitivity, 48%; specificity, 77%) and >0.1 for the combination of EOS% and hs-CRP (sensitivity, 76%; specificity, 61%)
software version 21.0 (SPSS). A P < .05 was considered to be statistically significant.

3 | RESULTS

3.1 | Baseline patient characteristics

We enrolled a total of 573 STEMI patients who underwent PCI. We excluded 7 patients who suffered from cancer, 21 patients because of missing EOS% and hs-CRP data, 12 patients because they had a previous myocardial infarction, and 15 patients who simultaneously suffered from inflammatory or allergic diseases. Finally, 518 STEMI patients who underwent PCI were studied in Figure 1. The baseline and clinical characteristics of the patients are reported in Table 1. Patients with MACEs were older than those who were MACE-free. Compared with the MACE-free group, the MACE group was more likely to have a more severe heart function, as shown by a higher proportion of patients with Killip class ≥ III, significantly lower SBP and LVEF. Patients who developed MACEs were less likely to be taking ACEI/ARB or β-blocker. EOS% was lower, and hs-CRP was higher in the MACE group than in the MACE-free group (0.1[0.0-0.2]% vs 0.3[0.1-0.7]%; P < .001 for EOS%, 9.2[4.3-20.0] mg/L vs 5.1[2.0-10.8] mg/L; P = .002 for hs-CRP, respectively). Except that the serum creatinine, neutrophil, and heart rate were higher in the MACE group, there was no statistical significance among other parameters.

3.2 | Prognostic accuracy of EOS% and hs-CRP for in-hospital outcomes

EOS% had a higher area under the curve (AUC) for the prediction of in-hospital cardiac events (0.71; 95% confidence interval [CI], 0.67-0.75) than hs-CRP (0.64; 95% CI, 0.59-0.68) as shown in Figure 2. The cutoff values were ≤0.3% for EOS% (sensitivity, 94%; specificity, 43%) and >11.8 mg/L for hs-CRP (sensitivity, 48%; specificity, 77%). EOS% improved the sensitivity and predictive capability of hs-CRP (sensitivity of combined biomarker model hs-CRP and

| Variables | None (n = 177) | One (n = 238) | Two (n = 103) | P |
|-----------|---------------|---------------|---------------|---|
| Male/female | 150/27 | 185/53 | 70/33a | .004 |
| Age (y) | 61.2 ± 12.0 | 62.3 ± 12.5 | 67.9 ± 11.8ab | .000 |
| Hypertension (n, %) | 97 (54.8) | 113 (47.5) | 59 (57.3) | .158 |
| Diabetes (n, %) | 52 (29.4) | 69 (28.9) | 39 (37.9) | .232 |
| CKD (n, %) | 9 (5.1) | 8 (3.4) | 7 (6.8) | .364 |
| Ischemic time (h) | 3 (2-5) | 5 (3-7)c | 5 (4-7)a | .000 |
| Stroke (n, %) | 2 (1.1) | 7 (2.9) | 6 (5.8) | .068 |
| SBP (mm Hg) | 125 (108-147) | 121 (108-140) | 124 (104-145) | .143 |
| DBP (mm Hg) | 78 (68-90) | 74 (66-87) | 74 (64-88) | .099 |
| Heart rate (bpm) | 78 (68-88) | 82 (70-92) | 90 (74-106)ab | .000 |
| Killip class on Admission (class ≥ III) | 3 (1.7%) | 33 (13.9%)c | 36 (34.9%)ab | .000 |
| Urea (mmol/L) | 5.6 (4.8-6.7) | 5.6 (4.6-6.8) | 5.9 (4.9-7.6) | .129 |
| Serum creatinine (µmol/L) | 73 (62-86) | 74 (64-89) | 81 (62-103)a | .040 |
| Neutrophil (×10⁹/L) | 7.6 (6.1-9.3) | 9.7 (8.0-11.9)c | 10.6 (8.7-13.6)a | .000 |
| TC (mmol/L) | 4.3 (3.7-5.1) | 4.4 (3.8-5.1) | 4.4 (3.9-5.3) | .393 |
| TG (mmol/L) | 1.7 (1.1-2.4) | 1.5 (0.9-2.3) | 1.5 (1.1-1.8) | .040 |
| HDL (mmol/L) | 1.1 (0.9-1.3) | 1.1 (0.9-1.3) | 1.1 (0.9-1.4) | .275 |
| LDL (mmol/L) | 2.8 (2.2-3.4) | 2.9 (2.3-3.4) | 2.9 (2.4-3.7) | .208 |
| Peak CK-MB (ng/mL) | 22.6 (4.9-59.5) | 37.9 (14.3-73.1)c | 58.2 (23.4-80.0)a | .000 |
| Peak troponin I (ng/mL) | 2.6 (0.5-9.8) | 4.6 (0.9-12.4) | 7.9 (1.2-27.1)ab | .000 |
| LVEF (%) | 58 (54-61) | 56 (52-60)c | 55 (49-59)a | .001 |
| β-blocker (n, %) | 108 (61.0) | 135 (56.7) | 59 (57.3) | .666 |
| ACEI or ARB (n, %) | 85 (48.0) | 106 (44.5) | 42 (40.8) | .503 |

Note: Versus, vs; other abbreviations as in Table 1.
aTwo group vs None group, adjusted P < .05.
bTwo group vs One group, adjusted P < .05.
cOne group vs None group, adjusted P < .05.
 EOS%, 76%; AUC of hs-CRP and EOS%; the difference of AUCs, 0.09; P = .007), but not the specificity (specificity of combined biomarker model hs-CRP and EOS%, 61%). When combining EOS% and hs-CRP, the AUC changed to 0.73 and had a sensitivity of 76% and a specificity of 61%. According to the cutoff EOS% value (>0.3% vs ≤0.3%) and hs-CRP value (≤11.8 mg/L vs >11.8 mg/L), all patients were regrouped into three groups (None, One, and Two) in Table 2. Patients were older in the Two group than the rest of the group. Patients in the None group had a higher percentage of male and lower serum creatinine than Two group. Shorter ischemic time, lower neutrophil, and higher LVEF on admission were found in None group. Patients in the Two group than the rest of the group. Patients in the None group had a higher percentage of male and lower serum creatinine than Two group. Shorter ischemic time, lower neutrophil, and higher LVEF on admission were found in None group. Patients in the Two group had the highest CK-MB, troponin I, and heart rate, whereas patients in the None group had the lowest values. The Two group had the highest proportion of patients with Killip class ≥ III. All the other parameters did not reveal any significant differences.

TABLE 3 Multivariate Cox regression analysis of in-hospital MACE

| Variables | Adjusted HR (95% CI) | p  |
|-----------|----------------------|----|
| Model I   |                      |    |
| Male      | 0.97 (0.52-1.83)     | .935 |
| Age       | 1.01 (0.99-1.04)     | .426 |
| Killip class ≥ III | 2.93 (1.63-5.27) | .000 |
| Combined EOS% and hs-CRP | .002 |
| None      | RF                   |    |
| One       | 7.83 (1.84-33.35)    | .005 |
| Two       | 13.29 (3.01-58.66)   | .001 |
| Model II  |                      |    |
| Neutrophil| 1.02 (0.95-1.10)     | .601 |
| SBP       | 0.99 (0.97-1.00)     | .013 |
| Heart rate| 1.01 (1.00-1.03)     | .125 |
| Combined EOS% and hs-CRP | .000 |
| None      | RF                   |    |
| One       | 8.56 (2.01-36.54)    | .004 |
| Two       | 16.78 (3.82-73.71)   | .000 |
| Model III |                      |    |
| Ischemic time | 1.04 (0.93-1.15) | .521 |
| Serum creatinine | 1.00 (1.00-1.00) | .060 |
| Combined EOS% and hs-CRP | .000 |
| None      | RF                   |    |
| One       | 8.94 (2.10-38.03)    | .003 |
| Two       | 19.89 (4.62-85.69)   | .000 |
| Model IV  |                      |    |
| LVEF      | 0.98 (0.95-1.01)     | .262 |
| β-blocker | 0.66 (0.35-1.24)     | .197 |
| ACEI or ARB| 0.61 (0.31-1.21)    | .156 |
| Combined EOS% and hs-CRP | .000 |
| None      | RF                   |    |
| One       | 8.12 (1.91-34.54)    | .005 |
| Two       | 16.38 (3.81-70.50)   | .000 |

Note: CI, confidence interval; HR, hazard ratio; other abbreviations as in Table 1.

3.3 Multivariate Cox regression analysis

In the univariate Cox regression analysis, age, Killip class ≥ III, SBP, neutrophil, heart rate, serum creatinine, ischemic time, LVEF, β-blocker and ACEI or ARB, and the two biomarkers (EOS% and hs-CRP) were associated with a high risk of in-hospital cardiovascular events. We first adjusted for age, sex, and Killip class ≥ III (Model I) and subsequently for the neutrophil, SBP, and heart rate (Model II). Additionally, we adjusted for ischemic time, serum creatinine (Model III), LVEF, β-blockers, and ACEI or ARB (Model IV), which did not weaken the relative risk associated with the Two group. In all adjustment models, patients in the One group and Two group proved to be continuously significant when predicting worsened in-hospital MACEs, compared with the None group (Table 3).

3.4 In-hospital outcomes

The Two group had the highest MACEs incidence rates than the other two groups (Table 4). In order to demonstrate which two groups had significant differences, we used chi-square test with Bonferroni correction. The results showed that P-value of Two group and None group was less than .001, P-value of Two group and One group was .004, and P-value of One group and None group was less than .001 (P < .017 was considered as statistical difference). Patients in the Two group had significantly higher MACEs incidence rates than...
None group, including cardiac rupture, cardiac arrest, malignant arrhythmia, and cardiac death (Table 4). Kaplan-Meier curves (Figure 3) confirmed the groups that predicted the worse clinical events. The highest risk of future cardiovascular events was observed in the Two group, implying that by combining the two markers, we can effectively identify high-risk patients. Patients in the None group had the lowest consequent risk of cardiovascular events with time.

4 | DISCUSSION

The purpose of this paper was to evaluate the prognostic ability of two biomarkers (EOS% and hs-CRP) in STEMI patients who had undergone PCI. The EOS% level was lower, and the hs-CRP level was higher in patients with in-hospital MACEs than in patients who were MACE-free. This was consistent with previous reports. We used a combined model including EOS% and hs-CRP to identify the risk stratification for in-hospital cardiovascular events; the model improved the prediction value of in-hospital adverse outcomes.

Both hs-CRP and eosinophils play an important role in the acute inflammatory response of myocardial infarction. Hs-CRP is a marker of inflammation and was demonstrated to be a strong predictor of adverse events in ACS patients. Previous findings showed that patients with acute myocardial infarction (AMI) had a decreased EOS% compared with angina patients. Only Konishi et al showed that the EOS% was a risk factor for adverse events occurring within
one year after STEMI, but it mainly was attributed to the higher 30-day clinical outcomes. In the present study, reduced EOS% levels were related to an increased incidence of in-hospital MACEs. The ROC curves showed that the sensitivity of EOS% was high, but the specificity was low, which was the opposite of hs-CRP. When a combined model including EOS% and hs-CRP was constructed, both the specificity and sensitivity were improved and the results were acceptable. In our analyses, the in-hospital MACEs hazard ratio dramatically increased by 13 to 19 times when combined with low EOS% and high hs-CRP (Two group), where the None group was taken as the reference. Compared with patients in the One group, the in-hospital MACEs hazard ratio of patients in the Two group nearly doubled. A stepwise increase in the incidences of in-hospital MACEs was found when moving from none to two biomarkers anomalies. Patients with low EOS% and elevated hs-CRP were found to have the highest risk. The EOS% provided additive prognostic information for hs-CRP, and their combination contributed to discriminate subgroups of patients with a great risk of cardiovascular events.

In the present study, the occurrence of MACEs seemed to be mainly attributed to a decrease in eosinophils. It is explained that eosinophils are attracted to the site of the lesion soon after AMI because the bone marrow cannot respond immediately with increased production. This consequently results in the consumption of eosinophils in the peripheral circulation. Eosinophils are leukocytes and can produce an array of cytokines and chemokines that are regulatory or proinflammatory. These molecules may contribute to the progression of an acute cardiac event. Eosinophils express cytokines such as IL-1, IL-3, IL-5, IL-6, IL-10, IL-13, tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), and granulocyte-macrophage colony-stimulating factor (GM-CSF), which modulate the acute inflammatory response. Chemokines include CC-chemokine ligand (CCL)5, CCL11, CCL24, CCL26, and CCL28, playing an important part in the postinfarction inflammatory response. Major basic protein (MBP) and eosinophilic cationic protein are two important molecules secreted by eosinophils, which induce thrombosis by enhancing the coagulation and fibrinolysis system. Activated eosinophils generate platelet-activating factor (PAF), which can induce platelet, leukocyte, and endothelial cell activation. Overall, eosinophils are recruited from the circulation into the region of infarction where they modulate acute inflammatory response and thrombosis through an array of mechanisms; hence, a declined eosinophils become an important prognostic marker of MACEs.

Another finding of the study was that patients with reduced EOS% and elevated hs-CRP had a high-risk tendency of cardiac rupture. Both eosinophils and hs-CRP are markers of inflammation, and it was reported that a higher expression of inflammatory markers after an infarction indicated a higher risk of cardiac rupture. Atkinson et al found that the number of eosinophils was higher in hearts that were associated with cardiac rupture than in control infarcted hearts. The mechanism of eosinophils attributed to cardiac rupture remains unclear. It might be related to toxic cationic proteins released by eosinophils inducing apoptosis and necrosis.

Our analysis was a single-center and retrospective study, and it used small sample size. The study had strict exclusion criteria, and the findings could not be generalized to patients who suffer from co-morbidities such as tumors, infections, or inflammatory disease. To our regret, the EOS serial data had not been collected before and after PCI for comparison.

5 CONCLUSIONS

In conclusion, our results demonstrated that reduced EOS% was associated with in-hospital MACEs in patients with STEMI after PCI. A combined model of EOS% and hs-CRP provided reasonable and acceptable specificity and sensitivity for STEMI patients after PCI. The model improved the prediction value of in-hospital adverse outcomes. The two biomarkers are rather inexpensive and readily available. It is necessary for the next large-scale studied to verify their role in MACEs.

FOUNDING INFORMATION

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CONFLICT OF INTERESTS

All authors declare no potential conflict of interests.

ETHICAL APPROVAL

This was a retrospective and observational study and registered at clinicaltrials.gov: identifier number NCT03740776. The study was approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University (approval NO.2018-035), and informed consent was obtained from the participants.

ORCID

Dong-ying Zhang https://orcid.org/0000-0002-0507-897X

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