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# Prognostic implication of systemic inflammatory state on antiplatelet effect in patients after percutaneous coronary intervention for ST-elevation myocardial infarction

## A retrospective cohort study

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**Abstract**

Patients with ST-elevation myocardial infarction (STEMI) show an inflammatory response. The level of systemic inflammation is known to affect platelet aggregation function and antiplatelet therapy, which leads to different clinical prognosis. This study aims to evaluate the prognostic implication of systemic inflammatory state in patients with STEMI undergoing percutaneous coronary intervention.

In this study, 203 patients with STEMI who underwent primary percutaneous coronary intervention were included. The patients were divided into 3 groups based on the inflammation levels assessed by tertiles of high-sensitivity C-reactive protein (hs-CRP) level on admission. Platelet aggregation evaluation was performed by residual platelet reactivity, which was assessed by the value of residual ADP-induced light transmittance aggregometry after clopidogrel maintenance dose therapy and in follow-up. Major adverse cardiac events (MACEs) were defined to include all-cause mortality, cardiovascular mortality, reinfarction, target vessel revascularization (TVR), cardiopulmonary resuscitation, advanced heart failure, ventricular fibrillation or ventricular tachycardia, and atrioventricular block.

Levels of white blood cell was observed to be significantly higher at high tertile levels. Residual ADP-induced platelet aggregation was significantly higher at high tertile levels after clopidogrel maintenance dose therapy and in follow-up. Multivariate analysis identified that reperfusion time, alanine aminotransferase, platelet count, ADP-induced light transmittance aggregometry in follow-up and hs-CRP was independent predictors of MACEs. Platelet inhibition function of clopidogrel decreases progressively at different inflammation levels. The different levels of hs-CRP were demonstrated to be associated with MACEs at follow-up assessments.

The presence of hs-CRP was not only significantly associated with platelet inhibition function, but was also a prognostic marker in STEMI.

**Abbreviations:** ACS = acute coronary syndrome, ADP = adenosine diphosphate, ALT = alanine aminotransferase, CAD = coronary artery disease, CRP = C-reactive protein, HDL-C = high-density lipoprotein cholesterol, IRA = infarct-related artery, LDL-C = low-density lipoprotein cholesterol, LTA = light transmittance aggregometry, MACEs = major adverse cardiac events, PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction, VF= ventricular fibrillation, VT = ventricular tachycardia, WBC = white blood cell.

**Keywords:** antiplatelet therapy, clinical prognosis, inflammation, ST-elevation myocardial infarction

## 1. Introduction

Platelet activation has a critical point in the pathogenesis of acute coronary syndrome (ACS).[1] It is a consolidate knowledge that platelets adhere to the damaged walls of blood vessels at sites of endothelial cell activation contributing to the development of chronic atherosclerotic plaques, and trigger the acute onset of

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*All data generated or analyzed during this study are included in this published article [and its supplementary information files]. the datasets generated during and/or analyzed during the current study are publicly available.*

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arterial thrombosis in response to atherosclerotic plaque rupture.[2] The dual antiplatelet therapy that combines aspirin (acetylsalicylic acid) and a platelet $P2Y_{12}$ receptor inhibitor is the standard antithrombotic strategy, which reduces atherothrombotic events and improves long-term clinical outcomes in patients who undergo percutaneous coronary intervention (PCI).[3,4] Despite the availability of newer platelet $P2Y_{12}$ receptor inhibitors, clopidogrel remains widely used, also because it allows a considerable cost-containment. Clopidogrel platelet reactivity during dual-antiplatelet therapy is a marker of vascular risk, in particular stent thrombosis, in ACS.[5]

Patients with ACS develop an inflammatory response, with elevated C-reactive protein (CRP) levels,[6] platelet activation, and aggregation.[7] CRP is reported as a systemic, downstream, sensitive, acute-phase marker of inflammation. There is a significant correlation between the CRP levels and adenosine diphosphate (ADP)-induced platelet aggregation values.[8] It has been considered that inflammation modifies platelet function and leads to increased platelet reactivity and reduced clopidogrel efficacy in coronary artery disease patients after PCI.[9]

NO information is yet available on the impact of inflammatory levels, measured in terms of high-sensitivity C-reactive protein (hs-CRP) levels, on platelet aggregation with clopidogrel during hospitalization and follow-up. Thus, this study aims to investigate clinical and prognostic implication of antiplatelet effect on platelet aggregation at different inflammation levels in patients with STEMI undergoing primary PCI.

## 2. Methods

### 2.1. Ethics statement

This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. It was also approved by the Research Ethics Committee of the Second Affiliated Hospital of Qiqihar Medical University, China (the ethics committee approval number: KY2020-003-01). Informed consent was obtained from each patient.

### 2.2. Study population

We identified 203 patients admitted for STEMI, who underwent primary PCI at the second Affiliated Hospital of Qiqihar Medical University (Qiqihar, China) between January 2013 and January 2019. The patients were divided into 3 groups based on the inflammation levels assessed by tertiles of hs-CRP level on admission. The tertiles of hs-CRP were as defined as per these cut-offs: low tertile ($0 <$ hs-CRP$< 2$, mg/L); intermediate tertile ($2 \leq$hs-CRP$\leq 10$, mg/L); and high tertile (hs-CRP$> 10$, mg/L). The inclusion criteria were: patient presenting within 12 hours from the onset of symptoms, defined as typical chest pain lasting for $>30$ minutes; (2) ST-segment elevation 1 mm in 2 contiguous electrocardiographic leads or new onset of complete left bundle-branch block; and primary PCI including balloon angioplasty, thrombus aspiration, and/or stent implantation performed. The exclusion criteria included known allergies to clopidogrel or ticagrelor; presence of thrombocytopenia (platelet count $< 80 \times 10^9$ cells/L) or anemia (hemoglobin $<10.0$ g/dL); any chronic illness, like cancer, liver cirrhosis, heart failure, or chronic kidney disease; a history of hemorrhagic disorder; use of tirofiban during PCI; long-term intake of oral dipyridamole, warfarin, abciximab, anti-inflammatory drugs, glucocorticoids, or a strong cytochrome P-450 3A inhibitor or inducer; and the presence of concomitant inflammatory conditions (such as connective tissue disease, inflammatory arthritis, or active infection).

### 2.3. Coronary angiography and stenting

All primary PCIs were performed at our hospital (Department of Cardiology, the Second Affiliated Hospital of Qiqihar Medical University, Qiqihar, China), which is a single tertiary interventional treatment center ($>$ 500 PCI cases per year), by experienced interventional cardiologists, with an experience of $>$200 PCI cases per year and not involved in the present study. The baseline demographics and angiographic characteristics, complications, and laboratory and physical examination data on hospitalization were recorded by systematically reviewing the patients' files.

Primary PCI was usually performed using the percutaneous radial artery approach; the femoral approach was used when an intra-aortic balloon pump was to be inserted. All angiographic data of the patients were assessed using the conventional technique from the catheterization laboratory records. The target artery was defined as being clinically significant when the vessel stenosis was $>50\%$. Blood flow in the infarct-related artery that received only primary PCI was graded based on the basis of the thrombolysis in myocardial infarction grade. A chewable loading dose of 300 mg aspirin and 600 mg clopidogrel was administered before the PCI. Success of the procedure was defined as $<20\%$ stenosis of the infarct-related artery with thrombolysis in myocardial infarction III grade flow, after primary PCI. After primary PCI, all patients were transferred to our cardiac care unit and received standard treatment for STEMI, consisting of 100 mg aspirin, 20 mg atorvastatin, 75 mg clopidogrel once a day.

### 2.4. Blood sampling and measurement of cytokine

Venous blood was collected from all patients within 72 hours after hospitalization. Platelet function was evaluated on the basis of residual platelet reactivity, which was recorded as the value of residual ADP-induced light transmittance aggregometry (LTA) at 72 hours, using a 4-channel AggRAM Remote Analyzer Module System (Helena Laboratories, Beaumont, TX) (Final ADP 20 μ mol/L-induced PA, %). High-sensitivity (hs)-CRP levels were measured using a commercially available immunonephelometric kinetic assay (BN ProSpec; Siemens, Tarrytown, NY) using Cardiophase hs-CRP reagents. The 12-hour fasting serum levels of blood glucose, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured using standard methods. Other biochemical measurements were performed using standard methods.

### 2.5. Definition

Reperfusion time was defined as the symptom-to-balloon time, and the door-to-balloon time was defined as the time between hospitalization and balloon dilation. Diabetes mellitus was diagnosed when a patient was on insulin or on oral hypoglycemic drugs or in patients not on insulin or oral hypoglycemic drugs but with casual plasma glucose level $>11.1$ mmol/L, fasting plasma glucose level $>7$ mmol/L, or glycosylated hemoglobin level $>6.5\%$. Hypertension was diagnosed when the systolic arterial

pressure was ≥ 140 mmHg and/or diastolic arterial pressure was ≥90 mmHg, and when the patient had been on antihypertensive drugs for a long time. Hyperlipidemia was defined as a fasting total serum cholesterol level >5.17 mmol/L, LDL-C level >3.15 mmol/L, or serum triglyceride level >1.70 mmol/L, or if the patient was on lipid-lowering agents owing to a medical history of hypercholesterolemia. Smoking was defined as present regular use of cigarettes or if the patient had quit smoking within the last year. Major adverse cardiac events (MACEs) were defined to include all-cause mortality, cardiovascular mortality, reinfarction, target vessel revascularization, cardiopulmonary resuscitation, advanced heart failure, ventricular fibrillation or ventricular tachycardia (VT or VF) and atrioventricular block. Platelet function related adverse cardiac events (ACEs) were defined as cardiovascular mortality, reinfarction, stroke and major bleeding.

### 2.6. Statistical analysis

Quantitative variables were expressed as mean value ± standard deviation, and qualitative variables were expressed as total number and percentage. The independent two-sample t-test or one-way analysis of variance (ANOVA) with post hoc Student-Newman-Keuls test was used to assess the differences between multiple sets of data. Categorical variables were also compared using the chi-square or Fisher's exact test. Correlations between the residual ADP-induced LTA and hs-CRP were assessed using Pearson's correlation analysis. Independent predictors of MACES were identified using multivariate logistic regression analyses. Statistical significance was indicated when a two-sided p-value was $< 0.05$. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL).

## 3. Results

### 3.1. Baseline characteristics

Two hundred and three patients (134 men and 69 women) were enrolled. The patients were categorized into three groups based on the inflammation levels assessed by tertiles of hs-CRP level on admission. The tertiles of hs-CRP were as defined as per these cut-offs: low tertile (0<hs-CRP<2, mg/L); intermediate tertile (2≤hs-CRP≤10, mg/L); and high tertile (hs-CRP>10, mg/L); these cut-offs were based on those used in the previous studies.[10] The baseline demographic, angiographic and medications characteristics of three groups are presented in Table 1. There were no significant differences in the baseline characteristics. Laboratory characteristics in admission are summarized in Table 2. Levels of residual ADP-induced platelet aggregation, and WBC were observed to be significantly different between the three groups.

### 3.2. Platelet function tests in the different inflammation levels

Correlations between residual ADP-induced platelet aggregation and hs-CRP levels are shown in Figure 1. hs-CRP levels was positively correlated residual ADP-induced platelet aggregation after clopidogrel maintenance dose therapy and in follow-up.

### 3.3. One year follow-up

During the follow-up period of 1 years, Only incidence of stroke as individual endpoint was observed to be significantly different between the three groups. Platelet function related adverse cardiac events was significantly lower in the low tertile group compared to the intermediate tertile and high tertile group (Table 3 and Fig. 2). Following multivariate logistic regression analysis, hs-CRP (odds ratio [OR] = 1.132; 95% confidence interval [CI] 1.009–1.270;, $P = .034$), platelet count (OR = 1.011; 95% CI 1.002–1.020; $P = .012$), ALT (OR = 1.016; 95% CI 1.003–1.030 $P = .019$), ADP-induced LTA in follow-up (OR = 1.113;95% CI 1.062–1.166; $P < .001$) and reperfusion time (OR = 0.997; 95% CI 0.994–1.000; $P = .05$) were demonstrated to be independently associated with MACEs (Table 4).

## 4. Discussion

To the best of our knowledge, this is the first study to investigate the clinical and prognostic implication of antiplatelet effect at different inflammation levels in patients with STEMI, who

**Table 1**

**Baseline demographic, angiographic, and medications categorized by hs-CRP values (n = 203).**

| | 0<hs-CRP<2 mg/L | 2≤hs-CRP≤10 mg/L | hs-CRP>10 mg/L | P |
|---|---|---|---|---|
| No. | 43 | 69 | 91 | NA |
| Age, y | 60.51 ± 9.96 | 59.36 ± 9.42 | 61.03 ± 10.95 | .591 |
| Men, n (%) | 30 (69.77) | 44 (63.77) | 60 (65.93) | .808 |
| Current smoker, n (%) | 12 (27.91) | 27 (39.13) | 33 (36.26) | .472 |
| Hypertension, n (%) | 25 (58.14) | 51 (73.91) | 52 (57.14) | .071 |
| Diabetes, n (%) | 8 (18.60) | 16 (23.19) | 16 (17.58) | .663 |
| Medical history of MI, n (%) | 4 (10.23) | 10 (14.49) | 5 (5.49) | .154 |
| Previous PCI, n (%) | 10 (23.26) | 16 (23.19) | 15 (16.48) | .494 |
| SBP, mmHg | 114.65 ± 24.42 | 111.09 ± 26.99 | 113.04 ± 28.37 | .786 |
| DBP, mmHg | 74.07 ± 14.15 | 72.25 ± 14.13 | 73.89 ± 18.40 | .777 |
| Reperfusion time, min | 295.12 ± 203.67 | 251.30 ± 171.56 | 273.19 ± 189.11 | .474 |
| Stent length, mean, mm | 27.64 ± 7.34 | 25.38 ± 7.03 | 25.40 ± 7.19 | .181 |
| Stent diameter, mean, mm | 3.10 ± 0.42 | 3.01 ± 0.34 | 3.07 ± 0.39 | .44 |
| ACEI/ARB before admission | 5 (11.63) | 7 (10.14) | 10 (10.98) | .968 |
| β-blocker before admission | 9 (20.93) | 13 (18.84) | 7 (7.69) | .055 |
| Intravenous omeprazole | 13 (30.23) | 16 (23.19) | 32 (35.19) | .262 |

Mean values (standard deviation) and % (n) were reported for continuous and categorical variables, respectively. ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blockers, DBP = diastolic blood pressure, MI = myocardial infarction, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, TIMI = thrombolysis in myocardial infarction.

**Table 2**

**Baseline laboratory characteristics in admission.**

| | 0<hs-CRP<2 mg/L | 2≤hs-CRP≤10 mg/L | hs-CRP>10 mg/L | *P* |
|---|---|---|---|---|
| Total cholesterol, mol/L | 4.38±0.79 | 4.19±0.98 | 4.50±0.92 | .104 |
| Triglyceride, mol/L | 1.74±0.83 | 1.63±0.62 | 1.63±0.75 | .676 |
| LDL-cholesterol, mol/L | 2.36±0.70 | 2.63±0.86 | 2.68±0.76[§] | .076 |
| HDL-cholesterol, mol/L | 2.36±0.70 | 2.63±0.86 | 2.88±0.76 | .212 |
| WBC, $\times 10^9$/L | 8.61±3.46 | 8.62±3.15[‡] | 10.18±3.21[§] | .004 |
| Platelet count, $10^9$/L | 206.60±52.94 | 209.13±53.65 | 207.16±62.82 | .968 |
| ALT, U/L | 42.63±35.04 | 49.57±22.64 | 45.92±36.61 | .161 |
| Creatinine, μmol/L | 85.07±22.95 | 81.00±14.90[‡] | 87.15±20.21 | .135 |
| Uric acid, μmol/L | 317.52±92.11 | 314.51±89.48 | 342.20±140.35 | .267 |
| ADP-induced LTA[*], % | 30.90±11.30[†] | 45.72±14.78[‡] | 55.95±14.12[§] | <.001 |

Mean values (standard deviation) and % (n) were reported for continuous and categorical variables, respectively. ADP = adenosine diphosphate, ALT = alanine aminotransferase, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, LTA = light transmittance aggregometry, WBC = white blood cell, WBC = white blood cell.

[*] Platelet function tests after clopidogrel maintenance dose therapy.

[†] Significance between 0<hs-CRP<2 group and 2≤hs-CRP≤10 group.

[‡] significance between 2≤hs-CRP≤10 group and hs-CRP>10 group.

[§] significance between 0<hs-CRP<2 group and hs-CRP>10 group.

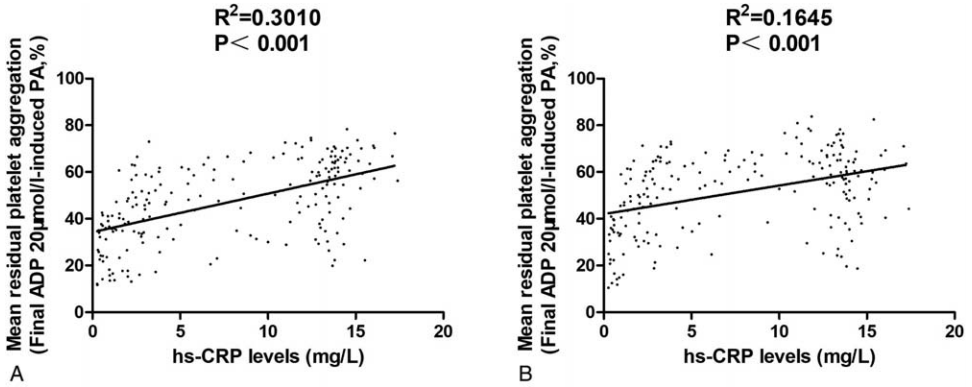


**Figure 1.** Correlations between residual ADP-induced platelet aggregation and hs-CRP levels after clopidogrel maintenance dose therapy (A) and in follow-up (B). ADP = adenosine diphosphate, hs-CRP = high-sensitivity C-reactive protein.

**Table 3**

**Comparison of different hsCRP values in follow-up.**

| | 0<hs-CRP<2 mg/L | 2≤hs-CRP≤10 mg/L | hs-CRP>10 mg/L | *P* |
|---|---|---|---|---|
| Platelet function related ACEs | 4 (9.30) | 7 (10.14) | 22 (24.16) | .022 |
| All-cause mortality, n (%) | 0 (0) | 2 (2.90) | 6 (6.59) | .161 |
| Cardiovascular mortality, n (%) | 0 (0) | 2 (2.90) | 4 (4.40) | .374 |
| Reinfarction, n (%) | 1 (2.33) | 2 (2.90) | 4 (4.40) | .782 |
| TVR, n (%) | 1 (2.33) | 0 (0) | 2 (2.20) | .456 |
| Stroke, n (%) | 1 (2.33) | 1 (1.45) | 8 (8.79) | .07 |
| CPR, n (%) | 0 (0) | 4 (5.80) | 4 (4.40) | .295 |
| Advanced heart failure, n (%) | 1 (2.33) | 3 (4.35) | 8 (8.79) | .265 |
| VT or VF, n (%) | 0 (0) | 2 (2.90) | 4 (4.40) | .374 |
| Atrial fibrillation, n (%) | 1 (2.33) | 3 (4.35) | 9 (9.89) | .181 |
| AVB (Grade I), n (%) | 0 (0) | 0 (0) | 2 (2.20) | .55 |
| Major bleeding, n (%) | 2 (4.65) | 2 (2.90) | 6 (6.59) | .562 |
| ADP-induced LTA, % | 35.80±14.62[*] | 53.36±13.77 | 57.66±15.17[†] | <.001 |

Mean values (standard deviation) and % (n) were reported for continuous and categorical variables, respectively. ACEs = adverse cardiac events, ADP = adenosine diphosphate, AF = atrial fibrillation, AVB = atrioventricular block, CPR = cardiopulmonary resuscitation, LTA = light transmittance aggregometry, TVR = target vessel revascularization, VF = ventricular fibrillation, VT = ventricular tachycardia.

[*] Significance between 0<hs-CRP<2 group and 2≤hs-CRP≤10 group.

[†] significance between 0<hs-CRP<2 group and hs-CRP>10 group.

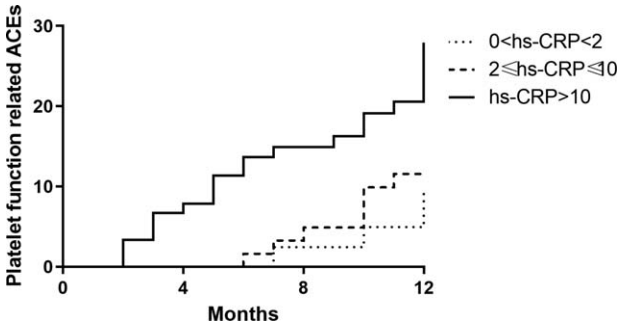


**Figure 2.** Platelet function related ACEs between the three different inflammation levels in follow-up. ACEs = adverse cardiac events.

underwent primary PCI. Our results demonstrated that a severe systemic inflammation is a strong independent predictor for MACEs in follow-up. Systemic inflammatory stimuli with hepatic effects or the products of the hepatic stimulation, such as C-reactive protein (CRP) and a host of other acute-phase reactants has attracted attention.[11] The hs-CRP levels seem to be predictive for cardiovascular events, which have a proficiency-testing program and widely available assays. Although new assays for other inflammatory markers, with accuracy, standardization, and other characteristics that are superior to those of the present assays, might be available in the future, currently, the hs-CRP assay is the best marker in the clinical practice.[11,12]

It has been considered that the sources of inflammation in the setting of ACS are: the inflammatory process at the site of the culprit plaque; the iatrogenic myocardial injury; and resulting from myocardial ischemia and necrosis. The latter is an additional source for a local and systemic inflammatory response.[13] A possible mechanism relates to the heavy infiltration of monocytes/macrophages that is characteristic of a thin fibrous cap on a vulnerable plaque.[14] It has been described that the systemic inflammatory response syndrome can develop in 25% of patients with acute myocardial infarction, and was independently associated with a poor outcome.[15,16] Excessive inflammatory response may be due to imbalance of the immune system caused by infarcted tissue, damaged hemodynamics, and adrenergic activation.[17]

Platelets play a crucial part in genesis and course of acute myocardial infarction (AMI).[18–20] As part of the innate immune system, they facilitate the recruitment of inflammatory cells to lesion sites in vessels, promoting endothelial dysfunction and initiating atherosclerosis-formation.[21,22] Platelet activating factors are a family of pro-inflammatory phospholipids that are synthesized throughout the body by specific stimulation of various cell types such as platelets, macrophages, monocytes, eosinophils, basophils, and endothelial cells.[23] Following atherosclerotic-plaque rupture or fissure, platelets aggregate, and conduce to the formation of an unstable thrombus potentially leading to reduced coronary flow or distal embolization.[24] Thus, antiplatelet therapy is the mainstay of treatment for patients with cardiovascular disease. Dual-antiplatelet therapy with aspirin and clopidogrel significantly reduces atherothrombotic events and improves long-term clinical outcomes in patients who undergo PCI.[25] However, despite dual-antiplatelet therapy, some patients still develop recurrent cardiovascular ischemic events, including stent thrombosis.[4] In our study, the clinical outcome of aspirin and clopidogrel showed that it achieved a worse inhibition of platelet aggregation and exerted a unstable antiplatelet effect in the higher hs-CRP levels. Use of anti-inflammatory agents after ACS may become a strategy to reduce the risk of recurrence among patients with persistently high concentrations of hs-CRP after ACS.[26] The inflammatory hypothesis of atherothrombosis was recently confirmed in the Canakinumab Antiinflammatory Thrombosis Outcome Study.[27] An anti-interleukin-1β antibody given to patients with a recent myocardial infarction and a hs-CRP level of ≥2 mg/L led to a 15% reduction of cardiovascular events.[28] Further studies are necessary in the future to address whether anti-inflammatory approaches can lead to decreased platelet reactivity and thus aid in the improvement of antiplatelet drug efficacy.

**Table 4**

**Multivariate regression analysis for predicting in-hospital MACE.**

| | OR | 95% CI | P |
|---|---|---|---|
| WBC | 0.965 | 0.834–1.116 | .631 |
| hs-CRP | 1.132 | 1.009–1.270 | .034 |
| Platelet count | 1.011 | 1.002–1.020 | .012 |
| ALT | 1.016 | 1.003–1.030 | .019 |
| Creatinine | 0.976 | 0.946–1.007 | .131 |
| Uric acid | 0.997 | 0.992–1.002 | .258 |
| ADP-induced LTA in admission | 1.022 | 0.988–1.058 | .201 |
| ADP-induced LTA in follow-up | 1.113 | 1.062–1.166 | <.001 |
| LDL-cholesterol | 0.796 | 0.233–2.726 | .717 |
| Reperfusion time | 0.997 | 0.994–1.000 | .05 |

ADP = adenosine diphosphate, ALT = alanine aminotransferase, CI = confidence interval, hs-CRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, LTA = light transmittance aggregometry, OR = odds ratio, WBC = white blood cell, WBC = white blood cell.

### 4.1. Limitations

The present study has some limitations. First, the number of patients was relatively small. Second, there is a possibility of significant referral bias because of the retrospective and single-center design of the study. Third, data on long-term events and follow-up were relatively insufficient and are planned to be included in a future study.

### 4.2. Future directions

In the future, a randomized, multicenter, comparative study is warranted to quantitatively assess systemic inflammatory state on antiplatelet effect in STEMI patients undergoing PCI.

## 5. Conclusions

Platelet inhibition function of clopidogrel decreases progressively at different inflammation levels. The different levels of hs-CRP were demonstrated to be associated with MACEs at follow-up assessments. The presence of hs-CRP was not only significantly associated with platelet inhibition function, but was also a prognostic marker in STEMI.

## Author contributions

**Data curation:** Hao Wang.
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**Validation:** Lanchun Sun.
**Writing – original draft:** Hairui Jiang.
**Writing – review & editing:** Hairui Jiang.

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