Association of platelet-to-lymphocyte count ratio with myocardial reperfusion and major adverse events in patients with acute myocardial infarction: a two-centre retrospective cohort study

Ailifeire Maimaiti, Yang Li, Yong-Tao Wang, Xiang Yang, Xiao-Mei Li, Yi-Ning Yang, Yi-Tong Ma

ABSTRACT

Objective Insufficient myocardial reperfusion for patients with acute myocardial infarction (AMI) during primary percutaneous coronary intervention (PPCI) has a great influence on prognosis. The aim of this study was to investigate the association of the platelet-to-lymphocyte ratio (PLR) with myocardial reperfusion and in-hospital major adverse cardiac events (MACEs) in patients with AMI undergoing PPCI.

Design Retrospective cohort study.

Setting Patients and researchers from two tertiary hospitals.

Participants A total of 445 consecutive AMI patients who underwent PPCI between January 2015 and December 2017 were enrolled. Patients were divided into two groups based on the PLR value: patients with PLR values in the third tertile were defined as the high-PLR group (n=150), and those in the lower two tertiles were defined as the low-PLR group (n=295). Explicit criteria for inclusion and exclusion were applied.

Interventions No interventions.

Primary and secondary outcome measures Primary outcome measures were defined as cardiovascular death, reinfarction or target vessel revascularisation. Secondary outcome measures were defined as stroke, non-lethal myocardial infarction, ventricular tachycardia/ventricular fibrillation and in-hospital mortality.

Results The high-PLR group had insufficient myocardial perfusion (23% vs 13%, p=0.003), greater postprocedural thrombolysis in myocardial infarction flow grade (0–2) (17% vs 10%, p=0.037), greater myocardial blush grade (0–1) (11% vs 4%, p=0.007) and higher B-type natriuretic peptide (BNP) (614±600 vs 316±429, p<0.001) compared with the low-PLR group. Multivariate logistic regression analysis indicated that the independent risk factors for impaired myocardial perfusion were high PLR (OR 1.256, 95% CI 1.056 to 1.670, p=0.015), the high-PLR group had significantly more MACEs (43% vs 32%, p=0.029).

Conclusions This study suggested that high PLR and BNP were independent risk factors for insufficient myocardial reperfusion in patients with AMI. Higher PLR was related to advanced heart failure and in-hospital MACEs in patients with AMI undergoing PPCI.

Strengths and limitations of this study

- The first multicentre retrospective cohort study to examine the relationship between platelet-to-lymphocyte ratio (PLR) and myocardial reperfusion.
- We only included patients with left anterior descending branch vascular occlusion among patients with acute myocardial infarction.
- We grouped the population according to PLR value.
- Our study population was small, and a larger sample size will be required for prospective clinical studies.
- This study focused on in-hospital screening and adverse events among participants and lacked long-term follow-up results.

INTRODUCTION

Acute myocardial infarction (AMI) is one of the leading causes of death worldwide.1 Emergency primary percutaneous coronary intervention (PPCI) is the first choice for patients with AMI to restore blood flow. Studies have shown that early reperfusion can effectively reduce the myocardial infarct (MI) size and restore heart function.2 Although blood flow of the occluded vascular artery is restored (thrombolysis in myocardial infarction (TIMI) grade 3 after PPCI), many patients still have insufficient myocardial perfusion.3 This could result in severe myocardial ischaemia, malignant arrhythmia, haemodynamic deterioration and other adverse outcomes.4-7 The insufficient myocardial perfusion is mainly due to microvascular obstruction (MVO).8 The main mechanism of MVO is ischaemia-reperfusion (IR) injury to coronary arteries. This injury involves multiple pathophysiological factors (calcium overload, oxidative stress, inflammation, and mitochondrial dysfunction) and multiple players (cardiomyocytes, microvasculature,
inflammatory cells and platelets), making it a complex system. Therefore, it is necessary to find the risk factors that affect myocardial reperfusion.

Platelet activation plays a critical role in the formation of acute thrombosis of coronary arteries. Increased platelet count is associated with increased mortality in patients with AMI. Previous studies have found that platelet-to-lymphocyte ratio (PLR) can be used as a predictor of long-term mortality and is an independent risk factor for no reflow after PPCI and increased mortality in hospital, and the increase in PLR is positively correlated with the 6-month all-cause mortality in ST-elevation myocardial infarction (STEMI) patients.

Studies have shown that the presence of MVO after PPCI as assessed by TIMI flow post-PPCI and myocardial blush grade (MBG) have all strongly been linked with worse outcomes in patients with AMI. The index of microcirculatory resistance (IMR) is a parameter for quantifying microcirculatory resistance. There are significant differences in the microvascular blood flow between the left anterior descending branch (LAD) and left circumflex branch, as well as the right coronary artery. Although previous studies have investigated the relationship between PLR and AMI, they have ignored the influence of myocardial ischaemic adaptation in different coronary arteries on myocardial reperfusion. To avoid the influence of this variation on the results, we only included AMI patients with proximal LAD blocking. Thus, this study intends to explore the effects of PLR on myocardial reperfusion and adverse events in patients with AMI and to provide guidance for the improvement of reperfusion therapy.

MATERIAL AND METHODS

Participants

This study is a multiple-centre retrospective cohort study. A total of 445 consecutive patients with AMI from two hospitals seen between January 2015 and December 2017 were reviewed. We analysed the clinical and angiographic data of consecutive patients diagnosed with AMI. The inclusion criteria were as follows: (1) they were eligible for the diagnostic criteria of STEMI; (2) there was ≤12 hours from the onset of symptoms to PPCI; (3) the results of angiography confirmed that the infarcted blood vessel was the proximal LAD; and (4) complete clinical data were collected. The exclusion criteria were as follows: (1) active infection; (2) history of systemic infectious diseases in the previous 2 weeks; (3) malignant tumour; (4) hepatitis; (5) chronic tuberculosis history; (6) history of heart failure; (7) history of percutaneous coronary intervention (PCI); and (8) long-term oral antplatelet or statin drugs. All patients received 300 mg of aspirin and 600 mg clopidogrel or 180 mg of ticagrelor before PPCI.

This study protocol conformed to the principles and guidelines of the Declaration of Helsinki. All participants or their close relatives provided written informed consent for participation before data collection.

Clinical data collection

Clinical data were collected from the medical records of hospitals by two physicians independently. Basic information: hospital number, telephone number and so on; and medical history and personal history: hypertension and grade, diabetes, hyperlipidaemia, stroke history, prehospital medication history and smoking history. Venous blood samples were drawn before PPCI. Blood test parameters and other measurements were determined by standard laboratory methods. Records of blood routine before PPCI: biochemical measurements, myocardial enzymes and B-type natriuretic peptide (BNP). Cardiac ultrasound was done after PPCI. The TIMI and MBG grades of patients were recorded by two interventional doctors in a blind manner. The number of diseased blood vessels, sizes of the stents, number of clots and use of tirofiban were determined by operation records.

Clinical definitions

The study population was divided into tertiles according to the PLR values at admission. High PLR (group 1, n=150) was defined as a value in the third tertile (≥165.33) and low PLR (group 2, n=295) as a value in the lower two tertiles (<165.33). Cardiovascular mortality was defined as unexplained sudden death, death due to AMI or malignant arrhythmia. Reinfarction was defined based on the universal definition of MI guidelines. Non-lethal myocardial infarction was defined as type1 or type2 myocardial infarction according to guidelines. Major adverse cardiac events (MACEs) were defined as cardiovascular death, reinfarction or target vessel revascularisation. Insufficient myocardial perfusion was defined as a post-operative TIMI grade less than 3 or a TIMI grade of 3 but with an MBG classification less than 2.

Statistical analysis

All data were analysed by SPSS V.24.0 for Windows. Continuous variables are presented as the mean±SD. If two groups of quantitative data were consistent with the normal distribution, then they were compared by the independent sample t test. If they did not fit the normal distribution, then they were compared by Wilcoxon’s rank test. Two groups of count data were compared by the χ2 test or, if the frequency was lower than 5, Fisher’s exact test. A backward stepwise multivariate logistic regression analysis was performed to identify independent predictors of insufficient myocardial perfusion. Statistical significance was defined as p<0.05.

Patient and public involvement

Participants were not involved in the study design, recruitment, implementation, article writing or data collection. Patients did not incur additional medical burden in the study. The results of the study will be disseminated to
all patients and medical institutions through academic conferences, news reports and health publicity.

RESULTS

The baseline characteristics of the two groups are presented in table 1. A total of 445 patients (136 from one medical centre, 309 from the other) were eligible. High-PLR patients were admitted to hospital with a significantly higher Killip class than low-PLR patients (86% vs 74.6%, p=0.006). The left ventricular ejection fraction of patients in the high-PLR group was significantly lower than that in the low-PLR group (34.8%±6.0 vs 37.4±7.1, p=0.006). Gender, hypertension, diabetes, history of stroke, smoking, hyperlipidaemia and time from symptom onset to intervention were not significantly different between the two groups (p>0.05).

The laboratory data of the two groups are presented in table 2. The preoperative white cell count (WCC) (9.5±4.1 vs 9.0±3.2, p=0.044) and red cell distribution width (RDW) (13.6±3.1 vs 13.2±2.3, p=0.026) in the low-PLR group were significantly lower. The peak values of BNP (614±600 pg/mL vs 316±429 pg/mL, p<0.001) and alanine aminotransferase (64.4±84.4 U/L vs 52.1±60.0 U/L, p=0.003) was significantly higher than in the high-PLR group. There was no significant difference in neutrophil count, monocyte count, haemoglobin, creatinine, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, C reactive protein, peak cardiac troponin T (cTnT) or peak creatine kinase-myocardial band.

The angiographic and procedural characteristics of the two groups are presented in table 3. In the high-PLR group, the average implanted stent diameter was significantly smaller (2.93±0.47 vs 2.96±0.40, p=0.015), thrombus aspiration was higher (64% vs 52%, p=0.015) and platelet count was higher (264.2±85.9 vs 203.5±74.6, p=0.006). The patients in the high-PLR group had significantly lower postprocedural TIMI grade (17% vs 10%, p=0.037) and MBG stage (11% to 4%, p=0.007) after PCI. In the high-PLR group, the incidence of insufficient myocardial perfusion was significantly increased (23% vs 13%, p=0.003). There was no significant difference in the number of diseased vessels, the number of stents used, the average implanted stent length or the use of tirofiban. The MACEs in the high-PLR group were significantly more common (43% vs 32%, p=0.004). There was no significant difference in non-lethal myocardial infarction, stroke, in-hospital mortality or ventricular tachycardia/ventricular fibrillation (table 4).

We performed univariate logistic regression analysis of factors affecting the sufficiency of myocardial perfusion, and the results showed that high BNP (OR 1.329, 95% CI 1.057 to 1.672, p=0.009) and high PLR (OR 1.254, 95% CI 1.001 to 1.571, p=0.051) contributed to the insufficient myocardial perfusion of PPCI patients. We included all factors to perform multivariate logistic regression analysis. We found that high PLR (OR 1.256, 95% CI 1.005 to 1.579 (p=0.056) and high BNP (OR 1.328, 95% CI 1.056
to 1.670 (p=0.015) were independent risk factors for insufficient myocardial perfusion (table 5).

**DISCUSSION**

In our study, after controlling for the effects of different coronary artery lesions on insufficient myocardial reperfusion, it was found that high PLR and BNP were independent risk factors for insufficient myocardial reperfusion after PPCI for patients with AMI. Earlier studies have shown that high PLR is significantly correlated with MACEs, Killip grade, ejection fraction (EF) value, platelet count, RDW, length/diameter of stent implantation and thrombus aspiration in patients with AMI.

The pathophysiological mechanism of insufficient myocardial reperfusion is that microvascular blood flow is hindered by MVO. The aetiological mechanisms are that: (1) platelet activation and adhesion, which increase cell death and aggregation, can affect myocardial flow; (2) increased endothelial permeability and subsequent recruitment of inflammatory cells into the site of infarction can lead to acute IR injury; (3) mitochondrial dysfunction caused by calcium overload and Receiver Operating Characteristic (ROS) accumulation can also lead to IR injury. PLR as an index contains information on platelet and lymphocyte counts in patients with AMI. It is more significant in predicting insufficient myocardial reperfusion after PPCI in patients with AMI than platelet or lymphocyte count. Platelets play a key role in the pathogenesis of AMI through the formation of platelet–fibrin complexes. Increasing platelet count has been associated with the occurrence of AMI. Activating platelets adhere to vascular endothelial cells and produce inflammatory cytokines, leading to mononuclear cell adhesion and migration, accelerating the progression of atherosclerotic plaques. These activating adhesion molecules and chemokines promote the activation of white cell count and produce reactive oxygen species and matrix metalloproteinases, causing plaque instability in atherosclerotic plaques. Gary et al found that increasing platelet volume can change blood viscosity and promote inflammation. Temiz et al found that increasing platelet activity was associated with a high incidence of cardiovascular events in hospital. These studies indicated that the increase in platelet count was significantly correlated with the occurrence of AMI and poor prognosis.

During the pathogenetic process of AMI, lymphocytes enter the IR-injured myocardial tissue and secrete interleukin-10 to inhibit the inflammatory response. The lymphocytes also secrete tissue factor (TF) and mmp-1 to promote the coagulation reaction. Studies have shown a correlation between decreased lymphocyte count and increased frequency of cardiovascular events in patients with AMI. A decrease in lymphocyte count caused by stress can increase the incidence of death in patients with AMI. Therefore, PLR may become a new indicator of thrombus formation, inflammatory state and short-term and long-term adverse outcomes of patients with AMI.

Based on the TIMI class after PCI, Yildiz et al divided acute STEMI patients into two groups: no-reflow and reflow. An analysis of routine blood examination before PCI and myocardial reperfusion showed that increasing the PLR value was an independent risk factor for the prediction of no-reflow in acute STEMI patients. Ayca et al used ROC curve analysis to show that a PLR >137 predicted adverse events for patients who had undergone...
PPCI, with a specificity of 67% and a sensitivity of 63%. Kurtul et al. found that PLR was significantly associated with the severity and complexity of coronary atherosclerosis in ACS patients who underwent PPCI. A higher PLR value was an independent predictor of an intermediate to high SXscore. Preintervention PLR was a strong and independent predictor of slow flow/no-reflow after PPCI in patients with acute STEMI. Ugur et al. found that higher PLR was associated with an increased risk for in-hospital adverse outcomes and 6-month all-cause mortality with STEMI after PPCI. PLR should be incorporated into the clinical practice of risk stratification for patients admitted with STEMI who undergo primary PCI.

Our study found that high BNP was an independent risk factor for insufficient myocardial reperfusion after PPCI in patients with AMI. BNP is a quantitative marker of heart failure that is significantly correlated with left ventricular systolic function. During the process of hypoxia, oedema-tosis and necrosis at the myocardial infarction site, cardiomyocytes can produce BNP through the transcription of the Natriuretic peptide precursor B (NPPB) gene in the endoplasmic reticulum. When occlusion of the proximal LAD causes hypoxia and oedema of myocardial cells, BNP will be secreted in large quantities. Elevated BNP leads to plasma concentrations of angiotensin II and endothelin-1 by activating the renin angiotensin system. This will further aggravate the reperfusion of ischaemic myocardium at the infarct site. BNP has been shown to be an independent risk factor for IR injury in ST-segment elevation AMI patients. Studies have shown that the increased secretion of BNP during myocardial ischaemia is mainly regulated by the PI3K/Akt/p70s6k signalling pathway, which has a protective effect on the myocardium. This change is an adaptation of myocardial cells to ischaemia. Therefore, the BNP level can reflect the severity of myocardial ischaemia, which is strongly related to insufficient myocardial reperfusion. This study also found that thrombus aspiration was associated with insufficient myocardial reperfusion in patients with AMI. At present, the role of thrombus aspiration in PPCI patients is still controversial. The TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) study showed that thrombus aspiration in PPCI patients did not reduce the total mortality at 30 days or 1 year. The TOTAL (ThrOmbectomy with PCI versus PCI ALone in Patients with STEMI) study showed that the main endpoints followed up for 180 days (6.9% vs 7.0%; p=0.86) and 1 year (7.8% vs 7.8%; p=0.991) were not significantly different between the thrombus aspiration group and non-thrombus aspiration group. In addition, a study showed that thrombus aspiration did not improve myocardial reperfusion in patients with long-term ischaemia, small infarction area and light thrombosis. Hoole et al. observed changes in IMR during PPCI and found that patients with relatively light thrombosis were prone to distal embolisation after thrombus aspiration, which would lead to microcirculation injury.

Limitations of this study: (1) the sample size of this study was small, and prospective clinical studies with larger samples are needed to confirm the findings. (2) This study did not evaluate the decline in the ECG ST segment after emergency PCI, but a former study showed that the ST fallback was consistent with the MBG grading results. (3) Long-term follow-up was not conducted, and further study is needed to evaluate the long-term prognosis of patients with AMI.

### Table 5: The independent predictors of insufficient myocardial reperfusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age</td>
<td>1.013 (0.983 to 1.033)</td>
<td>0.202</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.018 (0.999 to 1.278)</td>
<td>0.948</td>
</tr>
<tr>
<td>Killip class ≥II</td>
<td>1.167 (0.620 to 2.198)</td>
<td>0.632</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.985 (0.948 to 1.023)</td>
<td>0.436</td>
</tr>
<tr>
<td>WCC</td>
<td>1.049 (0.983 to 1.119)</td>
<td>0.151</td>
</tr>
<tr>
<td>Platelet</td>
<td>1.002 (0.999 to 1.005)</td>
<td>0.037</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>0.766 (0.542 to 1.082)</td>
<td>0.130</td>
</tr>
<tr>
<td>RDW</td>
<td>1.016 (0.928 to 1.112)</td>
<td>0.734</td>
</tr>
<tr>
<td>ALT</td>
<td>0.999 (0.995 to 1.003)</td>
<td>0.576</td>
</tr>
<tr>
<td>Stent length</td>
<td>1.007 (0.971 to 1.044)</td>
<td>0.710</td>
</tr>
<tr>
<td>Stent diameter</td>
<td>1.168 (0.643 to 2.124)</td>
<td>0.610</td>
</tr>
<tr>
<td>Thrombus aspiration</td>
<td>1.123 (0.673 to 1.872)</td>
<td>0.657</td>
</tr>
<tr>
<td>BNP</td>
<td>1.329 (1.057 to 1.672)</td>
<td>0.015</td>
</tr>
<tr>
<td>PLR</td>
<td>1.254 (1.001 to 1.571)</td>
<td>0.051</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; BNP, brain natriuretic peptide; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; WCC, white cell count.

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CONCLUSION
In conclusion, our study showed that high PLR and BNP on hospital admission could be used as independent risk factors for predicting insufficient myocardial reperfusion after PPCI in AMI patients with proximal LAD occlusion. High PLR is associated with higher MACE incidence during hospitalisation. PLR and BNP are convenient and inexpensive to detect in clinical practice. Clinicians can grade the risk of insufficient myocardial reperfusion in patients with AMI according to the PLR value.

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Contributors
AM and YL contributed equally to this work. AM and YT-W were responsible for the statistical analysis and write this paper. YL and XY provided the database. X-M and YY critically revised the paper for important intellectual content. YT-W was accountable for all aspects of the work and fund collection.

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Competing interests
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Data are available on reasonable request.

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