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Association of platelet to lymphocyte count ratio with myocardial reperfusion and major adverse events in patients with acute myocardial infarction

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ABSTRACT:

Objective: The aim of this study was to investigate the association of platelet to lymphocyte ratio (PLR) with myocardial reperfusion and in-hospital major adverse events（MACE） in patients with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (PPCI).

Design: Retrospective cohort study

Setting: Patients and researchers came 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 was defined as the high PLR group (n=150) and those in the lower 2 tertiles were defined as the low PLR group (n=295). Explicit criteria for inclusion and exclusion were made.

Interventions: No interventions

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

Results: The high PLR group had significantly higher Killip grade (86% vs. 74.6%, P=0.006), Ejection fraction (34.8%±6.0vs.37.4%±7.1, P=0.006), insufficient myocardial perfusion (23% vs. 13%, P=0.003) and lower postprocedural TIMI flow (17% vs. 10%, P=0.037), lower MBG grade (11% vs. 4%, P=0.007) compared with the low PLR. Multivariate logistic regression analysis indicated that the independent risk factors of impaired myocardial perfusion were

PLR (OR 1.002, 95% CI 1.000-1.005, P=0.056) and BNP (OR 1.001, 95% CI 1.000-1.001, P=0.015). The high PLR group had significantly higher MACEs (43% vs. 32%, P=0.029).

Conclusions: The study suggested that high PLR was an independent risk factor of impaired myocardial reperfusion in AMI patients. Higher PLR is related to advanced heart failure and in-hospital MACE in patients with AMI undergoing PPCI.

Trial registration: No registration

Keywords: Platelet to lymphocyte ratio; PLR; insufficient myocardial perfusion; acute myocardial infarction; AMI

Strengths and limitations of this study

1. Routine blood parameters were associated with insufficient myocardial perfusion in patients with acute myocardial infarction and adverse events in hospital.
2. PLR is an independent risk factor for insufficient myocardial perfusion in patients with acute myocardial infarction.
3. Sample size of this study was small, and prospective clinical studies with larger samples are needed to confirm the findings.
4. Long-term follow-up of this study was not conducted, and further study was needed to evaluate PLR on long-term prognosis of patients with AMI.

Introduction

Acute myocardial infarction (AMI) is one of the leading causes of death worldwide (1). Emergency coronary intervention (PPCI) is the first choice for AMI patients to recover the blood flow of occlusive coronary artery. Studies have shown that the early reperfusion can effectively reduce the area of myocardial infarction and restore the heart function (2). Although the blood flow of the occlusive vascular restored (TIMI grade is 3 after PPCI), many patients still had insufficient myocardial perfusion (3). This could result in severe myocardial ischemia, malignant arrhythmia, hemodynamic deterioration and other adverse outcomes (4-7). Therefore, it is necessary to find the risk factors that affect myocardial perfusion.

Platelets play a critical role in the formation of acute thrombosis of coronary arteries (8). Increased platelet count was associated with increased infarction area and adverse cardiovascular outcomes in AMI patients (9). Lymphocyte can inhibit

ischemia-reperfusion injury in AMI, and its counting increasing is associated with inflammatory response decreasing in infarction area (10-11). Lower lymphocyte count was associated with higher mortality in AMI (12). Previous studies have found that PLR can be used as a predictor of long-term mortality, an independent risk factor for non-recurrent flow after PPCI and increased mortality in hospital, and the increase of PLR is positively correlated with the 6-month all-cause mortality in STEMI patients (13-16).

Study on the effect of PLR on myocardial reperfusion and adverse events in patients with acute myocardial infarction have not be done. Thus, this study intends to explore the effects of PLR on myocardial reperfusion and adverse events in patients with acute myocardial infarction and to provide guidance for the improvement of reperfusion therapy.

Material and Methods

Patient and public involvement

This study is a multiple-center, retrospective, cohort study. A total of 445 consecutive AMI patients from two hospitals between January 2015 and December 2017 were respectively reviewed. We analyzed the clinical and angiographic data of consecutive patients diagnosed with acute myocardial infarction. The inclusion criteria as follows: 1. Eligible for the diagnostic criteria of STEMI.; 2. Within 12 hours from the onset of symptoms to PPCI; 3. The results of angiography confirmed that the infarcted blood vessels were left anterior descending (LAD). 4. Complete clinical data collection; The exclusion criteria as follows: 1. Active infection; 2.

History of systemic infectious diseases in two weeks; 3. Malignant tumor; 4. Hepatopathy; 5 chronic tuberculosis history; 6. History of heart failure; 7. History of PCI; 8. Long-term oral antiplatelet and statin drugs; All patients received 300 mg of aspirin and 600 mg clopidogrel or 180 mg of tigrel before PPCI. This study protocol was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Xinjiang Medical University and 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 collection was down by two physicians from electronic medical record system independently. Basic information: hospital number, telephone number, etc.; Previous medical history and personal history: hypertension and grade, diabetes, hyperlipidemia, stroke history, prehospital medication history, 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, Brain natriuretic peptide (BNP), cardiac ultrasound after PPCI; Two Interventional physicians read coronary angiography disc by blind method and record the rate of TIMI blood flow and myocardial blush grade (MBG) classification immediately after operation; The number of diseased blood vessels, size of the stents, clots, 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 universal definition of myocardial infarction (MI) guideline [17]. Non-lethal myocardial infarction was defined as Type1 and Type2 myocardial infraction according to guideline [17]. Major adverse cardiac events (MACEs) were defined as cardiovascular death, reinfarction, or target–vessel revascularization.

Insufficient myocardial perfusion was defined as a postoperative TIMI stage is grade less than 3, or the TIMI stage is grade 3, but the MBG classification is less than 2 (18).

Statistical analysis

All data were analyzed by SPSS V 24.0 for Windows. Continuous variables are presented as mean ± standard deviation. If the two groups of quantitative data are consistent with the normal distribution, then the independent sample t test would be performed. if it doesn't fit the normal distribution, then the Wilcoxon's rank test would be performed. The comparison between two groups of count data by chi-square test. But, if the frequency is lower than 5, Fisher's exact test would be performed. A backward stepwise multivariate logistic regression analysis was performed to identify independent predictors of insufficient myocardial perfusion. Receiver operating characteristic (ROC) analyses was performed to detect the cut off value of PLR in the

prediction of insufficient myocardial perfusion. Statistical significance was defined as $P < 0.05$.

Results

The baseline characteristics of the two groups were presented in table 1. A total of 445 patients (136 from one medical center,254 from the other) were eligible. The age of patients in high PLR group was higher than patients in low PLR group (62.2±14.1 vs. 59.5±12.2, P=0.117), but no statistical difference was found. High PLR patients were admitted to the 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, hyperlipidemia, and symptom onset to intervention between two groups were not statistically significant different (P > 0.05).

Table 1. Baseline clinical characteristics of patients

	Low PLR (n=295)	High PLR (n=150)	*P* value
Age , years x±s	59.5±12.2	62.2±14.1	0.117
Male , n(%)	196 (66.4%)	93 (62%)	0.335
Hypertension , n(%)	160 (54.2%)	80 (53.3%)	0.856
Diabetes , n(%)	80 (27.1%)	33 (22%)	0.241
Stroke , n(%)	20 (6.8%)	13 (8.7%)	0.473
Smoking , n(%)	130 (44.1%)	57 (38%)	0.220
Hyperlipidaemia , n(%)	16 (5.4%)	6 (4%)	0.513

Killip class ≥II，n(%)	220（74.6%）	129（86%）	0.006
Ejection fraction, x%±s	37.4±7.1	34.8±6.0	0.006
Symptom onset to intervention (hours)	7.15±4.80	7.00±4.83	0.608
≥6	131(44.4%)	66(44.0%)	0.935

The laboratory data of the two groups were presented in Table 2. Preoperative White blood cell count(WBC) (9.0 ± 3.2 vs. 9.5 ± 4.1, P=0.044) and red cell distribution width (RDW) (13.2±2.3 vs. 13.6±3.1, P=0.026) in the low PLR group was significantly lower. The peak value of BNP (316 ± 429 pg/ ml VS.614 ± 610 pg/ml, P < 0.001) and alanine aminotransferase (ALT) (52.1±60.0 U/Lvs. 64.4±84.4 U/L, P=0.003) was significantly higher than that in the high PLR group. There was no statistical difference in neutrophils count, monocyte count, hemoglobin, creatinine, total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), C-reactive protein (CRP), peak cTnT, peak CK-MB.

Table 2. Comparison of laboratory results

	Low PLR（n=295）	High PLR（n=150）	*P* value
WBC×10^9/L(x±s)	9.0±3.2	9.5±4.1	0.044
Neutrophil×10^3/L(x±s)	6.5±6.2	8.1±6.8	0.171
Monocyte×10^3/L(x±s)	1.0±4.6	0.5±0.3	0.167
Hemoglobin（g/L，x±s）	135.8±23.0	129.6±23.7	0.524
RDW（%，x±s）	13.2±2.3	13.6±3.1	0.026
ALT (U/L，x±s)	52.1±60.0	64.4±84.4	0.003
Creatinine (μmol/L，x±s)	78.4±36.3	76.3±30.8	0.336
Total cholesterol （μmol/L，x±s）	4.1±1.1	4.1±1.0	0.198

HDL-cholesterol （umol/L，x±s）	1.0±0.5	1.1±0.3	0.446
LDL-cholesterol （μmol/L，x±s）	2.5±0.9	2.5±0.8	0.880
CRP（mg/L，x±s）	16.7±26.6	17.8±32.0	0.611
Peak cTnT（U/L，x±s）	4.9±3.8	5.7±4.0	0.236
Peak CK-MB（U/L，x±s）	226±335	242±382	0.498
BNP（pg/ml，x±s）	316±429	614±600	<0.001

WBC: White blood cell count; RDW: Red cell distribution width; ALT: alanine aminotransferase; HDL: High density lipoprotein; LDL: Low density lipoprotein; CRP:C-reactive protein; CK-MB: Creatine kinase-myocardial band; BNP: Brain natriuretic peptide

The angiographic and procedural characteristics of two groups were 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), and thrombus aspiration was relatively higher (64% vs. 52%, P=0.015). The patients in 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 and the number of stent use, the average implanted stent length, the use of tirofiban. The MACE in the high PLR group was significantly higher (43% vs. 32%, P=0.004). There was no significant difference non-lethal myocardial infarction, Stroke, In-hospital mortality and Ventricular tachycardia/ventricular fibrillation (Table 4).

Table3. Angiographic and procedural characteristics of patients

	Low PLR（n=295）	High PLR（n=150）	*P* value
Number of diseased vessel			
1，n(%)	103（35%）	54（36%）	0.821
≥2，n(%)	192（65%）	96（64%）	
Number of stent use			
1，n(%)	119（40%）	66（44%）	0.459
≥2，n(%)	176（60%）	84（56%）	
Stent length, average (mm，x±s)	25.9±6.3	26.4±8.1	0.067
Stent diameter, average (mm，x±s)	2.96±0.40	2.93±0.47	0.015
Tirofiban use，n(%)	271（92%）	135（90%）	0.511
Thrombus aspiration，n(%)	153（52%）	96（64%）	0.015
Postprocedural TIMI grade			
0-2，n(%)	29(10%)	25(17%)	0.037
3，n(%)	266(90%)	125(83%)	
MBG grade			
0,1，n(%)	12(4%)	16(11%)	0.007
2,3，n(%)	283(96%)	134(89%)	
Insufficient myocardial reperfusion	37(13%)	35(23%)	0.003

TIMI: thrombolysis in myocardial infarction; MBG: Myocardial blush grades

Table4. In-hospital cardiac events and complications

	Low PLR（n=295）	High PLR（n=150）	*P* value
MACE	95（32%）	64（43%）	0.029

Non-lethal myocardial infarction，n(%)	7（2%）	6（4%）	0.335
Stroke，n(%)	18（6%）	11（7%）	0.619
In-hospital mortality，n(%)	2（1%）	4（3%）	0.186
Ventricular tachycardia/ventricular fibrillation，n(%)	69 (23%)	42 (28%)	0.288

MACE: Major adverse cardiac events (cardiovascular death, reinfarction, target–vessel revascularization)

We performed univariate Logistic regression analysis of factors affecting insufficient myocardial perfusion, the result showed that BNP (OR 1.001, 95% CI 1.000 to 1.001 (P = 0.005) and PLR (OR 1.003, 95% CI 1.000 to 1.005 (P = 0.010) can affect the insufficient myocardial perfusion of PPCI patients. We had included all factors to perform multivariate Logistic regression analysis. We found that PLR (OR 1.009, 95% CI 1.004 to 1.009 (P = 0.001) and peak CK - MB (OR 1.002, 95% CI 1.001 to 1.002 (P = 0.067) were independent factors of insufficient myocardial perfusion (Table 5).

Table5. The independent predictors of insufficient myocardial reperfusion

	Univariate		Multivariate	
Variable	OR（95%CI）	*P* value	OR（95%CI）	*P* value
Age	1.013 (0.983-1.033)	0.202	1.008 (0.988-1.029)	0.440
Male gender	1.018 (0.599-1.728)	0.948	1.005 (0.556-1.818)	0.987
Killip class ≥II	1.167 (0.620-2.198)	0.632	0.982 (0.460-2.098)	0.963
Ejection fraction	0.985 (0.948-1.023)	0.436	0.986 (0.947-1.027)	0.488
WBC	1.049 (0.983-1.119)	0.151	1.044 (0.977-1.116)	0.206
RDW	1.016 (0.928-1.112)	0.734	1.008 (0.911-1.115)	0.877
ALT	0.999 (0.995-1.003)	0.576	0.997 (0.993-1.002)	0.268
Stent length	1.007 (0.971-1.044)	0.710	1.005 (0.970-1.042)	0.766
Stent diameter	1.168 (0.643-2.124)	0.610	1.058 (0.580-2.029)	0.799
Thrombus aspiration	1.123 (0.673-1.872)	0.657	1.060 (0.626-1.798)	0.828
BNP	1.001 (1.000-1.001)	0.008	1.001 (1.000-1.001)	0.015
PLR	1.003 (1.000-1.005)	0.021	1.002 (1.000-1.005)	0.056

WBC: White blood cell count; RDW: Red cell distribution width; ALT: alanine aminotransferase: BNP: Brain natriuretic peptide; PLR: Platelet to lymphocyte ratio.

Discussion

Some of the AMI patients still had insufficient myocardial perfusion after receiving PPCI therapy, which would result in poor cardiac function recovery and chronic heart failure (19). Insufficient myocardial perfusion can also increase the long-term mortality of AMI patients (18). Therefore, it is important to find the independent risk factors of insufficient myocardial perfusion, so that we can identify the high-risk AMI patients before PPCI. It can guide us to make strategies for reperfusion therapy before PPCI.

The pathophysiological mechanism of insufficient myocardial reperfusion is about the microvascular blood flow is hindered by microcirculation injury (MVO) or dysfunction (20). The etiological mechanisms: 1) caused by the microthrombus blocking during the intervention producer; 2) endothelial cells protrusion, leukocyte infiltration and myocardial cell edema caused microvascular oppressing; 3) the necrosis of myocardial cells leads to the release of oxygen free radicals and proinflammatory cytokines, which would activate white blood cells and platelets to block the microvessels.

Platelets played a key role in the pathogenesis of AMI through the formation of platelet - fibrin complexes (8). The increasing platelet count was associated with the occurrence of AMI (21). Activating platelets adhered to the vascular endothelial cells and produced inflammatory cytokines, leading to mononuclear cell adhesion and migration, to accelerate the progression of atherosclerotic plaques. These activating adhesion molecules and chemokines promoted the activation of white blood cells and

produced reactive oxygen and matrix metalloproteinases to cause plaque instability in atherosclerotic plaques (22). Gary et al. found that increasing platelet volume can change blood viscosity and promote inflammation (23). Temiz et al. found that increasing platelet activity was associated with high incidence of cardiovascular events in-hospital (24). These studies indicated that the increasing of platelet count was significantly correlated with the occurrence of AMI and poor prognosis.

During the pathogenetic process of AMI, lymphocytes entered the ischemia-reperfusion injury myocardial tissue and secreted IL-10 to inhibit inflammatory response. Meanwhile, the lymphocytes also secreted TF and mmp-1 to promote the coagulation reaction (22). Studies have shown a correlation between lymphocyte count decreasing and cardiovascular events increasing in patients with AMI (10,25). Lymphocyte count decreasing caused by stress can increase the incidence of death in AMI patients (26). Therefore, PLR may become a new indicator of thrombus formation, inflammatory state, short-term and long-term adverse outcomes of patients with AMI.

Basing on the TIMI class after PCI, Abdulkadir et al. divided acute STEMI patients into two groups as no-reflow group and reflow group. An analysis of blood routine examination before PCI and myocardial reperfusion had presented that the increasing of PLR value is an independent risk factor for the prediction of no-reflow in acute STEMI patients (27). Burak et al. used the ROC curve analysis to present that a PLR>137 predicted adverse events for patients who had undergone PPCI with a specificity of 67% and a sensitivity of 63% (28). Alparslan et al. found that PLR is

significantly associated with the severity and complexity of coronary atherosclerosis in ACS patients who undergo PPCI. A higher PLR value is an independent predictor of an intermediate to high SXscore (15). Preintervention PLR was a strong and independent predictor of slow flow/no-reflow after PPCI in patients with acute STEMI (29). Murat et al. found that higher PLR is associated with increased risk for in-hospital adverse outcomes and 6-month all-cause mortality with STEMI after PPCI (16). PLR should be incorporated into the clinical practice of risk stratification for patients admitted with STEMI who underwent primary PCI.

This study found that high PLR was an independent risk factor of insufficient myocardial reperfusion in patients with AMI. High PLR were more likely to have major adverse events in hospital after PPCI. The results are consistent with the above studies. As an independent risk factor, PLR contained two kinds of cell subtype information, which has higher predictive value than any single index.

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 was still controversial (30,31). The TASTE test showed that thrombus aspiration in PPCI patients did not reduce the total mortality in 30 days and 1 year (32). TOTAL 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) between the thrombus aspiration group and non-thrombus aspiration group were no statistical difference (33). In addition, study showed that thrombus aspiration did not improve myocardial reperfusion in patients with long-period ischemia, small infarction area

and light thrombosis (34). Hoole et al. observed the changes in microvascular resistance (IMR) during PPCI and found that patients with relatively light thrombosis were prone to form distal embolization after the thrombus aspiration, which would lead to microcirculation injury (35).

This study also found that that peak value of BNP were significantly correlate with insufficient myocardial reperfusion in those patients with AMI. It is suggested that AMI area is large and the cardiac function is poor in these patients. Consistent with previous studies, these patients were prone to progression to chronic heart failure and increase long-term mortality, which requires close follow-up.

Limitations in this study:

1) 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 of ECG ST segment after emergency PCI, but former study showed that the ST fallback was consistent with the MBG grading results; 3) Long-term follow-up of this study was not conducted, and further study was needed to evaluate PLR on long-term prognosis of patients with AMI.

Conclusion

PLR was associated with insufficient myocardial perfusion after PPCI in patients with AMI. PLR increased AMI patients were more likely to have major cardiovascular adverse events in hospital after PCI.

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Conflict of interest

None.

Contributor ship statement

Ailifeire Maimaiti and Li Yang contributed equally to this work. Ailifeire Maimaiti and Yong-Tao Wang were responsible for statistical analysis and write this paper. Li Yang and Xiang Yang provided the database. Xiao-Mei Li and Yi-Ning Yang revised the paper critically for important intellectual content. Yi-Tong Ma was accountable for all aspects of the work and funds collection.

Data sharing statement

The data sets generated and analysed during the current study are available from the corresponding author upon reasonable request.

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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2-P3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4-P5
Objectives	3	State specific objectives, including any prespecified hypotheses	P5
Methods			
Study design	4	Present key elements of study design early in the paper	P5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P5-P6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	P6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P6-P7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	P6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6-P7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7
		(*b*) Describe any methods used to examine subgroups and interactions	P7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	P6
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P8-P9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	P10
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	P6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	P11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P11-P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P12-P15
Generalisability	21	Discuss the generalisability (external validity) of the study results	P15
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P16

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

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ABSTRACT:

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

Design: Retrospective cohort study

Setting: Patients and researchers came 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 was defined as the high PLR group (n=150) and those in the lower 2 tertiles were defined as the low PLR group (n=295). Explicit criteria for inclusion and exclusion were made.

Interventions: No interventions

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

Results: The high PLR group had insufficient myocardial perfusion (23% vs. 13%, P=0.003), postprocedural Thrombolysis in Myocardial Infarction (TIMI) flow grade (0-2) (17% vs. 10%, P=0.037), Myocardial blush grades (MBG) grade (0-1) (11% vs. 4%, P=0.007), B-type Natriuretic Peptide (BNP) (614±600 vs. 316±429, P<0.001) compared with the low PLR.

Multivariate logistic regression analysis indicated that the independent risk factors of impaired myocardial perfusion were PLR (OR 1.256, 95% CI 1.003-1.579, P=0.056) and BNP (OR 1.328, 95% CI 1.056-1.670, P=0.015). The high PLR group had significantly higher MACEs (43% vs. 32%, P=0.029).

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

Trial registration: No registration

Keywords: Platelet to lymphocyte ratio; PLR; insufficient myocardial perfusion; acute myocardial infarction; AMI

Strengths and limitations of this study

1. The first multicenter retrospective cohort study examined the relationship between PLR and myocardial reperfusion.
2. We only included the LAD vascular occlusion in patients with acute myocardial infarction.
3. We grouped the population according to the distribution of PLR values of the participants.
4. Our study population was small and required a larger sample size for prospective clinical studies.
5. The 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 coronary intervention (PPCI) is the first choice for AMI patients to restore blood flow. Studies have shown that the early reperfusion can effectively reduce the myocardial infarct (MI) size and restore the heart function (2). Although blood flow of the occluded vascular artery was restored (TIMI grade is 3 after PPCI), many patients still had insufficient myocardial perfusion (3). This could result in severe myocardial ischemia, malignant arrhythmia, hemodynamic deterioration and other adverse outcomes (4-7). It is mainly due to microvascular obstruction (MVO) (8). The main mechanism of microvascular obstruction is ischemia reperfusion (IR) injury of coronary arteries. There are multiple

pathophysiological factors (calcium overload, oxidative stress, inflammation, and mitochondrial dysfunction), and multiple roles (cardiomyocytes, microvasculature, inflammatory cells, and platelets), making it a complex system (9). 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 (10). Increased platelet count is associated with the MI size in AMI patients and can lead to adverse cardiovascular events (11). Inflammatory response plays an important role in the formation of atherosclerotic plaques and myocardial ischemia-reperfusion injury. Studies have shown that decreased lymphocyte count was associated with increased mortality in AMI patients (12-14). Previous studies have found that PLR can be used as a predictor of long-term mortality, an independent risk factor for no reflow after PPCI and increased mortality in hospital, and the increase of PLR is positively correlated with the 6-month all-cause mortality in STEMI patients (15-18).

Studies have showed that the presence of MVO after PPCI as assessed by TIMI flow post-PPCI and MBG have all strongly been linked with worse outcomes in AMI patients (19-20). 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 (LCX), as well as the right coronary artery (RC) (21). Although previous studies have investigated the relationship between PLR and AMI, they have ignored the influence of myocardial ischemic adaptation in different coronary artery

on myocardial reperfusion. To avoid the influence of this variation on the results, we only include AMI patients with proximal LAD blocking. Thus, this study intends to explore the effects of PLR on myocardial reperfusion and adverse events in AMI patients and to provide guidance for the improvement of reperfusion therapy.

Material and Methods

Participants

This study is a multiple-center, retrospective, cohort study. A total of 445 consecutive AMI patients from two hospitals between January 2015 and December 2017 were respectively reviewed. We analyzed the clinical and angiographic data of consecutive patients diagnosed with acute myocardial infarction. The inclusion criteria as follows: 1. Eligible for the diagnostic criteria of STEMI.; 2. Within 12 hours from the onset of symptoms to PPCI; 3. The results of angiography confirmed that the infarcted blood vessels were proximal left anterior descending (LAD). 4. Complete clinical data collection; The exclusion criteria as follows: 1. Active infection; 2. History of systemic infectious diseases in two weeks; 3. Malignant tumor; 4. Hepatopathy; 5 chronic tuberculosis history; 6. History of heart failure; 7. History of PCI; 8. Long-term oral antiplatelet and statin drugs; All patients received 300 mg of aspirin and 600 mg clopidogrel or 180 mg of tigrel before PPCI. This study protocol was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Xinjiang Medical University and 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, etc.; Previous medical history and personal history: hypertension and grade, diabetes, hyperlipidemia, stroke history, prehospital medication history, 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, BNP, cardiac ultrasound 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, size of the stents, clots, 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 universal definition of MI guideline. Non-lethal myocardial infarction was defined as Type1 and Type2 myocardial infraction according to guideline (22). Major adverse cardiac events (MACEs) were defined as cardiovascular death, reinfarction, or target–vessel revascularization.

Insufficient myocardial perfusion was defined as a postoperative TIMI stage is

grade less than 3, or the TIMI stage is grade 3, but the MBG classification is less than 2 (23).

Statistical analysis

All data were analyzed by SPSS V 24.0 for Windows. Continuous variables are presented as mean ± standard deviation. If the two groups of quantitative data are consistent with the normal distribution, then the independent sample t test would be performed. if it doesn't fit the normal distribution, then the Wilcoxon's rank test would be performed. The comparison between two groups of count data by chi-square test. But, if the frequency is lower than 5, Fisher's exact test would be performed. 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, and 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 were presented in table 1. A total of 445 patients (136 from one medical center,309 from the other) were eligible. High PLR patients were admitted to the 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, hyperlipidemia, and symptom onset to intervention between two groups were not statistically significant different (P > 0.05).

Table 1. Baseline clinical characteristics of patients

	High PLR (n=150)	Low PLR (n=295)	*P* value
Age , years x±s	62.2±14.1	59.5±12.2	0.117
Male , n(%)	93 (62%)	196 (66.4%)	0.335
Hypertension , n(%)	80 (53.3%)	160 (54.2%)	0.856
Diabetes , n(%)	33 (22%)	80 (27.1%)	0.241
Stroke , n(%)	13 (8.7%)	20 (6.8%)	0.473
Smoking , n(%)	57 (38%)	130 (44.1%)	0.220
Hyperlipidaemia , n(%)	6 (4%)	16 (5.4%)	0.513
Killip class ≥II , n(%)	129 (86%)	220 (74.6%)	0.006
Ejection fraction, x%±s	34.8±6.0	37.4±7.1	0.006
Symptom onset to intervention (hours)	7.00±4.83	7.15±4.80	0.608
≥6	66(44.0%)	131(44.4%)	0.935

The laboratory data of the two groups were presented in Table 2. Preoperative White blood cell count(WBC) (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 was significantly lower. The peak value of BNP (614 ± 610pg/ ml VS. 316 ± 429pg/ml, P < 0.001) and alanine aminotransferase (ALT) (64.4±84.4U/Lvs. 52.1±60.0U/L, P=0.003) was

significantly higher than that in the high PLR group. There was no statistical difference in neutrophils count, monocyte count, hemoglobin, creatinine, total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), C-reactive protein (CRP), peak cTnT, peak CK-MB.

Table 2. Comparison of laboratory results

	High PLR（n=150）	Low PLR（n=295）	*P* value
WBC×10^9/L(x±s)	9.5±4.1	9.0±3.2	0.044
Neutrophil×10^9/L(x±s)	8.1±6.8	6.5±6.2	0.171
Platelet×10^9/L(x±s)	264.2±85.9	203.5±74.6	0.006
Lymphocyte×10^9/L(x±s)	1.15±0.47	2.23±2.41	0.081
Monocyte×10^9/L(x±s)	0.5±0.3	1.0±4.6	0.167
Hemoglobin（g/L，x±s）	129.6±23.7	135.8±23.0	0.524
RDW（%，x±s）	13.6±3.1	13.2±2.3	0.026
ALT (U/L，x±s)	64.4±84.4	52.1±60.0	0.003
Creatinine (μmol/L，x±s)	76.3±30.8	78.4±36.3	0.336
Total cholesterol (μmol/L，x±s)	4.1±1.0	4.1±1.1	0.198
HDL-cholesterol (umol/L，x±s)	1.1±0.3	1.0±0.5	0.446
LDL-cholesterol (μmol/L，x±s)	2.5±0.8	2.5±0.9	0.880
CRP (mg/L，x±s)	17.8±32.0	16.7±26.6	0.611
Peak cTnT (U/L，x±s)	5.7±4.0	4.9±3.8	0.236
Peak CK-MB (U/L，x±s)	242±382	226±335	0.498

BNP（pg/ml，x±s）	614±600	316±429	< 0. 001

WBC: White blood cell count; RDW: Red cell distribution width; ALT: alanine aminotransferase; HDL: High density lipoprotein; LDL: Low density lipoprotein; CRP:C-reactive protein; CK-MB: Creatine kinase-myocardial band; BNP: Brain natriuretic peptide

The angiographic and procedural characteristics of two groups were 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 relatively 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 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 and the number of stent use, the average implanted stent length, the use of tirofiban. The MACEs in the high PLR group was significantly higher (43% vs. 32%, P=0.004). There was no significant difference non-lethal myocardial infarction, Stroke, In-hospital mortality and Ventricular tachycardia/ventricular fibrillation (Table 4).

Table3. Angiographic and procedural characteristics of patients

	High PLR（n=150）	Low PLR（n=295）	*P* value
Number of diseased vessel			
1，n(%)	54（36%）	103（35%）	0.821
≥2，n(%)	96（64%）	192（65%）	
Number of stent use			
1，n(%)	66（44%）	119（40%）	0.459

≥2，n(%)	84（56%）	176（60%）	
Stent length, average (mm，x±s)	26.4±8.1	25.9±6.3	0.067
Stent diameter, average (mm，x±s)	2.93±0.47	2.96±0.40	0.015
Tirofiban use，n(%)	135（90%）	271（92%）	0.511
Thrombus aspiration，n(%)	96（64%）	153（52%）	0.015
Postprocedural TIMI grade			
0-2，n(%)	25(17%)	29(10%)	0.037
3，n(%)	125(83%)	266(90%)	
MBG grade			
0,1，n(%)	16(11%)	12(4%)	0.007
2,3，n(%)	134(89%)	283(96%)	
Insufficient myocardial reperfusion	35(23%)	37(13%)	0.003

TIMI: thrombolysis in myocardial infarction; MBG: Myocardial blush grades

Table4. In-hospital cardiac events and complications

	High PLR（n=150）	Low PLR（n=295）	*P* value
MACEs	64（43%）	95（32%）	0.029
Non-lethal myocardial infarction，n(%)	6（4%）	7（2%）	0.335
Stroke，n(%)	11（7%）	18（6%）	0.619
In-hospital mortality，n(%)	4（3%）	2（1%）	0.186
Ventricular tachycardia/ventricular fibrillation，n(%)	42 (28%)	69 (23%)	0.288

MACE: Major adverse cardiac events (cardiovascular death, reinfarction, target–vessel revascularization)

We performed univariate Logistic regression analysis of factors affecting insufficient myocardial perfusion, the result showed that BNP (OR 1.329, 95% CI 1.057 to 1.672 (P = 0.015) and PLR (OR 1.254, 95% CI 1.001 to 1.571 (P = 0.041) can affect the insufficient myocardial perfusion of PPCI patients. We had included all factors to perform multivariate Logistic regression analysis. We found that PLR (OR 1.256, 95% CI 1.003 to 1.579 (P = 0.001) and BNP (OR 1.328, 95% CI 1.056 to 1.670 (P = 0.015) were independent factors of insufficient myocardial perfusion (Table 5).

Table5. The independent predictors of insufficient myocardial reperfusion

	Univariate		Multivariate	
Variable	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Age	1.013 (0.983-1.033)	0.202	1.008 (0.988-1.028)	0.440
Male gender	1.018 (0.599-1.728)	0.948	1.009 (0.554-1.839)	0.975
Killip class ≥II	1.167 (0.620-2.198)	0.632	0.980 (0.460-2.086)	0.958
Ejection fraction	0.985 (0.948-1.023)	0.436	0.986 (0.947-1.027)	0.488
WBC	1.049 (0.983-1.119)	0.151	1.044 (0.977-1.116)	0.206
Platelet	1.002 (0.999-1.005)	0.037	1.000 (0.996-1.005)	0.872
Lymphocyte	0.766 (0.542-1.082)	0.130	0.906 (0.611-1.344)	0.624
RDW	1.016 (0.928-1.112)	0.734	1.008 (0.911-1.115)	0.878
ALT	0.999 (0.995-1.003)	0.576	0.991 (0.993-1.002)	0.268
Stent length	1.007 (0.971-1.044)	0.710	1.005 (0.969-1.042)	0.793
Stent diameter	1.168 (0.643-2.124)	0.610	1.071 (0.571-2.009)	0.831
Thrombus aspiration	1.123 (0.673-1.872)	0.657	1.046 (0.614-1.780)	0.869
BNP	1.329 (1.057-1.672)	0.015	1.328 (1.056-1.670)	0.015
PLR	1.254 (1.001-1.571)	0.051	1.256 (1.003-1.579)	0.056

WBC: White blood cell count; RDW: Red cell distribution width; ALT: alanine aminotransferase: BNP: Brain natriuretic peptide; PLR: Platelet to lymphocyte ratio.

Discussion

In our study, after modifying the effects of different coronary artery lesions on insufficient myocardial reperfusion, it was found that PLR and BNP were independent risk factors for insufficient myocardial reperfusion after PPCI for AMI patients. In

addition, studies have also shown that high PLR is significantly correlated with MACEs, Killip grade, EF value, platelet count, RDW, length/diameter of stent implantation, and thrombus aspiration of AMI patients.

The pathophysiological mechanism of insufficient myocardial reperfusion is about the microvascular blood flow is hindered by MVO (9,24). The etiological mechanisms: 1) Platelets activation and adhesion that increase cell death and aggregation could effects on myocardial flow (25); 2) Increased endothelial permeability and subsequent recruitment of inflammatory cells into the site of infarction could lead to acute IR injury (26); 3) Mitochondrial dysfunction caused by calcium overload and ROS accumulation can also lead to IR injury (27) 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 AMI patients than platelet or lymphocyte count. Platelets played a key role in the pathogenesis of AMI through the formation of platelet - fibrin complexes (10). The increasing platelet count was associated with the occurrence of AMI (28). Activating platelets adhered to the vascular endothelial cells and produced inflammatory cytokines, leading to mononuclear cell adhesion and migration, to accelerate the progression of atherosclerotic plaques. These activating adhesion molecules and chemokines promoted the activation of white blood cells and produced reactive oxygen and matrix metalloproteinases to cause plaque instability in atherosclerotic plaques (29). Gary et al. found that increasing platelet volume can change blood viscosity and promote inflammation (30). Temiz et al. found that increasing platelet activity was associated with high incidence of cardiovascular events

in-hospital (31). These studies indicated that the increasing of platelet count was significantly correlated with the occurrence of AMI and poor prognosis.

During the pathogenetic process of AMI, lymphocytes entered the ischemia-reperfusion injury myocardial tissue and secreted IL-10 to inhibit inflammatory response. Meanwhile, the lymphocytes also secreted TF and mmp-1 to promote the coagulation reaction (29). Studies have shown a correlation between lymphocyte count decreasing and cardiovascular events increasing in patients with AMI (12,32). Lymphocyte count decreasing caused by stress can increase the incidence of death in AMI patients (33). Therefore, PLR may become a new indicator of thrombus formation, inflammatory state, short-term and long-term adverse outcomes of patients with AMI.

Basing on the TIMI class after PCI, Abdulkadir et al. divided acute STEMI patients into two groups as no-reflow group and reflow group. An analysis of blood routine examination before PCI and myocardial reperfusion had presented that the increasing of PLR value is an independent risk factor for the prediction of no-reflow in acute STEMI patients (34). Burak et al. used the ROC curve analysis to present that a PLR>137 predicted adverse events for patients who had undergone PPCI with a specificity of 67% and a sensitivity of 63% (35). Alparslan et al. found that PLR is significantly associated with the severity and complexity of coronary atherosclerosis in ACS patients who undergo PPCI. A higher PLR value is an independent predictor of an intermediate to high SXscore (17). Preintervention PLR was a strong and independent predictor of slow flow/no-reflow after PPCI in patients with acute

STEMI (36). Murat et al. found that higher PLR is associated with increased risk for in-hospital adverse outcomes and 6-month all-cause mortality with STEMI after PPCI (18). PLR should be incorporated into the clinical practice of risk stratification for patients admitted with STEMI who underwent primary PCI.

Our study found that BNP was an independent risk factor for insufficient myocardial reperfusion after PPCI in AMI patients. BNP is a quantitative marker of heart failure, which is significantly correlated with left ventricular systolic function (37). Besides, during the process of hypoxic, edematous, and necrotic at the myocardial infraction site, cardiomyocyte could produce BNP through the transcription of NPPB gene in endoplasmic reticulum (38). When occlusion of the proximal LAD causes hypoxia and edema of myocardial cells, BNP will be secreted in large quantities. Elevated BNP leads to plasma concentration of angiotensin II (Ang II) and endothelin-1 (ET-1) by activating renin angiotensin system (RAS) (39). This will further aggravate the reperfusion of ischemic myocardium at the infarct site. BNP has been shown to be an independent risk factor for ischemia reperfusion injury in ST-segment elevation AMI patients (40). Studies have shown that the increased secretion of BNP during myocardial ischemia is mainly regulated by the PI3K/Akt/p70s6k signaling pathway, which has a protective effect on myocardium (41). This change is an adaptation of myocardial cells to ischemia. Therefore, BNP level can reflect the severity of myocardial ischemia which is great 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 was still controversial (42,43). The TASTE test showed that thrombus aspiration in PPCI patients did not reduce the total mortality in 30 days and 1 year (44). TOTAL 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) between the thrombus aspiration group and non-thrombus aspiration group were no statistical difference (45). In addition, study showed that thrombus aspiration did not improve myocardial reperfusion in patients with long-period ischemia, small infarction area and light thrombosis (46). Hoole et al. observed the changes in microvascular resistance (IMR) during PPCI and found that patients with relatively light thrombosis were prone to form distal embolization after the thrombus aspiration, which would lead to microcirculation injury (47).

Limitations in this study: 1) 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 of ECG ST segment after emergency PCI, but former study showed that the ST fallback was consistent with the MBG grading results; 3) Long-term follow-up of this study was not conducted, and further study was needed to evaluate PLR on long-term prognosis of patients with AMI.

Conclusion

In a conclusion, our study showed that 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 hospitalization. PLR and BNP are convenient and

inexpensive detection methods in clinical practice. Clinicians can grade the risk of insufficient myocardial reperfusion in AMI patients according to the PLR value.

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Conflict of interest

None.

Contributor ship statement

Ailifeire Maimaiti and Li Yang contributed equally to this work. Ailifeire Maimaiti and Yong-Tao Wang were responsible for statistical analysis and write this paper. Li Yang and Xiang Yang provided the database. Xiao-Mei Li and Yi-Ning Yang revised the paper critically for important intellectual content. Yi-Tong Ma was accountable for all aspects of the work and funds collection.

Data sharing statement

The data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2-P3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4-P5
Objectives	3	State specific objectives, including any prespecified hypotheses	P5
Methods			
Study design	4	Present key elements of study design early in the paper	P5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P5-P6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	P6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P6-P7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	P6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6-P7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7
		(*b*) Describe any methods used to examine subgroups and interactions	P7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	P6
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P8-P9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	P10
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	P6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	P11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P11-P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P12-P15
Generalisability	21	Discuss the generalisability (external validity) of the study results	P15
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P16

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

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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

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ABSTRACT:

Objective: Insufficient myocardial reperfusion for acute myocardial infarction (AMI) patients 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 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 2 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 revascularization. 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 (TIMI) flow grade (0-2) (17% vs. 10%, P=0.037), greater myocardial blush grade (MBG) (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 1.003-1.579, P=0.056) and high BNP (OR 1.328, 95% CI 1.056-1.670, 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 AMI patients. Higher PLR was related to advanced heart failure and in-hospital MACEs in patients with AMI undergoing PPCI.

Trial registration: No registration

Keywords: Platelet to lymphocyte ratio; PLR; insufficient myocardial perfusion; acute myocardial infarction; AMI

Strengths and limitations of this study

1. The first multicentre retrospective cohort study to examine the relationship between PLR and myocardial reperfusion.
2. We only included patients with LAD vascular occlusion among patients with acute myocardial infarction.
3. We grouped the population according to PLR value.
4. Our study population was small, and a larger sample size will be required for prospective clinical studies.
5. 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 coronary intervention (PPCI) is the first choice for AMI patients 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 microvascular obstruction 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 (9). 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 (10). Increased platelet count is associated with the MI size in AMI patients and can lead to adverse cardiovascular events (11). The inflammatory response plays an important role in the formation of atherosclerotic plaques and myocardial ischaemia-reperfusion injury. Studies have shown that decreased lymphocyte count was associated with increased mortality in AMI patients (12-14). Previous studies have found that 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 STEMI patients (15-18).

Studies have shown that the presence of MVO after PPCI as assessed by TIMI flow post-PPCI and MBG have all strongly been linked with worse outcomes in AMI patients (19-20). 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 (LCX), as well as the right coronary artery (RC) (21). 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 AMI patients 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 AMI patients from two hospitals seen between January 2015 and December 2017 were reviewed. We analysed the clinical and angiographic data of consecutive patients diagnosed with acute myocardial infarction. 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 left anterior descending (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 two weeks; 3. Malignant tumour; 4. Hepatopathy; 5 Chronic tuberculosis history; 6. History of heart failure; 7. History of PCI; 8. Long-term oral antiplatelet or statin drugs. All patients received 300 mg of aspirin and 600 mg clopidogrel or 180 mg of ticagrelor before PPCI. This study protocol was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Xinjiang Medical University and 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, etc.; previous 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 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 type 1 or type2 myocardial infarction according to guidelines (22). Major adverse cardiac events (MACEs) were defined as cardiovascular death, reinfarction, or target vessel

revascularization.

Insufficient myocardial perfusion was defined as a postoperative TIMI grade less than 3 or a TIMI grade of 3 but with an MBG classification less than 2 (23).

Statistical analysis

All data were analysed by SPSS V 24.0 for Windows. Continuous variables are presented as the mean ± standard deviation. 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 chi-square 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).

Table 1. Baseline clinical characteristics of patients

	High PLR (n=150)	Low PLR (n=295)	*P* value
Age, years x±s	62.2±14.1	59.5±12.2	0.117
Male, n(%)	93 (62%)	196 (66.4%)	0.335
Hypertension, n(%)	80 (53.3%)	160 (54.2%)	0.856
Diabetes, n(%)	33 (22%)	80 (27.1%)	0.241
Stroke, n(%)	13 (8.7%)	20 (6.8%)	0.473
Smoking, n(%)	57 (38%)	130 (44.1%)	0.220
Hyperlipidaemia, n(%)	6 (4%)	16 (5.4%)	0.513
Killip class ≥II, n(%)	129 (86%)	220 (74.6%)	0.006
Ejection fraction, x%±s	34.8±6.0	37.4±7.1	0.006
Symptom onset to intervention (hours)	7.00±4.83	7.15±4.80	0.608
≥6	66(44.0%)	131(44.4%)	0.935

The laboratory data of the two groups are presented in Table 2. The preoperative white blood cell count (WBC) (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 brain natriuretic peptide (BNP) (614 ± 610 pg/ml vs. 316 ± 429 pg/ml, P < 0.001) and alanine aminotransferase (ALT) (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 (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), C-reactive protein (CRP), peak cTnT, or peak

CK-MB.

Table 2. Comparison of laboratory results

	High PLR (n=150)	Low PLR (n=295)	*P* value
WBC×10^9/L (x±s)	9.5±4.1	9. 0±3. 2	0. 044
Neutrophil×10^9/L (x±s)	8.1±6.8	6.5±6.2	0. 171
Platelet×10^9/L (x±s)	264.2±85.9	203.5±74.6	0. 006
Lymphocyte×10^9/L (x±s)	1.15±0.47	2.23±2.41	0. 081
Monocyte×10^9/L (x±s)	0. 5±0. 3	1.0±4.6	0. 167
Haemoglobin (g/L, x±s))	129.6±23.7	135.8±23.0	0. 524
RDW (%, x±s)	13. 6±3.1	13. 2±2.3	0. 026
ALT (U/L, x±s)	64.4±84.4	52.1±60.0	0. 003
Creatinine (μmol/L, x±s)	76.3±30.8	78.4±36.3	0. 336
Total cholesterol (μmol/L, x±s)	4. 1±1.0	4. 1±1. 1	0. 198
HDL-cholesterol (μmol/L, x±s)	1. 1±0. 3	1. 0±0. 5	0. 446
LDL-cholesterol (μmol/L, x±s)	2. 5±0. 8	2. 5±0. 9	0. 880
CRP (mg/L, x±s)	17.8±32.0	16.7±26.6	0. 611
Peak cTnT (U/L, x±s)	5.7±4.0	4.9±3.8	0. 236
Peak CK-MB (U/L, x±s)	242±382	226±335	0. 498
BNP (pg/ml, x±s)	614±600	316±429	< 0. 001

WBC: white blood cell count; RDW: red cell distribution width; ALT: alanine aminotransferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CRP: C-reactive protein; CK-MB: creatine kinase-myocardial band; BNP: brain natriuretic peptide

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).

Table 3. Angiographic and procedural characteristics of patients

	High PLR (n=150)	Low PLR (n=295)	*P* value
Number of diseased vessels			
1, n(%)	54 (36%)	103 (35%)	0.821
≥2, n(%)	96 (64%)	192 (65%)	
Number of stent use			
1, n(%)	66 (44%)	119 (40%)	0.459
≥2, n(%)	84 (56%)	176 (60%)	
Stent length, average (mm, x±s)	26.4±8.1	25.9±6.3	0.067
Stent diameter, average (mm, x±s)	2.93±0.47	2.96±0.40	0.015
Tirofiban use, n (%)	135 (90%)	271 (92%)	0.511
Thrombus aspiration, n (%)	96 (64%)	153 (52%)	0.015
Postprocedural TIMI grade			
0-2, n (%)	25(17%)	29(10%)	0.037
3, n (%)	125(83%)	266(90%)	
MBG grade			
0,1, n (%)	16(11%)	12(4%)	0.007
2,3, n (%)	134(89%)	283(96%)	
Insufficient myocardial reperfusion	35(23%)	37(13%)	0.003

TIMI: Thrombolysis in Myocardial Infarction; MBG: myocardial blush grade

Table 4. In-hospital cardiac events and complications

	High PLR (n=150)	Low PLR (n=295)	*P* value
MACEs	64 (43%)	95 (32%)	0.029

Non-lethal myocardial infarction, n (%)	6 (4%)	7 (2%)	0.335
Stroke, n (%)	11 (7%)	18 (6%)	0.619
In-hospital mortality, n (%)	4 (3%)	2 (1%)	0.186
Ventricular tachycardia/ventricular fibrillation, n (%)	42 (28%)	69 (23%)	0.288

MACEs: major adverse cardiac events (cardiovascular death, reinfarction, target vessel revascularization)

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 = 0.015) and high PLR (OR 1.254, 95% CI 1.001 to 1.571 (P = 0.041) 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 1.003 to 1.579 (P = 0.001) 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).

Table 5. The independent predictors of insufficient myocardial reperfusion

	Univariate		Multivariate	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.013 (0.983-1.033)	0.202	1.008 (0.988-1.028)	0.440
Male sex	1.018 (0.599-1.728)	0.948	1.009 (0.554-1.839)	0.975
Killip class ≥II	1.167 (0.620-2.198)	0.632	0.980 (0.460-2.086)	0.958
Ejection fraction	0.985 (0.948-1.023)	0.436	0.986 (0.947-1.027)	0.488
WBC	1.049 (0.983-1.119)	0.151	1.044 (0.977-1.116)	0.206
Platelet	1.002 (0.999-1.005)	0.037	1.000 (0.996-1.005)	0.872
Lymphocyte	0.766 (0.542-1.082)	0.130	0.906 (0.611-1.344)	0.624
RDW	1.016 (0.928-1.112)	0.734	1.008 (0.911-1.115)	0.878
ALT	0.999 (0.995-1.003)	0.576	0.991 (0.993-1.002)	0.268
Stent length	1.007 (0.971-1.044)	0.710	1.005 (0.969-1.042)	0.793
Stent diameter	1.168 (0.643-2.124)	0.610	1.071 (0.571-2.009)	0.831
Thrombus aspiration	1.123 (0.673-1.872)	0.657	1.046 (0.614-1.780)	0.869
BNP	1.329 (1.057-1.672)	0.015	1.328 (1.056-1.670)	0.015
PLR	1.254 (1.001-1.571)	0.051	1.256 (1.003-1.579)	0.056

WBC: white blood cell count; RDW: red cell distribution width; ALT: alanine aminotransferase: BNP: brain natriuretic peptide; PLR: platelet to lymphocyte ratio.

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 AMI patients. Earlier studies have shown that high PLR is significantly correlated with MACEs, Killip grade, EF value, platelet count, RDW, length/diameter of stent implantation, and thrombus aspiration in AMI patients.

The pathophysiological mechanism of insufficient myocardial reperfusion is that microvascular blood flow is hindered by MVO (9,24). The aetiological mechanisms are that 1) platelet activation and adhesion, which increase cell death and aggregation, can affect myocardial flow (25); 2) increased endothelial permeability and subsequent recruitment of inflammatory cells into the site of infarction can lead to acute IR injury (26); 3) mitochondrial dysfunction caused by calcium overload and ROS accumulation can also lead to IR injury (27). 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 AMI patients than platelet or lymphocyte count. Platelets play a key role in the pathogenesis of AMI through the formation of platelet-fibrin complexes (10). Increasing platelet count has been associated with the occurrence of AMI (28). 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 blood cells and produce

reactive oxygen species and matrix metalloproteinases, causing plaque instability in atherosclerotic plaques (29). Gary et al. found that increasing platelet volume can change blood viscosity and promote inflammation (30). Temiz et al. found that increasing platelet activity was associated with a high incidence of cardiovascular events in hospital (31). 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 ischaemia-reperfusion-injured myocardial tissue and secrete IL-10 to inhibit the inflammatory response. The lymphocytes also secrete TF and mmp-1 to promote the coagulation reaction (29). Studies have shown a correlation between decreased lymphocyte count and increased frequency of cardiovascular events in patients with AMI (12,32). A decrease in lymphocyte count caused by stress can increase the incidence of death in AMI patients (33). 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, Abdulkadir 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 (34). Burak 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% (35). Alparslan 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 (17). Preintervention PLR was a strong and independent predictor of slow flow/no-reflow after PPCI in patients with acute STEMI (36). Murat 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 (18). 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 AMI patients. BNP is a quantitative marker of heart failure that is significantly correlated with left ventricular systolic function (37). During the process of hypoxia, oedematosis, and necrosis at the myocardial infarction site, cardiomyocytes can produce BNP through the transcription of the NPPB gene in the endoplasmic reticulum (38). 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 (Ang II) and endothelin-1 (ET-1) by activating the renin angiotensin system (RAS) (39). This will further aggravate the reperfusion of ischaemic myocardium at the infarct site. BNP has been shown to be an independent risk factor for ischaemia-reperfusion injury in ST-segment elevation AMI patients (40). 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 (41). 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 (42,43). The TAPAS study showed that thrombus aspiration in PPCI patients did not reduce the total mortality at 30 days or 1 year (44). The TOTAL 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 (45). 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 (46). Hoole et al. observed changes in microvascular resistance (IMR) during PPCI and found that patients with relatively light thrombosis were prone to distal embolization after thrombus aspiration, which would lead to microcirculation injury (47).

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.

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 hospitalization. PLR and BNP are convenient and inexpensive to detect in clinical practice. Clinicians can grade the risk of insufficient myocardial reperfusion in AMI patients according to the PLR value.

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Conflict of interest

None declared.

Contributor ship statement

Ailifeire Maimaiti and Li Yang contributed equally to this work. Ailifeire Maimaiti and Yong-Tao Wang were responsible for the statistical analysis and write this paper. Li Yang and Xiang Yang provided the database. Xiao-Mei Li and Yi-Ning Yang critically revised the paper for important intellectual content. Yi-Tong Ma was accountable for all aspects of the work and fund collection.

Data sharing statement

The data sets generated and analysed during the current study are available from the corresponding author upon reasonable request.

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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2-P3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4-P5
Objectives	3	State specific objectives, including any prespecified hypotheses	P5
Methods			
Study design	4	Present key elements of study design early in the paper	P5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P5-P6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	P6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P6-P7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	P6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6-P7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7
		(*b*) Describe any methods used to examine subgroups and interactions	P7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	P6
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P8-P9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	P10
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	P6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	P11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P11-P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P12-P15
Generalisability	21	Discuss the generalisability (external validity) of the study results	P15
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P16

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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

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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

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ABSTRACT:

Objective: Insufficient myocardial reperfusion for acute myocardial infarction (AMI) patients 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 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 2 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 revascularization. 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 (TIMI) flow grade (0-2) (17% vs. 10%, P=0.037), greater myocardial blush grade (MBG) (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 1.003-1.579, P=0.056) and high BNP (OR 1.328, 95% CI 1.056-1.670, 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 AMI patients. Higher PLR was related to advanced heart failure and in-hospital MACEs in patients with AMI undergoing PPCI.

Trial registration: No registration

Keywords: Platelet to lymphocyte ratio; PLR; insufficient myocardial perfusion; acute myocardial infarction; AMI

Strengths and limitations of this study

1. The first multicentre retrospective cohort study to examine the relationship between PLR and myocardial reperfusion.
2. We only included patients with LAD vascular occlusion among patients with acute myocardial infarction.
3. We grouped the population according to PLR value.
4. Our study population was small, and a larger sample size will be required for prospective clinical studies.
5. 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 coronary intervention (PPCI) is the first choice for AMI patients 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 microvascular obstruction 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 (9). 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 (10). Increased platelet count is associated with the MI size in AMI patients and can lead to adverse cardiovascular events (11). The inflammatory response plays an important role in the formation of atherosclerotic plaques and myocardial ischaemia-reperfusion injury. Studies have shown that decreased lymphocyte count was associated with increased mortality in AMI patients (12-14). Previous studies have found that 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 STEMI patients (15-18).

Studies have shown that the presence of MVO after PPCI as assessed by TIMI flow post-PPCI and MBG have all strongly been linked with worse outcomes in AMI patients (19-20). 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 (LCX), as well as the right coronary artery (RC) (21). 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 AMI patients 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 AMI patients from two hospitals seen between January 2015 and December 2017 were reviewed. We analysed the clinical and angiographic data of consecutive patients diagnosed with acute myocardial infarction. 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 left anterior descending (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 two weeks; 3. Malignant tumour; 4. Hepatopathy; 5 Chronic tuberculosis history; 6. History of heart failure; 7. History of PCI; 8. Long-term oral antiplatelet or statin drugs. All patients received 300 mg of aspirin and 600 mg clopidogrel or 180 mg of ticagrelor before PPCI. This study protocol was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Xinjiang Medical University and 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, etc.; previous 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 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 type 1 or type2 myocardial infarction according to guidelines (22). Major adverse cardiac events (MACEs) were defined as cardiovascular death, reinfarction, or target vessel

revascularization.

Insufficient myocardial perfusion was defined as a postoperative TIMI grade less than 3 or a TIMI grade of 3 but with an MBG classification less than 2 (23).

Statistical analysis

All data were analysed by SPSS V 24.0 for Windows. Continuous variables are presented as the mean ± standard deviation. 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 chi-square 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).

Table 1. Baseline clinical characteristics of patients

	High PLR (n=150)	Low PLR (n=295)	*P* value
Age, years x±s	62.2±14.1	59.5±12.2	0.117
Male, n(%)	93 (62%)	196 (66.4%)	0.335
Hypertension, n(%)	80 (53.3%)	160 (54.2%)	0.856
Diabetes, n(%)	33 (22%)	80 (27.1%)	0.241
Stroke, n(%)	13 (8.7%)	20 (6.8%)	0.473
Smoking, n(%)	57 (38%)	130 (44.1%)	0.220
Hyperlipidaemia, n(%)	6 (4%)	16 (5.4%)	0.513
Killip class ≥II, n(%)	129 (86%)	220 (74.6%)	0.006
Ejection fraction, x%±s	34.8±6.0	37.4±7.1	0.006
Symptom onset to intervention (hours)	7.00±4.83	7.15±4.80	0.608
≥6	66(44.0%)	131(44.4%)	0.935

The laboratory data of the two groups are presented in Table 2. The preoperative white blood cell count (WBC) (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 brain natriuretic peptide (BNP) (614 ± 610 pg/ml vs. 316 ± 429 pg/ml, P < 0.001) and alanine aminotransferase (ALT) (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 (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), C-reactive protein (CRP), peak cTnT, or peak

CK-MB.

Table 2. Comparison of laboratory results

	High PLR (n=150)	Low PLR (n=295)	*P* value
WBC×10^9/L (x±s)	9.5±4.1	9. 0±3. 2	0. 044
Neutrophil×10^9/L (x±s)	8.1±6.8	6.5±6.2	0. 171
Platelet×10^9/L (x±s)	264.2±85.9	203.5±74.6	0. 006
Lymphocyte×10^9/L (x±s)	1.15±0.47	2.23±2.41	0. 081
Monocyte×10^9/L (x±s)	0. 5±0. 3	1.0±4.6	0. 167
Haemoglobin (g/L, x±s))	129.6±23.7	135.8±23.0	0. 524
RDW (%, x±s)	13. 6±3.1	13. 2±2.3	0. 026
ALT (U/L, x±s)	64.4±84.4	52.1±60.0	0. 003
Creatinine (μmol/L, x±s)	76.3±30.8	78.4±36.3	0. 336
Total cholesterol (μmol/L, x±s)	4. 1±1.0	4. 1±1. 1	0. 198
HDL-cholesterol (μmol/L, x±s)	1. 1±0. 3	1. 0±0. 5	0. 446
LDL-cholesterol (μmol/L, x±s)	2. 5±0. 8	2. 5±0. 9	0. 880
CRP (mg/L, x±s)	17.8±32.0	16.7±26.6	0. 611
Peak cTnT (U/L, x±s)	5.7±4.0	4.9±3.8	0. 236
Peak CK-MB (U/L, x±s)	242±382	226±335	0. 498
BNP (pg/ml, x±s)	614±600	316±429	< 0. 001

WBC: white blood cell count; RDW: red cell distribution width; ALT: alanine aminotransferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CRP: C-reactive protein; CK-MB: creatine kinase-myocardial band; BNP: brain natriuretic peptide

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).

Table 3. Angiographic and procedural characteristics of patients

	High PLR (n=150)	Low PLR (n=295)	*P* value
Number of diseased vessels			
1, n(%)	54 (36%)	103 (35%)	0.821
≥2, n(%)	96 (64%)	192 (65%)	
Number of stent use			
1, n(%)	66 (44%)	119 (40%)	0.459
≥2, n(%)	84 (56%)	176 (60%)	
Stent length, average (mm, x±s)	26.4±8.1	25.9±6.3	0.067
Stent diameter, average (mm, x±s)	2.93±0.47	2.96±0.40	0.015
Tirofiban use, n (%)	135 (90%)	271 (92%)	0.511
Thrombus aspiration, n (%)	96 (64%)	153 (52%)	0.015
Postprocedural TIMI grade			
0-2, n (%)	25(17%)	29(10%)	0.037
3, n (%)	125(83%)	266(90%)	
MBG grade			
0,1, n (%)	16(11%)	12(4%)	0.007
2,3, n (%)	134(89%)	283(96%)	
Insufficient myocardial reperfusion	35(23%)	37(13%)	0.003

TIMI: Thrombolysis in Myocardial Infarction; MBG: myocardial blush grade

Table 4. In-hospital cardiac events and complications

	High PLR (n=150)	Low PLR (n=295)	*P* value
MACEs	64 (43%)	95 (32%)	0.029

Non-lethal myocardial infarction, n (%)	6 (4%)	7 (2%)	0.335
Stroke, n (%)	11 (7%)	18 (6%)	0.619
In-hospital mortality, n (%)	4 (3%)	2 (1%)	0.186
Ventricular tachycardia/ventricular fibrillation, n (%)	42 (28%)	69 (23%)	0.288

MACEs: major adverse cardiac events (cardiovascular death, reinfarction, target vessel revascularization)

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 = 0.015) 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 1.003 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).

Table 5. The independent predictors of insufficient myocardial reperfusion

	Univariate		Multivariate	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.013 (0.983-1.033)	0.202	1.008 (0.988-1.028)	0.440
Male sex	1.018 (0.599-1.728)	0.948	1.009 (0.554-1.839)	0.975
Killip class ≥II	1.167 (0.620-2.198)	0.632	0.980 (0.460-2.086)	0.958
Ejection fraction	0.985 (0.948-1.023)	0.436	0.986 (0.947-1.027)	0.488
WBC	1.049 (0.983-1.119)	0.151	1.044 (0.977-1.116)	0.206
Platelet	1.002 (0.999-1.005)	0.037	1.000 (0.996-1.005)	0.872
Lymphocyte	0.766 (0.542-1.082)	0.130	0.906 (0.611-1.344)	0.624
RDW	1.016 (0.928-1.112)	0.734	1.008 (0.911-1.115)	0.878
ALT	0.999 (0.995-1.003)	0.576	0.991 (0.993-1.002)	0.268
Stent length	1.007 (0.971-1.044)	0.710	1.005 (0.969-1.042)	0.793
Stent diameter	1.168 (0.643-2.124)	0.610	1.071 (0.571-2.009)	0.831
Thrombus aspiration	1.123 (0.673-1.872)	0.657	1.046 (0.614-1.780)	0.869
BNP	1.329 (1.057-1.672)	0.015	1.328 (1.056-1.670)	0.015
PLR	1.254 (1.001-1.571)	0.051	1.256 (1.003-1.579)	0.056

WBC: white blood cell count; RDW: red cell distribution width; ALT: alanine aminotransferase: BNP: brain natriuretic peptide; PLR: platelet to lymphocyte ratio.

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 AMI patients. Earlier studies have shown that high PLR is significantly correlated with MACEs, Killip grade, EF value, platelet count, RDW, length/diameter of stent implantation, and thrombus aspiration in AMI patients.

The pathophysiological mechanism of insufficient myocardial reperfusion is that microvascular blood flow is hindered by MVO (9,24). The aetiological mechanisms are that 1) platelet activation and adhesion, which increase cell death and aggregation, can affect myocardial flow (25); 2) increased endothelial permeability and subsequent recruitment of inflammatory cells into the site of infarction can lead to acute IR injury (26); 3) mitochondrial dysfunction caused by calcium overload and ROS accumulation can also lead to IR injury (27). 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 AMI patients than platelet or lymphocyte count. Platelets play a key role in the pathogenesis of AMI through the formation of platelet-fibrin complexes (10). Increasing platelet count has been associated with the occurrence of AMI (28). 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 blood cells and produce

reactive oxygen species and matrix metalloproteinases, causing plaque instability in atherosclerotic plaques (29). Gary et al. found that increasing platelet volume can change blood viscosity and promote inflammation (30). Temiz et al. found that increasing platelet activity was associated with a high incidence of cardiovascular events in hospital (31). 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 ischaemia-reperfusion-injured myocardial tissue and secrete IL-10 to inhibit the inflammatory response. The lymphocytes also secrete TF and mmp-1 to promote the coagulation reaction (29). Studies have shown a correlation between decreased lymphocyte count and increased frequency of cardiovascular events in patients with AMI (12,32). A decrease in lymphocyte count caused by stress can increase the incidence of death in AMI patients (33). 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, Abdulkadir 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 (34). Burak 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% (35). Alparslan 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 (17). Preintervention PLR was a strong and independent predictor of slow flow/no-reflow after PPCI in patients with acute STEMI (36). Murat 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 (18). 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 AMI patients. BNP is a quantitative marker of heart failure that is significantly correlated with left ventricular systolic function (37). During the process of hypoxia, oedematosis, and necrosis at the myocardial infarction site, cardiomyocytes can produce BNP through the transcription of the NPPB gene in the endoplasmic reticulum (38). 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 (Ang II) and endothelin-1 (ET-1) by activating the renin angiotensin system (RAS) (39). This will further aggravate the reperfusion of ischaemic myocardium at the infarct site. BNP has been shown to be an independent risk factor for ischaemia-reperfusion injury in ST-segment elevation AMI patients (40). 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 (41). 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 (42,43). The TAPAS study showed that thrombus aspiration in PPCI patients did not reduce the total mortality at 30 days or 1 year (44). The TOTAL 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 (45). 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 (46). Hoole et al. observed changes in microvascular resistance (IMR) during PPCI and found that patients with relatively light thrombosis were prone to distal embolization after thrombus aspiration, which would lead to microcirculation injury (47).

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.

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 hospitalization. PLR and BNP are convenient and inexpensive to detect in clinical practice. Clinicians can grade the risk of insufficient myocardial reperfusion in AMI patients according to the PLR value.

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Conflict of any competing interests

None declared.

Contributor ship statement

Ailifeire Maimaiti and Li Yang contributed equally to this work. Ailifeire Maimaiti and Yong-Tao Wang were responsible for the statistical analysis and write this paper. Li Yang and Xiang Yang provided the database. Xiao-Mei Li and Yi-Ning Yang critically revised the paper for important intellectual content. Yi-Tong Ma was accountable for all aspects of the work and fund collection.

Data sharing statement

The data sets generated and analysed during the current study are available from the corresponding author upon reasonable request.

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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2-P3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4-P5
Objectives	3	State specific objectives, including any prespecified hypotheses	P5
Methods			
Study design	4	Present key elements of study design early in the paper	P5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P5-P6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	P5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	P6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P6-P7
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P6
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	P6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P6-P7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P7
		(*b*) Describe any methods used to examine subgroups and interactions	P7
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	P6
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P8-P9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	P10
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	P6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	P11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	P11-P12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P12-P15
Generalisability	21	Discuss the generalisability (external validity) of the study results	P15
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P16

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.