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Original Article

Association Between the Platelet-to-Lymphocyte Ratio and the No-Reflow Phenomenon and Thrombolysis in Myocardial Infarction Flow 3 After Primary Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction

Afshin Amirpour[1]*, MD; Reihane Zavar[1], MD; Ali Ramezani Nejad[1], MD

ABSTRACT

Background: Atherosclerosis is one of the major causes of cardiovascular mortality. Inflammation has been proven to have a role in this process, and inflammatory markers can predict the prognosis of atherosclerotic events such as acute coronary syndrome and ST-elevation myocardial infarction.

Method: We sought to assess the prognostic value of the blood cell count and its components—platelets, C-reactive protein, cholesterol, triglycerides, creatinine, and troponin—in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention.

Results: Significant prognostic values were found for the neutrophil count, platelet count, fasting blood sugar, cholesterol, triglycerides, low-density lipoprotein, creatinine, and C-reactive protein.

Conclusions: The platelet-to-lymphocyte ratio had prognostic value for predicting reflow after primary percutaneous coronary intervention. Nevertheless, C-reactive protein, platelet count, fasting blood sugar, cholesterol, triglycerides, low-density lipoprotein, and creatinine were more valuable in terms of predicting the outcome of percutaneous coronary intervention in patients with ST-elevation myocardial infarction. ***(Iranian Heart Journal 2017; 18(4):12-20)***

KEYWORDS: Platelet, Lymphocyte, No-reflow, STEMI, TIMI

[1] Department of cardiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, IR Iran.
***Corresponding Author:** Afshin Amirpour, MD
Email: Afshinamirpour.ras@gmail.com **Tel:** 09131072678

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Atherosclerosis is a multifactorial disease—with dyslipidemia, dysglycemia, smoking, and endothelial injury along with genetic predisposition contributing to its pathogenesis. [1-3] The main cause of cardiovascular diseases is atherosclerosis, which also serves as the biggest cause of cardiovascular mortality in the world. [4] Recently, it has been reported that atherosclerosis consists of an active inflammatory process rather than a simply passive injury with the infiltration of lipids. [1, 5,6]

Therefore, inflammation has a key role in the start and progression of atherosclerosis as well as in stable and unstable angina. [7, 8]

Inflammation is the characteristic feature in all stages of atherothrombosis, and inflammatory biomarkers may prove useful in the detection, staging, and prognosis of patients with coronary artery disease (CAD). [9] The presence of inflammation at the site of the atherosclerotic lesion has a major pathogenic role in the formation of the plaque and subsequently its rupture. [10, 11] In the wake of the rupture of an atheroma, a thrombus will form and the occlusion of certain coronary arteries will happen—resulting in the necrosis of the subtended myocardial tissue. Of all CAD complications, the most common is acute coronary syndrome (ACS)—comprising ST-segment-elevation myocardial infarction (STEMI), non-STEMI, and unstable angina pectoris. [10]

Recent studies have demonstrated that the neutrophil-to-lymphocyte ratio (NLR), which is calculated by counting white blood cell subtypes, acts as a new prognostic and inflammatory marker in cardiovascular diseases. [8, 12, 13] Lately, an increased NLR has been reported to be associated with the increased openness of the infarcted vessel before intervention, no-reflow phenomenon after angioplasty, and also increased mortality in patients with acute STEMI. [14-16] Platelet activation is a major factor in the development of ACS. In addition, lymphopenia indicates physiological stress and poor general conditions. [17, 18] Recent research has shown that the platelet-to-lymphocyte ratio can be considered a new prothrombotic and inflammatory marker, especially in cancer patients. [19, 20]

The strategy used for acute MI includes thrombolytic therapy or primary percutaneous coronary intervention (PCI), which is more invasive and more expensive. Primary PCI is associated with the no-reflow phenomenon as a complication, which increases mortality and morbidity. Accordingly, in the present study, we sought to investigate whether the platelet-to-lymphocyte ratio could be a predictor in the primary PCI strategy. Additionally, we evaluated the prognostic value of other laboratory data such as inflammatory indicators in this prediction.

METHOD

The present cross-sectional descriptive analytical study recruited 196 patients, who underwent primary PCI due to acute STEMI within 6 hours of symptom onset at Chamran Hospital between September 2015 and April 2017. Acute STEMI was defined as more than 30 minutes of chest pain with ST-segment elevations equal to or greater than 1 mm in 2 adjacent electrocardiogram leads or new left bundle branch block and a more-than-twofold increase from the normal range in cardiac enzymes.

Patients with cardiogenic shock on admission, active infection, systemic inflammatory disorders, cancer, blood disorders, liver disease, kidney failure, recent thrombolytic reception, and autoimmune diseases were excluded from study.

The required sample size was calculated to be 98 patients in each group, using the $n=\frac{2(Z_1+Z_2)^2\sigma^2}{d^2}$ formula. To achieve a confidence level of 0.95 and power of 0.80, we considered Z_1 and Z_2 to be 1.96 and 0.84, respectively, according to the normal distribution table. Moreover, σ is the standard deviation of the platelet-to-lymphocyte ratio in each group and d is the maximum acceptable error in the estimates, considered equal to 0.4σ.

Sampling

Demographic data—including age, sex, history of previous angioplasty, diabetes, hypertension, hyperlipidemia, and family history of premature CAD—were collected by the investigators using a questionnaire. Before the intervention, all the patients received 300 mg of aspirin and

600 mg of oral clopidogrel. Additionally, 5000 units of heparin was injected intravenously just before the start of the intervention.

Angiography and Angioplasty Stages

After the prepping and draping of the femoral area, the femoral artery was punctured and the arterial sheath was inserted. Next, the left catheter was inserted under guidance of fluoroscopy to view the left marginal, left anterior descending, and left circumference vessels. Then, the the right catheter was inserted and the right coronary artery and its branches were explored. Thereafter, the vascular injury culpable for the acute infarction was subjected to angioplasty. Subsequently, at the discretion of the interventionist, balloon dilatation or post-dilatation was done. Afterward, stenting (bare-metal or drug-eluting) and injection into the coronary arteries to restore Thrombolysis in Myocardial Infarction (TIMI) flow 3 or aspiration of the thrombus were done.

The patients undergoing angioplasty were assessed via the TIMI flow grading method based on the intervention result. Therefore, they were divided into 2 groups: the no-reflow group (TIMI flows 0, 1, and 2) and the TIMI flow 3 group.

All the aforementioned demographic factors were matched between the 2 groups.

Blood samples were obtained from the study subjects in citrate-based tubes from within the first 6 hours of admission to the emergency department. The values of the complete blood cell count, blood glucose, creatinine, and lipid profile were determined using accepted standard methods. C-reactive protein and cardiac enzymes were measured in the whole study population. Thereafter, the platelet-to-lymphocyte ratio and the NLR were calculated.

Echocardiography was performed with a Vivid 3 device (GE Medical System) before PCI and also 48 hours afterward to determine the left ventricular ejection fraction and the diastolic function.

Data Analysis

Descriptive statistics, tables, graphs, and central and dispersion parameters were used to describe the demographic data. The T-test and the Mann–Whitney test were utilized for comparisons. All the analyses were conducted with SPSS, version 22. In all the tests, the significance level was considered 0.05.

RESULTS

Demographic Information

The study population comprised 196 patients: 98 in the no-reflow group and 98 in the TIMI flow 3 group. The study sample was recruited from among patients who underwent primary PCI due to acute STEMI within 6 hours of symptom onset at Chamran Hospital between September 2015 and April 2017. The mean age of the subjects was 64.14 years, with a standard error of mean of 1.207. The mean age of the no-reflow group was 65.19 ± 19.487 years and the mean age of the TIMI flow 3 group was 63.08 ± 13.858 years, with the difference between the 2 groups failing to constitute statistical significance ($P = 0.383$) (Table 1).

There were 158 (80.6%) male and 39 (19.4%) female patients: 78 male and 20 female patients in the no-reflow group and 80 male and 18 female patients in the TIMI flow 3 group. The 2 groups were more or less homogenous in terms of gender (Table 1).

Among the subjects, there were 110 diabetic and 86 nondiabetic individuals; this finding is consistent with previous investigations showing that diabetes is a risk factor. Moreover, there were 26 nondiabetic and 72 diabetic patients in the no-reflow group and 60 nondiabetic and 38 diabetic patients in the TIMI flow 3 group. The difference between the 2 groups was statistically extremely significant; thus, it can be concluded that diabetes is a major risk factor for cardiovascular diseases (4.366-fold higher risk) (Table 1).

As is shown in Table 2, the mean fasting blood sugar level was statistically significantly different between the 2 groups (184.09 in the

no-reflow group and 88.05 in the TIMI flow 3 group) (P <0.001).

The white blood cell count was not significantly different between the 2 study groups (P = 0.840), and nor was the neutrophil count significantly different between the groups (P = 0.103)—although its percentile tended toward statistical significance (P = 0.041). Moreover, the study groups were not statistically significantly different in terms of the lymphocyte count (P = 0.175). It has been shown that the lymphocyte count is changed in tandem with the white blood cell count; consequently, the lymphocyte percentile showed no significant difference between the 2 groups (P = 0.155). Importantly, the difference between the groups vis-à-vis the platelet count constituted significant statistical difference (P = 0.004).

Regarding the lipid profile and the levels of cholesterol, triglycerides, and low-density lipoprotein were statistically different between the 2 groups. However, the difference between the groups apropos the level of high-density lipoprotein was not statistically significant (P = 0.197). Higher levels of cholesterol, triglycerides, and low-density lipoprotein were found in the no-reflow group, where a worse medical background was expected.

In addition, the creatinine level was significantly different between the 2 study groups (P <0.001), suggesting that kidney dysfunction is accompanied by cardiac and coronary dysfunction.

Among the cardiac markers, the difference between the study groups concerning the troponin level was not statistically meaningful (P = 0.099). The level of C-reactive protein, as an inflammatory indicator, was significantly different between the 2 groups (P = 0.016). Therefore, inflammation plays a major role in atherosclerotic lesion and vascular changes.

According to our results, several components of the blood cell count were of prognostic value; nonetheless, none of them had meaningful prognostic value. The neutrophil-to-platelet ratio, platelet-to-white blood cell ratio, platelet-to-lymphocyte ratio, and NLR had P values of 0.151, 0.070, 0.604, and 0.182—respectively (Table 2).

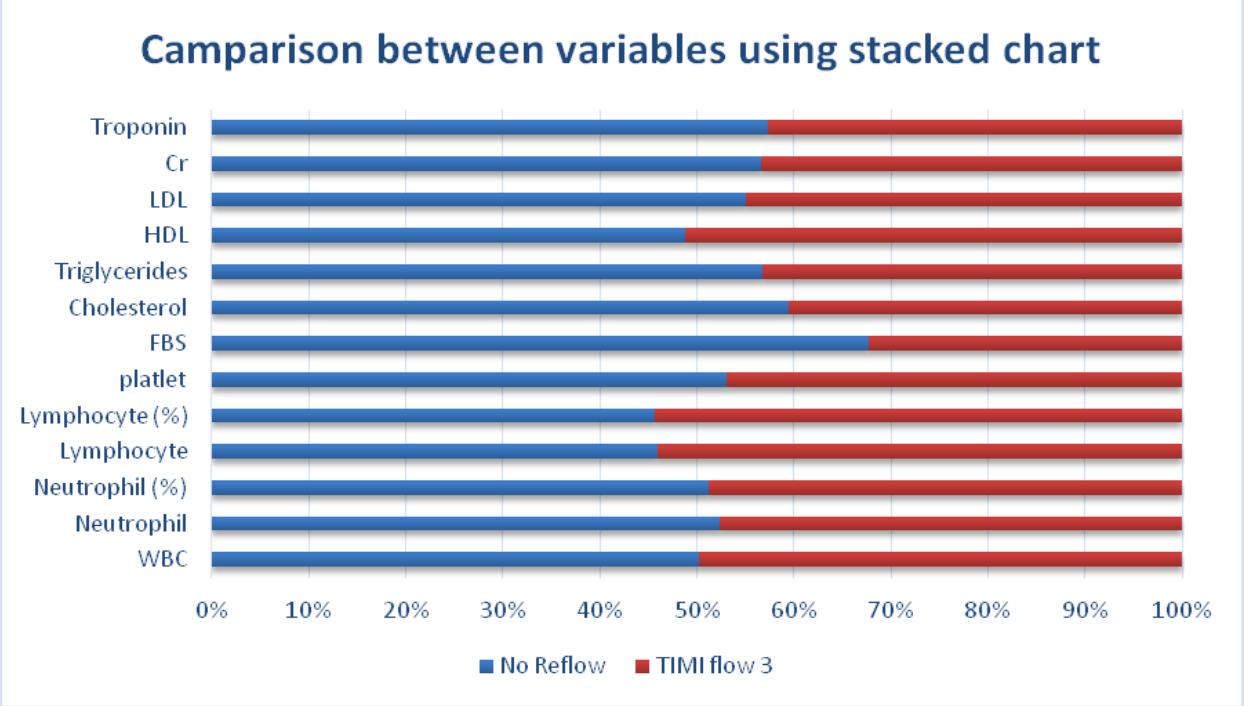

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Table 1 . Demographic information

Demographic Factor	No-Reflow Group	TIMI Flow 3 Group	*P*
Age	65.19±19.487	63.08±13.858	0.383
Gender			
male	78 (39.7%)	80 (40.8%)	
female	20 (10.2%)	18 (9.1%)	
Diabetes			
diabetic	72	38	
nondiabetic	26	60	

Table 2 . Comparison of the variables between the 2 study groups

	No-Reflow Group Mean	TIMI Flow 3 Group Mean	*P*
WBC (mil/mL)	10414.29	10313.97	0.840
Neutrophil (per µL)	8070.87	7348.12	0.103
Neutrophil (%)	75.76	72.06	0.041
Lymphocyte (per µl)	1766.08	2072.48	0.175
Lymphocyte (%)	18.53	22.03	0.155
Platelet (per µl)	214.72	190.14	0.004
FBS (mg/dL)	184.09	88.05	0.000
Cholesterol (mg/dL)	210.14	143.38	0.000
Triglycerides (mg/dL)	155.35	118.11	0.012
HDL (mg/dL)	39.09	40.99	0.197
LDL (mg/dL)	106.74	87.39	0.000
Cr (mg/dL)	1.33	1.02	0.000
Troponin (µg/L)	6.33	4.71	0.099
CRP (mg/L)	16.97	12.75	0.016
$\frac{\text{Neutrophil}}{\text{Platelet}}$	0.038	0.042	0.151
$\frac{\text{Platelet}}{\text{Lymphocyte}}$	22.09	20.14	0.070
$\frac{\text{Platelet}}{\text{Lymphocyte}}$	158.765	188.536	0.604
$\frac{\text{Neutrophil}}{\text{Lymphocyte}}$	6.202	5.343	0.182

TIMI, Thrombolysis in Myocardial Infarction; WBC, White blood cells; FBS, Fasting blood sugar; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; Cr, Creatinine; CRP, C-reactive protein

DISCUSSION

In the current study, we aimed to determine whether the platelet-to-lymphocyte ratio could have prognostic value for predicting reflow after primary PCI.

Many previous investigations have suggested that the white blood cell count and its subtype counts can be a valuable inexpensive available method for predicting the outcome in cardiac diseases. [21, 22] A previous study concluded that many of the white blood cell subtypes had prognostic value for short- and long-term outcomes. Among them, the total while blood cell count, neutrophil count, monocyte count, and with lower confidence the lymphocyte count were remarkable. Leukocytes through their role in atherosclerosis have an important role in rendering individuals susceptible to cardiovascular diseases, both in normal healthy persons and individuals having various types of heart diseases like stable and unstable angina as well as MI. Similarly, this relationship is seen across leukocyte subtypes, predicting future

cardiovascular disease risk. To exert this effect, they act in different ways such as becoming involved in vascular plaques, promoting inflammation, inducing hypercoagulopathy, and expanding the infarction. [24] Among all the white blood cell subtypes, neutrophils have the highest predictive value and when combined with the total while blood cell count, monocyte count, or lymphocyte count at different ratios, they are of higher prognostic value. In addition, drawing upon the indication of the 2 factors of the cell blood count and inflammation confers more accurate prognoses; therefore, a combination of neutrophils and C-reactive protein has a higher predicting value. [1, 23] One of the most important and valuable ratios is the NLR, with the greatest accepted predictive value for CAD risk assessment. [1] This ratio has multiple uses and many prognostic suggestions. Notably, the NLR is used for predicting the short-term outcome and the long-term mortality in patients with STEMI and is suggested to be included in the STEMI risk-assessment model. [15, 22] Further, considering hemoglobin and the NLR together augments the predictive value of the NLR. [21] In addition, it is suggested that the NLR can have prognostic value for atrial fibrillation following coronary artery bypass graft surgery, 6-month mortality rate of patients with ACS, cardiac arrest in stable CAD, severity of atrial fibrillation, need for intensive care unit care, and finally TIMI flow grading post primary PCI. [12, 16, 17, 25-29] The NLR is also a useful inflammatory immune response indicator inasmuch as a higher NLR indicates a more advanced inflammatory disease. [30] It is also deserving of note that T lymphocytes play a role in atherosclerosis and acute MI. [31] In the present study, we focused on the role of neutrophils and lymphocytes in the no-reflow phenomenon: our results demonstrated a significant role for the neutrophil count and a negative role for the lymphocyte count.

Recently, it has been suggested that atherosclerosis and ischemic stroke have elements of inflammation and all the molecules and factors involved in inflammatory reactions can play a role in promoting CAD. Therefore, inflammation biomarkers such as C-reactive protein can be used for the detection and prognosis of cardiovascular diseases. [9] In addition to the cells responsible for inflammation, several other factors are also believed to have a role. The role of platelets in plaque formation causing vascular events of ACS has yet to be comprehensively studied. [9] Sarma et al [18] reported that platelet-to-platelet adhesion and aggregation played a major role in vascular events in ACS. Molecules inhibiting this adhesion have therapeutic use in ACS. Of similar importance, interactions between platelets and leukocytes are currently under investigation in ACS treatment because of the promoting effects of leukocytes on platelet adhesion. Thus, the platelet-to-leukocyte ratio and especially the platelet-to-neutrophil ratio could be effective in vascular events and consequently MI. In the present study, we endeavored to find out whether the platelet-to-lymphocyte ratio could have prognostic value in predicting the outcome of primary PCI. The platelet count alone is inversely associated with a good outcome (TIMI flow 3) and the difference is significant. However, previous studies have suggested that the platelet-to-lymphocyte ratio prior to intervention can be a strong and independent predicator of reflow. [32, 33] According to the findings of this study, the platelet-to-lymphocyte ratio cannot be deemed a significant tool for prediction. This result may be in consequence of concurrent changes in the lymphocyte and platelet counts. Repeating the study in various conditions and in various

groups, especially with larger sample sizes, is needed if our results are to be confirmed.

Consistent with the role of inflammation in atherosclerotic events, several previous studies have demonstrated that higher levels of C-reactive protein can increase susceptibility to atherothrombosis and consequently ischemic stroke. [34] High-sensitivity C-reactive protein is shown to be directly and independently associated with major adverse cardiac events and the prognosis of patients with ACS. [10, 14] This effect is independent of other risk factors like smoking and lipid-related risk factors. [34] In the current study, we found a positive correlation between the levels of C-reactive protein and the no-reflow phenomenon; this is consistent with the results reported by previous studies. Combining other inflammatory factors such as the erythrocyte sedimentation rate or considering a combination of the complete blood cell count and inflammatory factors may lead to a different prognostic role; this needs confirmation in future studies.

Papa et al [26] concluded that considering the NLR, C-reactive protein, left ventricular ejection fraction, fasting blood glucose, and serum iron all together could confer a better prognostic tool for cardiac arrest and nonfatal MI. In this study, it was concluded that the chances for diabetic individuals to be admitted to the hospital for primary PCI were higher than those among the nondiabetic individuals. In addition, there was a strong effect of diabetes on the TIMI flow following PCI. Therefore, diabetic individuals tend to experience the no-reflow phenomenon after PCI more frequently.

CONCLUSIONS

In the present study, we could not find prognostic value for the platelet-to-lymphocyte ratio in predicting reflow after primary PCI. Nonetheless, considering C-reactive protein, platelet count, fasting blood sugar, cholesterol, triglycerides, low-density lipoprotein, and creatinine may confer a more valuable tool for predicting the PCI outcome in patients with STEMI. Additional studies are needed to better determine their clinical prognostic value.

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