Biomedical Research 2017; 28 (20): 8963-8968 *ISSN 0970-938X*
www.biomedres.info

Relationship between platelet to lymphocyte ratio and coronary angiography timing in patients with NSTEMI.

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Abstract

Objective: To investigate the usefulness of PLR in predicting severity and complexity of coronary atherosclerosis as assessed by the SXscore in patients with Non ST elevation myocardial infarction NSTEMI who underwent nonurgent coronary angiography (CA).

Background: In NSTEMI patients, there is a debate whether early angiography and revascularization is beneficial compared with a more conservative approach. Platelet to lymphocyte ratio (PLR) is a new prognostic marker that gives idea about inflammation and aggregation pathways and may predict coronary atherosclerotic burden. PLR can be used to select patients who should go under angiography earlier due to excessive ischemic load.

Methods: We retrospectively evaluated 111 consecutive patients who presented with NSTEMI and underwent non-urgent coronary angiography between July 2016 and March 2017. The PLR was calculated as the ratio of the platelet count to the lymphocyte count. The Syntax scores SX of all patients were calculated. A low SX score was defined as ≤ 22, an intermediate score as 23 to 32, and a high score as ≥ 33.

Results: 92 patients (82.8%) had low SX scores (≤ 22), 19 patients (17.1%) had intermediate to high SX scores (≥ 23). Patients in the intermediate to high SX score group had significantly higher PLR 263 (219-366) *vs.* 117 (82-144.5) p<0.001. In ROC analysis PLR of 178 or lower predicted a low SX score defined as ≤ 22 with a sensitivity of 91.3% and specificity of 100%.

Conclusion: In patients with NSTEMI, PLR has significant association with syntax score and may be used for risk stratification and assessing optimal timing for coronary angiography.

Keywords: Platelet, Lymphocyte, NSTEMI, SYNTAX score.

Accepted on October 25, 2017

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality throughout the world [1,2]. It has a complex pathophysiology, and inflammation seems to play an important role in CAD [3]. Previous studies have shown that higher levels of inflammatory markers are associated with the severity of CAD and worse cardiovascular outcome [4]. Although endothelial damage has been known as the triggering factor for the formation of atherosclerotic plagues, inflammatory process is responsible in the initiation and progression of the atherosclerosis [3] Previous studies have demonstrated an association between high circulating platelet count and major adverse cardiovascular outcomes in patients with CAD as well as in healthy adults [5-7]. Platelet to lymphocyte ratio (PLR) is a new prognostic marker that integrates the risk prediction of these two parameters. It gives an idea about both the aggregation and inflammation pathways, and it may be more valuable than either platelet or lymphocyte count alone in the prediction of coronary atherosclerotic burden. The burden of coronary atherosclerosis is closely associated with prognosis in acute coronary syndrome (ACS) [8]. The SYNTAX score (SXscore) is an angiographic scoring system based on the severity and complexity of coronary lesions [9]. The SXscore has been shown to be able to predict mortality and morbidity at early and late follow-up in patients with ACS [10-12]. Patients with ACS may present an ST-segment elevation myocardial infarction (STEMI), non ST-segment elevation myocardial infarction (NSTEMI), or unstable angina. Current STEMI guidelines recommend urgent angiography followed by immediate mechanical opening of the infarct-related coronary artery to restore coronary flow (reperfusion therapy), a strategy that has been shown to reduce mortality. In NSTEMI patients, however, there has been continued debate over the last 10 years whether "immediate," "urgent," or "early" angiography and revascularization is more beneficial than a more "conservative" or "selective invasive" approach [13]. Since it is well known that inflammatory response is closely associated with the pathogenesis of coronary atherosclerosis, we aimed to investigated the usefulness of PLR in predicting severity and complexity of coronary atherosclerosis as assessed by the SXscore in patients with non-ST-segment ACS who underwent non-urgent

coronary angiography (CA). By this way, we also investigated if PLR can be used to select patients who should go through angiography earlier due to excessive ischemic load.

Methods

The present study is a single-center and retrospectively designed study, consisting of eligible consecutive patients who were hospitalized at our institution because of NSTEMI and underwent non-urgent coronary angiography (CAG) between July 2016 and March 2017. A total of 111 age and gender matched patients were admitted for analysis. Exclusion criteria consisted of hematologic disorders, active infectious or inflammatory diseases, rheumatologic diseases, severe renal or liver disease, chronic renal disease, use of glucocorticoids, and malignancy. Since the SXscore has been used only for patients with native coronary artery lesions, patients with histories of CAD (bypass grafting and/or coronary stent history) were also excluded. NSTEMI was diagnosed when characteristic chest pain lasted ≥ 20 min with or without associated ST-segment depression ≥ 0.1 mV and/or T-wave inversion in 2 contiguous leads on the electrocardiogram or no electrocardiographic abnormalities and presence or absence of increased levels of troponin.

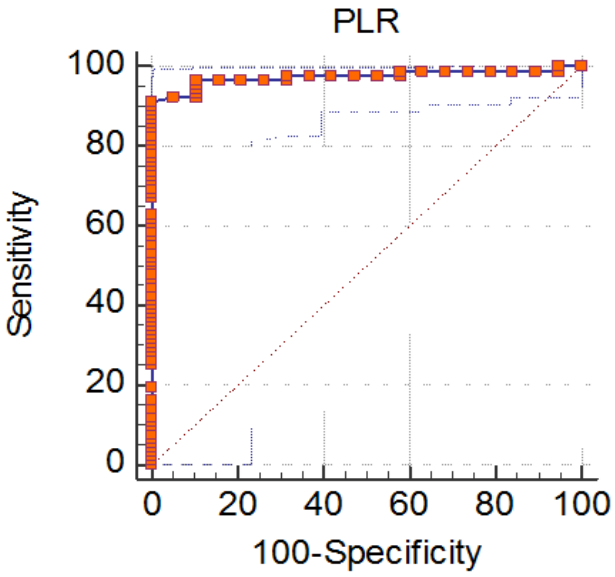

Figure 1. *Receiver operating characteristic analysis for platelet-to-lymphocyte ratio to predict syntax score (area under the curve is 0.975).*

Hyperlipidaemia was defined as serum total cholesterol ≥ 240 mg/dL, serum triglyceride ≥ 200 mg/dL, low-density lipoprotein cholesterol ≥ 130 mg/dL, previously diagnosed hyperlipidaemia, or use of lipid-lowering medication. Hypertension was defined as a systolic blood pressure (SBP) of 140 mm Hg or higher, a diastolic blood pressure (DBP) of 90 mm Hg or higher, or taking antihypertensive medication. Diabetes mellitus was defined as a fasting plasma glucose ≥ 126 mg/dl, 2-hour plasma glucose during oral glucose tolerance test (75 g) ≥ 200 mg/dl, hemoglobin-A1c ≥ 6.5%, random plasma glucose ≥ 200 mg/dl, or the use of an antidiabetic agent. The total numbers of white blood cells (WBCs), lymphocytes, neutrophils, monocytes, platelets, platecrit, platelet distribution width, mean platelet volume, hemoglobin, hematocrit, and lipid profiles were measured for all patients. The PLR was calculated as the ratio of the platelet count to the lymphocyte count.

The SXscores of all patients were calculated by two independent experienced interventional cardiologists who were blinded to the identities and clinical information of the patients from baseline diagnostic CA. Each lesion with ≥ 50% diameter stenosis in vessels ≥ 1.5 mm in diameter was scored using version 2.1 of the on-line calculator at www.syntaxscore.com. The SXscore was defined as low if ≤ 22, intermediate if ≥ 23 and ≤ 32, and high if ≥ 33 [14]. By this definition, patients with SXscores ≥ 23 were considered to have moderate to severe CAD. Thus, the patients were divided into 2 groups, those with low SXscores (≤ 22) and those with intermediate or high SXscores (≥ 23).

Table 1. *Baseline clinical and angiographic characteristics of the subjects.*

		SYNTAX Score		
		≤ 22 (n=92)	≥ 23 (n=19)	p
Age		57.58 ± 9.23	58.42 ± 9.17	0.717
Gender	Female	23 (25)	5 (26.32)	0.904
	Male	69 (75)	14 (73.68)	
Ejection Fraction		44.73 ± 8.5	39.74 ± 8.07	0.021*
Diabetes Mellitus	No	47 (51.09)	10 (52.63)	0.999
	Yes	45 (48.91)	9 (47.37)	
Hypertension	No	37 (40.22)	7 (36.84)	0.999
	Yes	55 (59.78)	12 (63.16)	
Hyperlipidemia	No	54 (58.7)	8 (42.11)	0.212
	Yes	38 (41.3)	11 (57.89)	

All analyses were performed using R 3.3.2v program (open access). Continuous variables were defined as means and standard deviation; categorical variables were given as percentages. Hematologic parameters and the PLR, which was derived from these parameters, were checked for normal distribution using Shapiro-Wilks test. Based on the distribution pattern of variables, Independent Samples t-test (for normally distributed parameters) or Mann Whitney U test (for not normally distributed parameters) was used. Categorical variables were compared by the chi-square test. Pearson's correlations were used to analyze the correlation between PLR and SXscore. Receiver-operating characteristic analyses were used to detect the cut-off value of PLR in the prediction of intermediate to high SXscore in order to select patients to be prioritized for coronary angiography; p values <0.05 were considered significant. The study protocol was approved by the local ethics committee.

Results

A total of 111 patients with non-ST-segment ACS who underwent non-urgent CA were enrolled in the study. The mean age was 57.7 ± 9.21 years; 28 of the patients (25.2%) were women. The sample was divided into two groups based on the results of CA and syntax scores. While 92 patients (82.8%) had low SXscores (≤ 22), 19 patients (17.1%) had intermediate to high SXscores (≥ 23). The differences in the baseline clinical characteristics of the patients with low and intermediate to high SXscores are outlined in Table 1. The groups were similar in age and sex. The presence of coronary risk factors such as hypertension, diabetes mellitus, and hyperlipidemia was also similar. Left ventricular ejection fraction (LVEF) values were significantly lower in patients with intermediate to high SXscores (≥ 23).

Baseline laboratory characteristics of the patients are given in Table 2. According to the admission laboratory results, patients in the intermediate to high SXscore group had significantly higher platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR) and neutrophil count. On the other hand, while platelet count was similar, lymphocyte and monocyte counts were significantly lower in the intermediate to high SXscore group. Receiver-operating characteristic analyses were used to detect the cut-off value of PLR (Tables 3). A PLR value of 178 or lower predicted a low SXscore defined as ≤ 22 with a sensitivity of 91.3% and specificity of 100% (Figure 1).

Table 2. Baseline laboratory characteristics of the subjects.

	SYNTAX Score		
	≤ 22 (n=92)	≥ 23 (n=19)	p
Platelet	253.08 ± 64.06	276.11 ± 106.08	0.372
Platecrit	0.26 ± 0.07	0.28 ± 0.1	0.243
Platelet distribution width (PDW)	13.8 (12.5-15.45)	13.6 (11.8-15.7)	0.925
Mean platelet volume (MPV)	10.67 ± 0.94	10.64 ± 0.91	0.897
Hemoglobin-b	13.16 ± 1.76	12.93 ± 1.51	0.595
Hematocrit	39.5 (36.1-42.8)	40.5 (36.7-42.2)	0.882
WBC	10764.13 ± 2980.84	10978.95 ± 3465.48	0.783
Lymphocyte	2.34 ± 0.84	1 ± 0.39	p<0.001*
Neutrophil	7.21 ± 3	9.43 ± 3.48	0.005*
Monocyte	0.79 ± 0.27	0.5 ± 0.31	p<0.001*
High density lipoprotein (HDL)	38.24 ± 9.17	40.84 ± 11.08	0.280
Low density lipoprotein (LDL)	120.47 ± 35.37	134 ± 38.63	0.138
Triglyceride	131.5 (97.5-205.5)	99 (77-191)	0.062
Platelet to Lymphocyte Ratio (PLR)	117 (82-144.5)	263 (219-366)	p<0.001*
Neutrophil to Lymphocyte Ratio (NLR)	2.84 (2.1-4.495)	9.63 (7.04-13.2)	p<0.001*

Discussion

In the present study, we have shown that PLR at admission is an independent predictor of the prevalence of more complex coronary artery lesions (SXscore ≥ 23) in patients with NSTEMI. In addition, the study has shown that a cut-off value for PLR can be detected to predict the severity of CAD in patients with NSTEMI while they have not yet been evaluated with coronary angiography. Platelets and inflammation play an important role in the pathophysiology of CAD. The role of inflammation in CAD has been studied extensively, and a consistent relationship between various inflammatory markers and CVD has been established in the past [15-17]. In cases of sustained inflammation, lymphocyte counts decrease due to increased lymphocyte apoptosis. Also, ongoing inflammatory conditions lead to increased proliferation in megakaryocytic series and relative thrombocytosis.

Lymphocytopenia is a common finding in chronic inflammatory states because of increased lymphocyte apoptosis. Moreover, the leukocyte production in bone marrow makes a shift towards increasing neutrophils and decreasing lymphocytes in response to stress. Lymphocytes represent a more convenient immune response, while neutrophils cause a destructive inflammatory reaction [18]. The diagnostic and prognostic usefulness of a low lymphocyte count was demonstrated in patients with ACS and stable CAD, respectively [19,20]. The circulating platelets may contribute

to the initiation of atheromatous plaque formation and trigger its complications [7]. High platelet and low lymphocyte counts in circulation have been suggested to be risk indicators of worse cardiovascular outcomes in previous studies [5-7,18-21]. A recently developed new prognostic marker, high PLR, integrates the predictive risk of these two parameters together. The advantage of PLR calculation could be that it reflects the condition of both aggregation and inflammatory pathways, and it may be more valuable than either platelet or lymphocyte count alone in the prediction of coronary atherosclerotic burden.

Table 3. *The receiver operating characteristic (ROC) curve analysis of platelet-to-lymphocyte ratio to predict syntax score.*

AUC (area under the ROC curve)	0.975
Standard error	0.0135
95% Confidence interval	0.926 to 0.995
Z statistic	35.272
Significance level P (Area=0.5)	<0.0001
Youden index	0.913
Criterion	≤ 178
Sensitivity	91.3
Specificity	100

In this study, we also found a significant association between platelet lymphocyte ratio (PLR) and The SYNTAX score in patients with NSTEMI. The mechanisms of the relation between PLR and SXscore are not clear. One of the possible mechanisms may be an increased inflammatory response. Balta et al. demonstrated that PLR may be a useful inflammatory marker in clinical practice [22]. Platelets, as an acute phase reactant, may also increase in number in response to various stimuli (systemic infection, inflammatory conditions, bleeding, and tumors), resulting in overproduction of proinflammatory cytokines [23,24]. Higher platelet counts may reflect underlying inflammation, as several inflammatory mediators stimulate megakaryocytic proliferation and produce relative thrombocytosis. Another likely mechanism may be the increased physiologic stress induced by ACS. It has been proposed that in response to physiologic stress during myocardial ischemia or infarction, there is release of cortisol and catecholamine, redistribution of lymphocytes to lymphatic organs, and apoptosis, which lead to lymphopenia [25]. High level of physiologic stress means high levels of cortisol and catecholamine, which may translate into a lower lymphocyte count.

In patients with NSTEMI, optimal time for coronary angiography is not defined as clearly as in STEMI except in some circumstances. Current NSTEMI guidelines recommend the assessment of ischemic risk and bleeding risk using validated risk scores in each individual patient to decide on pharmacological and invasive management [26,27]. The guidelines recommend urgent or immediate transfer to the catheterization laboratory for patients with ongoing signs and symptoms of ischemia and for patients with hemodynamic or electric instability. An early invasive management in high-risk patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is recommended; high-risk features include the evidence of myocardial necrosis resulting in troponin elevations, ongoing myocardial ischemia with dynamic ST-segment changes on the electrocardiogram, the presence of diabetes mellitus, and a history of a recent percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Meta-analyses of the randomized control trials comparing an early invasive management strategy with a more conservative or selective invasive management have shown that an early invasive management reduced the composite of death or MI, in particular in patients with high ischemic risk scores [28,29]. In summary, early intervention is recommended in high-risk ACS patients and implemented in most centers.

According to our findings, higher PLR values on admission were significantly associated with intermediate to high SXscores in patients with NSTEMI. To our knowledge, this is the first study to have investigated the role of PLR as a predictor measure of CAD severity and ischemic load to give priority to patients in terms of coronary angiography timing in patients with NSTEMI although Kurtul et al. reported in a previous study that PLR at admission is significantly associated with the severity and complexity of coronary atherosclerosis in a heterogeneous patient population consisting both STEMI and NSTEMI [30].

Study Limitations

This study has a few limitations. Firstly, platelet functions were not measured and also PLR was based on a single measurement. It would be interesting to know if the PLR changes over time and if the PLR on subsequent tests remains a predictor of the severity of coronary disease. Second, we used a retrospective design for this study, which is not the best design to follow up the effect of coronary angiography timing in terms of both morbidity and mortality. A longer period of follow-up may be necessary to assess the accuracy of deciding the coronary angiography time based on PLR at admission. Finally, all patients were from a single center and the sample size was not large. Despite the limitations of the study, we observed that individuals with higher PLR are significantly more likely to have higher SYNTAX scores. Therefore, further large-scale, prospective studies are needed to gain more information about predicting CAD severity before performing coronary angiography in patients with NSTEMI.

Conclusion

In patients with NSTEMI, PLR has significant association with the SYNTAX score. Future research needs to investigate the relationship with longitudinal data to establish a decision in terms of timing of coronary angiography in patients undergoing non-urgent CAG. PLR is easy to access and inexpensive, so before performing coronary angiography, it

appears to be additive to conventional risk factors and commonly used biomarkers for risk stratification and assessing optimal timing for coronary angiography. It can help to identify individuals at high risk for advanced CAD who might need an earlier therapeutic approach and closer clinical follow-up.

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