Relationship between platelet-to-lymphocyte ratio and coronary slow flow

Muhammed Oylumlu, Adnan Doğan, Mustafa Oylumlu[1], Abdülkadir Yıldız[1], Murat Yüksel[1], Fethullah Kayan[1], Celal Kilit, Basri Amasyalı

Department of Cardiology, Faculty of Medicine, Dumlupınar University; Kütahya-*Turkey*
[1]Department of Cardiology, Faculty of Medicine, Dicle University; Diyarbakır-*Turkey*

Abstract

Objective: The coronary slow flow phenomenon (CSFP), which is characterized by delayed distal vessel opacification in the absence of significant epicardial coronary disease, is an angiographic finding. The aim of this study is to investigate the association between platelet-to-lymphocyte ratio (PLR) and coronary blood flow rate.

Methods: This is a retrospective observational study. It was based on two medical centers. A total of 197 patients undergoing coronary angiography were included in the study, 95 of whom were patients with coronary slow flow without stenosis in coronary angiography and 102 of whom had normal coronary arteries and normal flow.

Results: The PLR was higher in the coronary slow flow group compared with the control groups (p=0.001). In the correlation analysis, PLR showed a significant correlation with left anterior descending (LAD) artery thrombolysis in myocardial infarction (TIMI) frame count. After multiple logistic regression, high levels of PLR were independently associated with coronary slow flow, together with hemoglobin.

Conclusion: PLR was higher in patients with CSFP, and we also showed that PLR was significantly and independently associated with CSFP. *(Anatol J Cardiol 2015; 15: 391-5)*

Keywords: coronary artery disease, slow flow phenomenon, platelet count, lymphocyte count

Introduction

The coronary slow flow phenomenon (CSFP), which is characterized by delayed distal vessel opacification in the absence of significant epicardial coronary disease, is an angiographic finding. Tambe et al. (1) first described this phenomenon in 1972. It was reported that the incidence of CSFP was 1% in patients who underwent coronary angiography for suspicion of coronary heart disease (2). Although several studies have shown that endothelial and microvascular dysfunction, inflammation, increased platelet activation, and homocysteine may play roles in CSFP, the etiopathogenesis of this condition is unclear (3-5). Endothelial-mediated metabolic autoregulation is very important in the regulation of coronary circulation, and the most important agents for this regulation are nitric oxide (NO) and endothelin. Impaired endothelial function in patients with CSFP was reported in the literature; when these patients were compared to normal coronary artery patients, they had lower levels of NO and higher levels of endothelin 1 (4, 6). Clinically, this phenomenon is most commonly seen in young men and smokers, presenting with acute coronary syndrome, with most patients undergoing angiography after admission (7). The clinical course is a quite debilitating period. Over 80% of patients experience recurrent chest pain, and almost 20% needs readmission to the coronary care unit (7).

Increased platelet activation has a great effect in the initiation and progression of atherosclerosis (8). On the other hand, a low peripheral blood lymphocyte count was reported to be related with major adverse cardiovascular outcomes (9, 10). In some recent studies, platelet-to-lymphocyte ratio (PLR) was investigated and revealed to have a close relation with major adverse cardiovascular outcomes (11, 12). In some cancer studies, the PLR was also disclosed to be a significant inflammatory marker to predict mortality (13, 14).

We hypothesized that PLR may be associated with CSFP, because an increased PLR was shown to be closely associated with inflammation and atherosclerosis. Therefore, in this study, we aimed to evaluate the relationship between coronary blood flow rate and PLR.

Address for Correspondence: Dr. Muhammed Oylumlu, Dumlupınar Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 43020, Kütahya-*Türkiye*
Phone: +90 505 215 79 14 Fax: +90 274 265 22 85 E-mail: muhammedoylumlu@yahoo.com

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Methods

Study population

This is a retrospective observational study. It was based on two medical centers: namely, Dicle University School of Medicine, Evliya Çelebi Education and Research Hospital Department of Cardiology; and the Dumlupınar University School of Medicine Research Hospital Department of Cardiology. In total, 197 patients were included in the study between January 2011 and July 2013, 95 of whom were patients with slow coronary flow without any stenosis at coronary angiography and 102 of whom had normal coronary arteries and normal flow.

Patients who had coronary artery disease in the coronary angiography and who had undergone surgical or percutaneous revascularization were excluded from the study. Similarly, patients with left ventricular dysfunction (ejection fraction <60%), significant valvular heart disease, acute coronary syndrome, coronary artery ectasia, old myocardial infarction, hypothyroidism, hyperthyroidism, hypertrophic cardiomyopathy, restrictive cardiomyopathy, dilated cardiomyopathy, acute or chronic hepatic and renal failure, chronic obstructive pulmonary disease, peripheral artery disease, congenital heart disease, malignancies, autoimmune diseases, and acute or chronic infectious disease were also excluded from the study.

Biochemical and hematological parameters

Antecubital venous blood was drawn from the patients in the morning after a 12-hour fast. The analyses were conducted with an automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois). It revealed the patients' total and differential leukocyte count measures, and standard techniques were used for routine biochemical tests.

Angiographic analysis

The femoral approach using the Judkins technique was used to perform coronary angiographies. Coronary arteries were displayed at the cranial and caudal angles in the right and left oblique at 15 frames per second (fps). During the angiography, the contrast agent, iopromide (Ultravist 370, Schering AG, Berlin, Germany), was used in all patients and control participants. The coronary flow was independently quantified by two observers who were blinded to the clinical details of individual participants. They used the thrombolysis in myocardial infarction frame count (TFC) (15). For each coronary artery, the time of the contrast to reach the distal decisive points was expressed as the number of frames. The moment when the contrast agent touched both sides of the coronary arteries and started to proceed was taken as a starting point, and the final point was taken for the left anterior descending artery (LAD) when the contractive agent reached the mustache; for the right coronary artery (RCA), this was the moment when the first side branch of the posterolateral artery was observed; and for the circumflex artery (Cx), this was the moment when the distal bifurcation of the longest branch was displayed (15). The difference between the first and last frames was evaluated as the number of frames. As the images were obtained at 15 frames/s, the number of frames was multiplied by 2 to get the corrected TFC. The mean reference values of normal frame numbers was described (15). In our study, two standard deviations above these mean reference values were included: 38 for LAD, 28 for Cx, and 26 for RCA were considered as CSFP.

Statistical analysis

SPSS, version 18.0 for Windows (SPSS Inc, Chicago, Illinois, USA) was used for the data analyses. The normality of the distribution of continuous variables was verified by the Kolmogorov-Smirnov test. Continuous variables were indicated as means±standard deviation; categorical variables were defined as percentages. The independent-sample t-test and the Mann-Whitney U test were used for continuous variables, and the chi-square test was conducted for categorical variables. The Pearson test was used for the correlation analysis. Statistical significance was defined as $p<0.05$. Variables for which the p value was <0.05 in the univariate analysis were assessed by multiple logistic regression analysis to evaluate the independent predictors of coronary slow flow. All variables found to be significant in the univariate analysis were included in the logistic regression model, and the results are shown as odds ratio (OR) with 95% confidence intervals (CIs).

Results

The study population consisted of 95 patients with coronary slow flow (men 57%, mean age: 53.0±10.3 years) and a control group of 102 patients with normal coronary arteries (men 53%, mean age: 54.2±11.4 years). Baseline demographic, hematological, and angiographic characteristics of the patients are shown in Table 1. In the coronary slow flow group, higher hemoglobin and PLR values were observed. The left anterior descending artery thrombolysis in myocardial infarction (LAD TIMI) frame count positively correlated with PLR value and hemoglobin ($r=0.154$, $p=0.047$ and $r=0.226$, $p=0.003$; respectively) in the Pearson correlation analysis (Fig.1). On multiple logistic regression analysis, a high level of PLR was significantly and independently associated with CSFP (OR: 1.015, 95% CI: 1.007-1.023, $p<0.001$), together with hemoglobin (OR: 1.298, 95% CI: 1.069-1.577, $p=0.009$, Table 2).

Discussion

In this study, in patients who underwent coronary angiography, it was demonstrated that there is an independent relationship between PLR and coronary slow flow phenomenon. In the results of the statistical analysis, PLR and CSFP proved to have a positive correlation. The unique nature of this study arises from the fact that to our best knowledge, it is the first report on the relationship between PLR and CSFP.

The coronary angiography revealed CSFP as delayed distal vessel opacification in the absence of significant coronary ste-

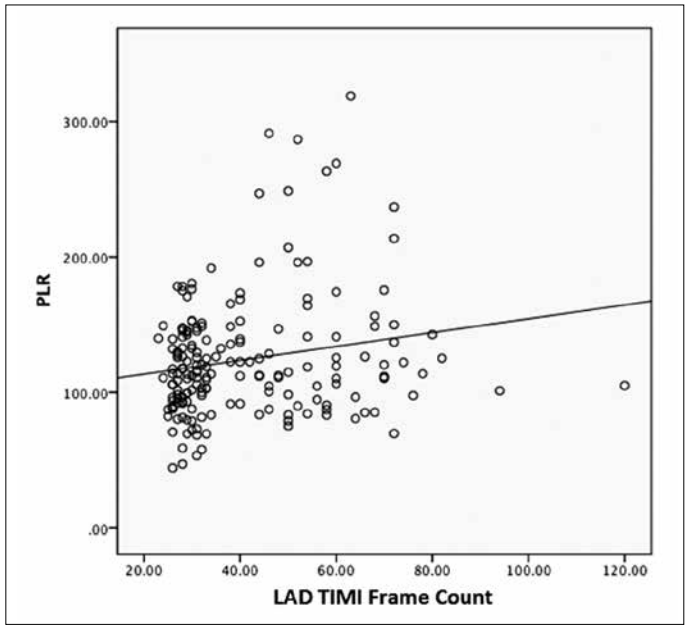

Figure 1. Pearson correlation analysis of PLR value and hemoglobin with LAD TIMI frame count
PLR - platelete to lymphocyte ratio

nosis. The angiographic clinical entity mechanism remains unknown, although several hypotheses have been proposed. Among these are inflammation, endothelial dysfunction, changes in blood rheological properties, and conditions associated with increased platelet volume (16-19).

In a study with patients with typical or atypical chest pain, Tambe et al. (1) defined the term CSFP. In the study, abnormally high small-vessel resistance due to impairment of coronary microcirculation was reported. They also proposed that small-vessel disease was responsible for this unusual angiographic finding (1).

Mangieri et al. (20) conducted left ventricular endomyocardial biopsies and reported thickening of the vessel walls with luminal size reduction, mitochondrial abnormalities, and glycogen content reduction. Besides, during angiography, they also reported normalization of the progress of dipyridamole and contrast agent, resulting from increased resting tone of small coronary arteries. Further, this could be normalized with the use of a vasodilator.

Inflammation plays a role as an important pathogenic insulting factor for various cardiovascular diseases, along with coronary heart disease. Therefore, the neutrophil-to-lymphocyte ratio (NLR) has been reported to effect various inflammatory diseases, including some cardiovascular diseases (21, 22). NLR is also an important factor in cardiovascular diseases in terms of morbidity and mortality (23). The close relationship between CSFP and inflammation was suggested based on some important data (24). In a study, it was revealed that NLR is an independent predictor in CSFP (25).

Previous studies have focused on the association between higher platelet and lower lymphocyte counts with adverse cardiovascular outcomes. In a relatively recent study with patients with non-ST-segment elevation MI, it was illustrated that a higher value of PLR plays a role as a marker of long-term mortality (11). Furthermore, PLR was also considered an inflammation marker in patients with cardiac and noncardiac disorders (26). Recently, it was demonstrated that activated platelets may have a major role in increased atherogenesis (27). Sünbül et al. (12) studied patients with hypertension and described the PLR as a

Table 1. Baseline characteristics of control and coronary slow flow groups

Variables	CSF n=95	Normal coronary flow n=102	*P*
Age, years, (%)	53.0±10.3	54.2±11.4	0.443
Male gender, n (%)	54 (56.8)	54 (52.9)	0.582
Hypertension, n (%)	36 (37.8)	46 (45.0)	0.305
Diabetes mellitus, n (%)	21 (22.1)	25 (24.5)	0.828
Smoking, n (%)	30 (31.5)	26 (25.4)	0.344
Glucose, mg/dL	116.3±45.8	112.2±37.0	0.486
Urea, mg/dL	31.6±8.4	32.9±9.8	0.310
Creatinine, mg/dL	0.82±0.16	0.84±0.20	0.346
Total cholesterol, mg/dL	190.7±42.3	198.3±40.1	0.208
HDL-cholesterol, mg/dL	45.4±13.2	44.6±13.5	0.657
LDL-cholesterol, mg/dL	115.3±37.6	120.4±35.5	0.341
Triglyceride, mg/dL	150.6±78.3	172.0±94.3	0.093
Hemoglobin, g/dL	14.2±1.6	13.7±1.6	0.047
RDW, (%)	13.8±1.5	14.1±2.4	0.239
White blood cell count, 10^3/μL	7.6±2.4	7.7±2.3	0.726
Neutrophil count, 10^3/μL	4.7±2.2	4.7±2.0	0.936
Lymphocyte count, 10^3/μL	2.0±0.7	2.2±0.6	0.127
MPV, fL	8.5±1.0	8.7±1.0	0.157
Platelet, count, 10^3/μL	249.8±62.7	236.2±57.1	0.113
PLR	135.4±54.1	113.4±31.1	0.001
NLR	2.7±1.8	2.3±1.3	0.161
LAD TFC, (frames)	56.2±14.5	29.1±2.6	<0.001
Cx TFC, (frames)	37.0±8.1	18.4±1.8	<0.001
RCA TFC, (frames)	37.4±9.2	17.8±1.8	<0.001

Cx - circumflex; HDL - high-density lipoprotein; LAD - left anterior descending; LDL - low-density lipoprotein; MPV - mean platelet volume; NLR - neutrophil-to-lymphocyte ratio; PLR - platelet-to-lymphocyte ratio; RCA - right coronary artery; RDW - red cell distribution width; TFC - TIMI frame count

Table 2. Significant predictors of coronary slow flow in univariable and multiple logistic regression analyses

Variables	Univariate analysis		Multiple logistic regression analysis	
	Odds ratio (95% CI)	*P*	OR (95% CI)	*P*
PLR	1.012 (1.005-1.020)	0.001	1.015 (1.007-1.023)	<0.001
Hemoglobin	1.199 (1.001-1.436)	0.049	1.298 (1.069-1.577)	0.009

CI - confidence interval; OR: odds ratio; PLR - platelet-to-lymphocyte ratio

significant predictor of non-dipper status. Gary et al. (28) also illustrated the close relation of increased PLR with patients at high risk for critical limb ischemia. Additionally, PLR has also been proven to be a prognostically significant factor in patients with various cancers (29, 30).

Among the widely used indices of hemoconcentration are hematocrit and hemoglobin concentration, which are routinely reported, along with other hematological variables (31, 32). Hematocrit is defined as the ratio of red cells to plasma volume, and it is generally used to offer a correct estimate of variations in plasma volume. In a study (33), hemoglobin and hematocrit values as indicators of hemoconcentration were significant in patients with coronary slow flow. In a similar vein, patients with coronary slow flow had statistically higher hemoglobin values than the control group in our study.

In the literature we reviewed so far, there was no study focusing on the relationship between PLR and coronary slow flow phenomenon. Therefore, the current study is the first one to demonstrate that PLR is an independent predictor of CSFP. The fact that we found elevated PLR values in the current study might help us better understand the pathogenesis of coronary slow flow phenomenon. It should also be highlighted that PLR is an inexpensive and readily available marker, and therefore, it may be valuable in predicting patients with CSFP.

Study limitations

Among the limitations of our study is the relatively small sample size. Another limitation was the fact that we were not able to evaluate the prognostic value of PLR in patients with CSFP. In the study, we only studied patients retrospectively, and it would have been better if we had followed the patients to further discover the association of PLR with adverse cardiac events. Additionally, usage of a single blood sample will not prediction the persistence of PLR over time. Patients' being hypotensive during the procedure might lead to a wrong diagnosis of CSFP. As our study was conducted retrospectively, there were no data available regarding patients' blood pressure values during the procedure. Furthermore, in our clinic, coronary angiography is conducted manually and at 15/fps. These are the main limitations of the current study.

Conclusion

Our findings revealed that patients with CSFP had increased PLR values, which leads to the conclusion that PLR is significantly and independently associated with CSFP. Moreover, PLR could be an important risk factor in patients with CSFP. As we consider that PLR is one of the parameters of routine CBC, which is easily available, cheap, and easily calculated, it can be suggested that the PLR may be used in the prediction of CSFP. However, further studies are needed to clearly disclose the pathophysiologic role of PLR in CSFP.

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