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.

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

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

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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.
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 (Ultrasound 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 (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).

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 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-
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 glyco- gen 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
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 hemococoncentration 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 hemococoncentration 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 predict the persistence of PLR over time. Patients’ being hypertensive 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.

Conflict of interest: None declared.

References

1. Tambe AA, Demery MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries a new angiographic finding. Am Heart J 1972; 84: 66-71. [CrossRef]
2. Goel PK, Gupta SK, Agarwal A, Kapoor A. Slow coronary flow: a distinct angiographic subgroup in syndrome X. Angiology 2001; 52: 507-14. [CrossRef]
3. Selçuk MT, Selçuk H, Temizhan A, Maden O, Ulupinar H, Baysal E, et al. Asymmetric dimethylarginine plasma concentrations and L-arginine/asymmetric dimethylarginine ratio in patients with slow coronary flow. Coron Artery Dis 2007; 18: 545-51. [CrossRef]
4. Sęgizin AT, Sığırcı A, Barutçu I, Topal E, Sęgizin N, Özdemir R, et al. Vascular endothelial function in patients with slow coronary flow. Coron Artery Dis 2003; 14: 155-61. [CrossRef]
5. Yoon HJ, Jeong MH, Cho SH, Kim KH, Lee MG, Park KH, et al. Endothelial dysfunction and increased carotid intima-media thickness in the patients with slow coronary flow. J Korean Med Sci 2012; 27: 614-8.
6. Pekdemir H, Polat G, Cin VG, Çamsari A, Çiçek D, Akkus MN, et al. Elevated plasma endothelin-1 levels in coronary sinus during rapid right atrial pacing in patients with slow coronary flow. Int J Cardiol 2004; 97: 35-41. [CrossRef]
7. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon - a new coronary microvascular disorder. Cardiology 2002; 97: 197-202. [CrossRef]
8. Tsiara S, Elisaif M, Jagroop IA, Mikhailidis DP. Platelets as predictor of vascular risk: is there a practical index of platelet activity? Clin Appl Thromb Hemost 2003; 9: 177-90. [CrossRef]
9. Acanfora D, Gheorghiade M, Trojano L, Furgi G, Pasini E, Picone C, et al. Relative lymphocyte count: a prognostic indicator of mortality in elderly patients with congestive heart failure. Am Heart J 2001; 142: 167-73. [CrossRef]
10. Ommen SR, Gibbons RJ, Hodge DO, Thomson SP. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol 1997; 79: 812-4. [CrossRef]
11. Azab B, Shah N, Akerman M, McGinn Jr JT. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST elevation myocardial infarction. J Thromb Thrombolysis 2012; 34: 326-34. [CrossRef]
12. Sünbül M, Gerin F, Durmuş E, Kivrak T, Sarı I, Tigen K, et al. Asymmetric dimethylarginine plasma concentrations and L-arginine/asymmetric dimethylarginine ratio in patients with slow coronary flow. Coron Artery Dis 2007; 18: 545-51. [CrossRef]
13. Smith RA, Bosonnet L, Ratary M, Sutton R, Neoptolemos JP, Campbell F, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg 2009; 197: 466-72. [CrossRef]
14. Smith RA, Ghanéh P, Sutton R, Ratary M, Campbell F, Neoptolemos JP. Prognosis of resected ampullary adenocarcinoma by preoperative serum CA19-9 levels and platelet-lymphocyte ratio. J Gastrointest Surg 2008; 12: 1422-8.
15. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996; 93: 879-88. [CrossRef]

16. Kopetz V, Kennedy J, Harezstyn T, Stafford I, Willoughby SR, Beltrame JF. Endothelial function, oxidative stress and inflammatory studies in chronic coronary slow flow phenomenon patients. Cardiology 2012; 121: 197-203. [CrossRef]

17. Xia S, Deng SB, Wang Y, Xiao J, Du JL, Zhang Y, et al. Clinical analysis of the risk factors of slow coronary flow. Heart Vessels 2011; 26: 480-6. [CrossRef]

18. Ari H, Ari S, Erdoğan E, Tiryakioğlu O, Huysal K, Koca V, et al. The effects of endothelial dysfunction and inflammation on slow coronary flow. Turk Kardiyol Dern Ars 2010; 38: 327-33.

19. Çelik T, Yüksel UC, Bugan B, İlyiyoy A Çelik M, Demirkol S, et al. Increased platelet activation in patients with slow coronary flow. J Thromb Thrombolysis 2010; 29: 310-5. [CrossRef]

20. Mangieri E, Macchiarelli G, Ciavolella M, Barilla F, Avella A, Martinotti A. Slow coronary flow: clinical and histopathological features in patients with otherwise normal epicardial coronary arteries. Cathet Cardiovasc Diagn 1996; 37: 375-81. [CrossRef]

21. Kaya H, Ertaş F, İslamoğlu Y, Kaya Z, Atılgan ZA, Çil H, et al. Association between neutrophil to lymphocyte ratio and severity of coronary artery disease. Clin Appl Thromb Hemost 2014; 20: 50-4. [CrossRef]

22. Sönmez O, Ertaş G, Bacaksız A, Taşal A, Erdoğan E, Ağaoğlu E, et al. Relation of neutrophil-to-lymphocyte ratio with the presence and complexity of coronary artery disease: an observational study. Anatol Kardiyol Derg 2013; 13: 662-7.

23. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther 2013; 11: 55-9. [CrossRef]

24. Kalay N, Aytekin M, Kaya MG, Özbek K, Karayakalı M, Söğüt E, et al. The relationship between inflammation and slow coronary flow: increased red cell distribution width and serum uric acid levels. Turk Kardiyol Dern Ars 2011; 39: 463-8. [CrossRef]

25. Doğan M, Akyel A, Çimen T, Bilgin M, Sunman H, Kasapkara HA, et al. Relationship Between Neutrophil to Lymphocyte Ratio and Slow Coronary Flow. Clin Appl Thromb Hemost 2013 Jul 26. [Epub ahead of print]

26. Dotsenko O, Chaturvedi N, Thom SA, Wright AR, Mayet J, Shore A, et al. Platelet and leukocyte activation, atherosclerosis and inflammation in European and South Asian men. J Thromb Haemost 2007; 5: 2036-42. [CrossRef]

27. Shoji T, Koyama H, Fukumoto S, Maeno T, Yokoyama H, Shinohara K, et al. Platelet activation is associated with hypoadiponectinemia and carotid atherosclerosis. Atherosclerosis 2006; 188: 190-5. [CrossRef]

28. Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One 2013; 8: e67688. [CrossRef]

29. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg 2010; 200: 197-203. [CrossRef]

30. Raungkaewmanee S, Tangjitgamol S, Manusirivithaya S, Sriajipracharoen S, Thavaramara T. Platelet to lymphocyte ratio as a prognostic factor for epithelial ovarian cancer. J Gynecol Oncol 2012; 23: 265-73. [CrossRef]

31. Costill DL, Fink W. Plasma volume changes following exercise and thermal dehydration. J Appl Physiol 1974; 37: 521-5.

32. Greenleaf JE, Convertino VA, Mangseth GR. Plasma volume during stress in man: Osmolarity and red cell volume. J Appl Physiol 1979; 47: 1031-8.

33. Kargın R, Emiroğlu Y, Pala S, Akgakoğlu M, Aung SM, Candan O, et al. Association of indicators of dehydration and haemoconcentration with the coronary slow flow phenomenon. Koşuyolu Kalp Derg 2010; 13: 6-10.