Association between platelet to lymphocyte ratio and saphenous vein graft disease in patients with stable angina pectoris

Harun Kundi, Ahmet Balun, Hülya Çiçekcioğlu, Mustafa Çetin, Emrullah Kızıltunç, Zehra Güven Çetin, Feridun Vasfi Ulusoy, Ender Örnek

Department of Cardiology, Ankara Numune Education and Research Hospital; Ankara-*Turkey*

Abstract

Objective: In this study, we aimed to investigate the relation of platelet to lymphocyte ratio (PLR) in saphenous vein graft disease (SVGD) in patients with stable angina pectoris after coronary artery bypass graft surgery.

Methods: A total of 455 patients were included in the study. There were 210 patients with SVGD and 245 patients without SVGD. The effects of different variables on SVGD were computed in logistic regression analysis.

Results: The platelet count, lymphocyte count, PLR, high-density lipoprotein (HDL), Na, and ALT were significantly associated with SVGD. In multivariate regression analysis, HDL and PLR were found to be significantly associated with SVGD.

Conclusion: To the best of our knowledge, this is the first study showing the significant association of PLR with SVGD. This study suggests that PLR can be used as a marker of SVGD because it is an easily available and inexpensive test. *(Anatol J Cardiol 2016; 16: 349-53)*

Keywords: inflammation, saphenous vein graft disease, platelet to lymphocyte ratio

Introduction

Coronary artery bypass graft surgery (CABG) is a widely used treatment option for the revascularization of stenotic coronary arteries. Saphenous venous and arterial grafts are commonly used in CABG. Patency rates of saphenous vein graft (SVG) is relatively low, and 10-year patency rate for SVG was reported to be 61% (1).

Platelets are known to play a role in atherosclerosis (2). Also, previous studies demonstrated the role of platelets in saphenous vein graft disease (SVGD). It was shown that high mean platelet volume, platelet distribution width, plateletcrit, and platelet count were associated with SVGD (3-5). Lymphocytes were also shown to play role in the chronic inflammation of atherosclerosis (6), and a histopathological study demonstrated that lymphocytes were associated with SVGD (7).

Platelet to lymphocyte ratio (PLR) has been defined as a new prognostic marker in coronary artery disease (CAD). Increased PLR has been demonstrated to be associated with adverse outcomes and low left ventricular function in patients with acute coronary syndrome (ACS) (8, 9). A high PLR correlated with in-hospital mortality in patients with ST-elevated myocardial infarction (10, 11), severity of CAD (12), and no reflow in patients with ST-segment elevation myocardial infarction (13). However, no studies till date have investigated PLR in SVGD.

In this study, we aimed to investigate the predictive value of PLR in SVGD patients with stable angina pectoris (SAP).

Methods

Patients

After gaining approval for the study protocol by local Ethics Committee of our hospital, we retrospectively analyzed the electronic patient record system of our hospital and found 7586 patients who underwent coronary angiography due to various reasons in our clinic between January 2008 and April 2014. Among them, 455 cases with SVG that fulfilled the inclusion criteria were included in the study. There were 210 patients with SVGD and 245 patients without SVGD. There were 283 (62.2%) male patients. The mean age of the patients was 68.45±10.08 years (Table 1).

Inclusion and exclusion criteria

Inclusion criteria were the presence of a previous coronary artery bypass graft (CABG) surgery at least 1 year ago, SVG-use during CABG, and the presence of SAP. The exclusion criteria were the presence of ACS, decompensated heart fail-

Address for Correspondence: Dr. Harun Kundi, Ankara Numune Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Ankara-*Türkiye* Phone: +90 532 352 93 93 E-mail: harunkundi@hotmail.com

Accepted Date: 31.03.2015 **Available Online Date:** 05.05.2015

DOI:10.5152/akd.2015.6224

Table 1. Baseline clinical characteristics of patients with or without saphenous vein graft disease, and the comparison of the groups for parameters that were studied (univariate analysis)

		SVGD positive n=210 (46.2%)	SVGD negative n=245 (53.8%)	Total n=455 (100%)	*P* value
Age, mean±SD		67±11	69±9	68±10	0.518
Gender	Male, n,%	136 (64.7%)	147 (60%)	283 (62.2%)	0.078
	Female, n %	74 (35.3%)	98 (40%)	172 (37.8%)	0.215
LVEF, %, mean±SD		55±5	57±5	56±6	0.143
Hb, gr/dL, median (IQR)		13.7 (12.5-14.6)	13.4 (13-14)	13.6 (13-14.40)	0.120
WBC count/µL, mean±SD		9206±3403	8864±4160	9022±3829	0.041*
Neutrophil count,/µL, mean±SD		6780±3257	5967±3941	6342±3660	0.160
Platelet count, x10^9/L, median (IQR)		236 (197-275)	226 (148-258)	226 (183-267)	<0.001*
Lymphocyte count/µL, mean±SD		1526±658	2019±806	1792±780	<0.001*
PLR, mean±SD		179±68	119±45	147±64	<0.001*
Creatinine, mg/dL, mean±SD		0.99±0.31	1.08±0.31	1.04±0.31	0.657
Na, mEq/L, mean±SD		138±3.4	139±3.3	139±3.4	0.692
Total cholesterol, g/dL median (IQR)		183 (147-214)	180 (145-203)	180 (147-206)	0.784
LDL, g/dL, mean±SD		112±38	108±35	110±36	0.624
HDL, g/dL, mean±SD		37±14	40±9	39±12	0.006*
ALT, U/L, median (IQR)		21 (17-34)	17 (13-24)	19 (14-27)	<0.001*
TSH, ıu/mL, mean±SD		2.2±0.4	2.1±0.7	2.1±0.8	0.588
GGT, U/L, median (IQR)		26 (15-44)	28 (16-35)	27 (16-44)	0.871

ALT - alanine aminotransferase; GGT - gamma glutamyl transferase; HDL - high density lipoprotein; IQR - interquartile range; LDL - low density lipoprotein; LVEF - left ventricular ejection fraction; PLR - platelet to lymphocyte ratio; SD - standard deviation; SVGD - saphenous vein graft disease; TSH - thyroid stimulating hormone; WBC - white blood cell.
*statistically significant

ure, atrial fibrillation, congenital valvular disease, idiopathic dilated or hypertrophic cardiomyopathy, congenital heart disease, renal failure (serum creatinine>2.0 mg/dL), severe hepatic disease, malignant neoplasms, infection, and inflammatory diseases.

Data collection

All patients were hospitalized and underwent coronary angiography and echocardiography. Coronary angiography was performed according to the Judkins technique. An aortic root angiography was performed, and at least two planes were obtained for all SVG images. At least one SVG with ≥50% stenosis was defined as SVGD, and the patients were divided into two groups based on the presence or absence of SVGD.

Transthoracic echocardiography was performed within 72 h of the patients' admission to the hospital. Left ventricular ejection fraction (LVEF) was calculated by the Simpson's method.

Peripheral venous blood samples of the patients were obtained on their admission to the inpatient ward. An automated blood cell counter (Beckman Coulter analyzer, California, USA) was used for measuring complete blood count parameters. Blood biochemistry parameters levels that were measured were: creatinine, Na, alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), total cholesterol, high-density lipoprotein (HDL), low- density lipoprotein (LDL), gamma-glutamyl transferase (GGT), and thyroid stimulating hormone (TSH).

Statistical analysis

SPSS 22.0 statistical package program (SPSS Inc. Chicago, IL, USA) was used to perform all data analyses. Kolmogorov-Smirnov test was used to analyze the distribution pattern. Continuous data were presented as median and interquartile range or mean+standard deviation. The effects of different variables on SVGD were computed in univariate logistic regression analysis. The variables included were age, gender, LVEF, hemoglobin, WBC, neutrophil, lymphocyte and platelet counts, PLR, creatinine, Na, total cholesterol, LDL, HDL, ALT, TSH, and GGT.

Variables that had an unadjusted p value of <0.10 in logistic regression analysis were identified as potential risk markers and then included in the full model. We eliminated potential risk markers with likelihood ratio tests with reduced model using stepwise multivariate logistic regression analyses. The variables found to be significant in univariate logistic regression analysis were considered as potential risk markers and included in multivariate regression analysis. A p value of <0.05 was considered statistically significant with a confidence interval of 95%. The receiver operating characteristics (ROC) curve was used to show the sensitivity and specificity of PLR, and the optimal cut-off value for predicting SVGD.

Results

There were 210 (46.2%) patients with SVGD (mean age, 67.40±11.15 years, 65% males), and 245 (53.8%) patients without SVGD (mean age, 69.36±9.10 years, 60% males). Baseline characteristics of the patients and comparison of the studied parameters with relation to the presence of SVGD are presented in Table 1. There were no differences between the two groups for LVEF, age, gender, neutrophil count, hemoglobin levels, total cholesterol, Na, creatinine, LDL, TSH, or GGT. However, ALT, white blood cell (WBC) count, HDL, PLR, and lymphocyte count were significantly correlated with SVGD. Multivariate regression analysis model showed that HDL levels (β=0.945, 95% CI 0.924-0.926, p<0.001) and PLR (β=1.032, 95% CI 1.019-1.045, p<0.001) were significantly correlated with the patency of the vein graft (Table 2). It was found that patients with SVGD had higher PLRs compared to those without SVGD (Fig.1).

Finally, ROC analysis was performed to determine the cut-off value of PLR to predict SVGD. The cut-off value of PLR on admission to predict SVGD in all study population was 147, with a sensitivity of 75.2% and a specificity of 73.9% (area under curve=0.800, 95% CI 0.75-0.84, p<0.001; Fig. 2).

The patients were divided into two groups on the basis of a PLR level cut-off value of 147. WBC, neutrophil counts, and female gender were significantly higher in the group with higher PLR (Table 3).

Discussion

In this study, we demonstrated that PLR, an easily available and inexpensive test, provided relevant information regarding the presence of SVGD in patients with SAP. To our knowledge, this is the first study in literature indicating PLR as an independent marker in SVGD.

The effectiveness of CABG is hindered by the obstruction of SVG after surgery. The causes of SVG failure differ according to the time period after surgery. Thrombosis is the dominant factor in graft failure in the first month after CABG, intimal hyperplasia between 1 and 12 months, and atherosclerosis is the main pathogenic insult to venous graft failure 12 months after surgery (14). We included patients who had CABG >1 year ago in our study to minimize the graft failure factors related to the surgery itself.

Histopathologically, atheroma plaque has a small lipid core with a thick fibrous cap in chronic SAP, low rupture risk, narrows the arterial lumen, and produces symptoms (15). On the other hand, it was shown that the saphenous vein graft atheroma contained more foam and inflammatory cells including multinucleate giant cells compared to the native coronary atheroma (16). These findings indicate that inflammation plays a role in SVDG, similar to native CAD.

Table 2. Multiple logistic regression analysis showing independent predictors of saphenous vein graft disease

			95% Confidence interval	
	P	β	**Lower**	**Upper**
Lymphocyte/μL	0.243	1.001	1.000	1.001
WBC/μL	0.073	0.946	0.913	0.977
Platelet, x10^9/L	0.068	1.000	1.000	1.000
PLR	<0.001*	1.032	1.019	1.045
HDL, g/dL	<0.001*	0.945	0.924	0.966
ALT, U/L	0.193	1.063	0.970	1.165

ALT - alanine aminotransferase; HDL - high density lipoprotein; PLR - platelet-to-lymphocyte ratio; WBC - white blood cell, *Statistically significant.

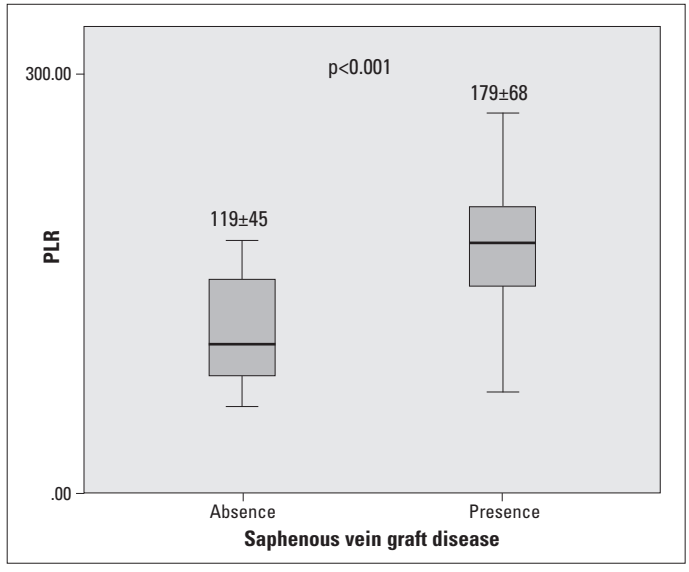

Figure 1. The levels of platelet to lymphocyte ratio in patients with and without saphenous vein graft disease
PLR - platelet to lymphocyte ratio

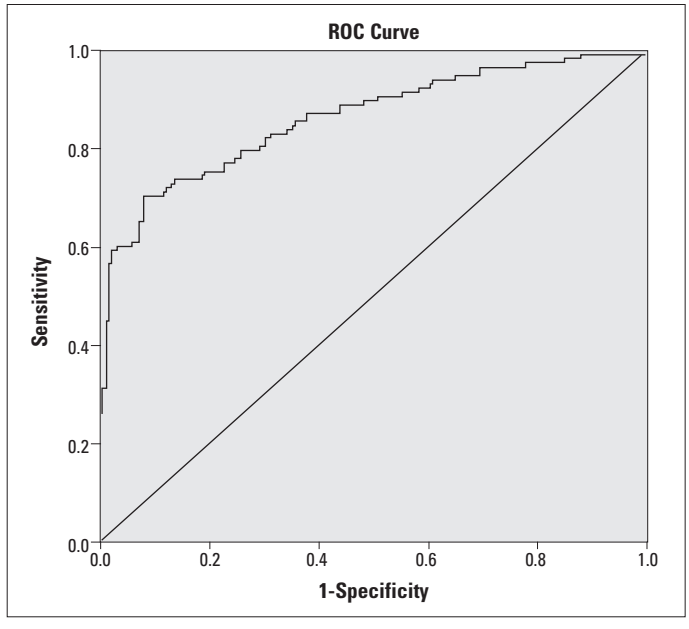

Figure 2. The receiver operating characteristic (ROC) curve of platelet to lymphocyte ratio for the prediction of saphenous vein graft disease

Table 3. Clinical characteristics of the study patients according to the cut-off level of platelet lymphocyte ratio

		PLR<147 (283) n (%)	PLR ≥147 (172) n (%)	*P*
Gender	Female, n, %	92 (32.5%)	80 (46.5%)	0.013*
	Male, n, %	191 (67.5%)	92 (53.5%)	0.367
Age, mean±SD		67±8	68±10	0.323
LVEF, %, mean±SD		56±6	55±5	0.070
WBC count/μL, mean±SD		8621±2315	9440±4914	0.025*
Hemoglobin, g/dL, median (IQR)		13.6 (12.3-13.9)	13.5 (12-13.7)	0.286
Neutrophil count/μL, mean±SD		5030 (3850-6550)	5950 (4580-7240)	<0.001*
Total cholesterol, mg/dL, mean±SD		180±45	178±37	0.204
LDL, mg/dL, mean±SD		118±39	112±31	0.370
HDL, mg/dL, mean±SD		37±13	34±12	0.082
TSH, ıu/mL, mean±SD		1.89±0.92	1.73±0.81	0.115

HDL - high density lipoprotein; LDL - low density lipoprotein; LVEF - left ventricular ejection fraction; PLR - platelet to lymphocyte ratio; TSH - thyroid stimulating hormone; WBC - white blood cell; *Statistically significant

Various studies investigated the inflammatory and hemostatic biomarkers in SAP. An inflammatory biological profile, including CRP, fibrinogen, and von Willebrand factor, distinguished patients with previous multiple acute coronary events from those with long-standing stable angina and predicted acute coronary instability (17). On the other hand, a large population-based observational study conducted in initially asymptomatic middle-aged men indicated that higher circulating levels of hs-CRP, ICAM1, interleukin 6, and interleukin 18 were equally predictive of SA and ACS, after adjustment for traditional risk factors (18). In a recent study, Açar et al. (8) showed that PLR was significantly higher in patients with poor coronary collateral circulation compared to those with good coronary collateral circulation (patients with SAP and chronic total occlusion). However, no studies till date have investigated PLR as a marker in SVGD.

Ongoing inflammatory conditions lead to increased proliferation in the megakaryocytic series and relative thrombocytosis (19). Previous studies demonstrated the relationship of adverse cardiovascular outcomes with both increased platelet and decreased lymphocyte counts (20-22). In addition, the diagnostic usefulness of low lymphocyte count was shown in patients with myocardial infarction, and its prognostic utility was demonstrated in patients with CAD (23, 24). In our study, we found higher platelet and lower lymphocyte counts in patients with SVGD and SAP when compared to those who had SAP after CABG, in the absence of SVGD. Our results indicated that high platelet and low lymphocyte counts might indicate poor outcome after CABG, in favor of SVGD.

PLR has the advantage of reflecting both activated coagulation and inflammatory pathways. In addition, PLR may be superior to individual platelet or lymphocyte counts in predicting impaired reperfusion (25). Kurtul et al. (26) showed that PLR was closely related to the severity of atherosclerosis. In another study, Azab et al. (9) revealed that adverse cardiovascular outcome in non-ST-segment elevation myocardial infarction was significantly associated with higher PLR. In our study, we investigated PLR as a marker in SVGD, for the first time in the literature, and found high PLR in patients with SVGD. Our results indicate that high PLR may be a poor prognostic factor for the development of SVGD after CABG, as it is shown to be associated with the adverse outcomes after ST-segment elevation myocardial infarction (10, 11, 13).

Significanly higher HDL levels in patients without SVGD may be regarded as an expected finding. However, high WBC counts in SVGD patients may be incidental because we excluded patients with infection and inflammatory diseases. The same is true for higher ALT levels found in the same group.

Study limitations

Our study has some limitations that must be taken into account when evaluating the results. First, previous medical treatment options were not clearly indicated due to the retrospective nature of our study. The comorbidities of the patients, including diabetes mellitus and hypertension, cannot be determined either due to the same reason. In addition, PLR was not compared with other inflammatory markers, such as CRP, fibrinogen, or myeloperoxidase, because of the retrospective nature of our study. As a result of these limitations, our results may not apply to all SAP patients after CABG.

Conclusion

We found significantly higher PLR in patients with SVGD and SAP compared to those without SVGD. PLR may be used in daily clinical practice to predict SVGD because it is a quickly accessible, widely used, and inexpensive test. Further prospective trials would better identify the clinical significance of PLR in patients with SVGD and SAP.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - E.Ö., H.K.; Design - H.K.; Supervision - H.K., M.Ç.; Research - H.K., E.K.; Materials - Z. G. Ç.; Data collection &/or processing - H.K., A.B.; Analysis &/or interpretation - F.V.U.; Literature search - H.Ç.; Writing - H.K.; Critical review - E.Ö., H.K.

References

1. Goldman S, Zadina K, Moritz T, Ovitt T, Sethi G, Copeland JG, et al. Long-term patency of saphenous vein and left internal mammary artery grafts after coronary artery bypass surgery: results from a Department of Veterans Affairs Cooperative Study. J Am Coll Cardiol 2004; 44: 2149-56.
2. Von Hundelshausen P, Schmitt MM. Platelets and their chemokines in atherosclerosis-clinical applications. Front Physiol 2014; 5: 294.
3. Tavil Y, Şen N, Yazıcı HU, Hızal F, Açıkgöz SK, Turfan M, et al. Relationship between elevated platelet volume and saphenous vein graft disease. Clin Invest Med 2010; 33: E161-7.
4. Ege M, Güray U, Güray Y, Açıkgöz S, Demirkan B. Platelet distribution width and saphenous vein disease in patients after CABG. Herz 2013; 38: 197-201.
5. Akpınar I, Sayın MR, Gürsoy YC, Karabağ T, Küçük E, Büyükuysal MC, et al. Plateletcrit. A platelet marker associated with saphenous vein graft disease. Herz 2014; 39: 142-8.
6. Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al; Intermountain Heart Collaborative Study Group. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol 2005; 45: 1638-43.
7. Bikdeli B, Hassantash SA, Pourabdollah M, Kalantarian S, Sadeghian M, Afshar H, et al. Histopathologic insight into saphenous vein bypass graft disease. Cardiology 2012; 123: 208-15.
8. Açar G, Kalkan ME, Avcı A, Alizade E, Tabakcı MM, Toprak C, et al. The relation of platelet-lymphocyte ratio and coronary collateral circulation in patients with stable angina pectoris and chronic total occlusion. Clin Appl Thromb Hemost 2015; 21: 462-8.
9. 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.
10. Temiz A, Gazi E, Güngör Ö, Barutçu A, Altun B, Bekler A, et al. Platelet/lymphocyte ratio and risk of in-hospital mortality in patients with ST-elevated myocardial infarction. Med Sci Monit 2014; 20: 660-5.
11. Oylumlu M, Yıldız A, Oylumlu M, Yüksel M, Polat N, Bilik MZ, et al. Platelet-to-lymphocyte ratio is a predictor of in-hospital mortality patients with acute coronary syndrome. Anatol J Cardiol 2015; 15: 277-83.
12. Yüksel M, Yıldız A, Oylumlu M, Akyüz A, Aydın M, Kaya H, et al. The association between platelet/lymphocyte ratio and coronary artery disease severity. Anatol J Cardiol 2014 Jul 11.
13. Yıldız A, Yüksel M, Oylumlu M, Polat N, Akyüz A, Acet H, et al. The utility of the platelet-lymphocyte ratio for predicting no reflow in patients with ST-segment elevation myocardial infarction. Clin Appl Thromb Hemost 2015; 21: 223-8.
14. Parang P, Arora R. Coronary vein graft disease: pathogenesis and prevention. Can J Cardiol 2009; 25: e57-e62.
15. Tsaknis G, Tsangaris I, Ikonomidis I, Tsantes A. Clinical usefulness of novel serum and imaging biomarkers in risk stratification of patients with stable angina. Dis Markers 2014; 2014: 831364.
16. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. Circulation 1998; 97: 916-31.
17. Bogaty P, Poirier P, Simard S, Boyer L, Solymoss S, Dagenais GR. Biological profiles in subjects with recurrent acute coronary events compared with subjects with long-standing stable angina. Circulation 2001; 103: 3062-8.
18. Empana JP, Canoui-Poitrine F, Luc G, Juhan-Vague I, Morange P, Arveiler D, et al; PRIME Study Group. Contribution of novel biomarkers to incident stable angina and acute coronary syndrome: the PRIME Study. Eur Heart J 2008; 29: 1966-74.
19. Ferroni P, Vazzana N, Riondino S, Cuccurullo C, Guadagni F, Davì G. Platelet function in health and disease: from molecular mechanisms, redox considerations to novel therapeutic opportunities. Antioxid Redox Signal 2012; 17: 1447-85.
20. Acet H, Ertaş F, Akıl MA, Oylumlu M, Polat N, Yıldız A, et al. New inflammatory predictors for non-valvular atrial fibrillation: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio. Int J Cardiovasc Imaging 2014; 30: 81-9.
21. Yıldız A, Yüksel M, Oylumlu M, Polat N, Akıl MA, Acet H. The association between the neutrophil/lymphocyte ratio and functional capacity in patients with idiopathic dilated cardiomyopathy. Anatol J Cardiol 2015; 15: 13-7.
22. Arbel Y, Finkelstein A, Halkin A, Birati EY, Revivo M, Zuzut M, et al. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis 2012; 225: 456-60.
23. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105: 1135-43.
24. Sönmez O, Ertaş G, Bacaksız A, Tasal A, Erdoğan E, Asoğlu E, et al. Relation of neutrophil-to-lymphocyte ratio with the presence and complexity of coronary artery disease: an observational study. Anatol J Cardiol 2013; 13: 662-7.
25. Oylumlu M, Yıldız A, Yüksel M, Korkmaz A, Aydın M, Bilik MZ, et al. Usefulness of platelet-lymphocyte ratio to predict stent thrombosis in patients with ST elevation myocardial infarction. Koşuyolu Kalp Dergisi 2014; 17: 81-5.
26. Kurtul A, Murat SN, Yarlioglues M, Duran M, Ergun G, Açıkgöz SK, et al. Association of platelet-to-lymphocyte ratio with severity and complexity of coronary artery disease in patients with acute coronary syndromes. Am J Cardiol 2014; 114: 972-8.