Kocaeli Med J 2019; 8; 1:40-45

Koroner arter baypas greftleme sonrası yeni başlangıçlı atrial fibrilasyonda trombosit-lenfosit oranının prediktif değeri

Predictive value of platelet-lymphocyte ratio in new-onset atrial fibrillation after coronary artery bypass grafting

Nuray Kahraman Ay

Bezmialem Vakıf Üniversitesi Tıp Fakültesi, Kardiyoloji Kliniği, İstanbul, Türkiye.

ÖZ

GİRİŞ ve AMAÇ: *Yüksek trombosit-lenfosit oranının(TLO) sistemik inflamasyon ve kardiyak mortalite ile ilişkisi bilinmektedir. Koroner arter baypas greftleme (KABG) sonrası yeni başlangıçlı atrial fibrilasyon inflamatuvar süreçlerle ilişkilidir. Bu çalışmada bir inflamasyon belirteci olan TLO' nun KABG sonrası yeni başlangıçlı atrial fibrilasyon ile ilişkisi araştırıldı.*

YÖNTEM ve GEREÇLER: *Çalışmaya izole KABG uygulanan 245 hasta dahil edildi. Postoperatif atrial fibrilasyon (AF) gelişen 57(23.1%) hasta (AF grup) ve normal sinüs ritminde (NSR grup) takip edilen 188(76.7%) hasta olmak üzere iki gruba ayrıldı. Gruplar arası klinik ve labaratuvar bulgular karşılaştırıldı. Lojistik regresyon modeli oluşturularak postoperatif AF ile değişkenler arasındaki ilişki araştırıldı.*

BULGULAR: *Yüksek yoğunluklu lipoprotein(HDL) ve lenfosit sayısının NSR grubunda anlamlı düzeyde yüksek olduğu(p<0.05), nötrofil–lenfosit oranının(NLO) ve TLO'nun ise AF grubunda anlamlı düzeyde yüksek olduğu tespit edildi(p<0.05). Multivaryant regresyon analizinde TLO'nun postoperatif AF gelişimi ile ilişkili olduğu tespit edildi(OR: 1.05 CI: 1.01-1.09, p: 0.02).*

TARTIŞMA ve SONUÇ: *Preoperatif TLO'nun KABG sonrası yeni başlangıçlı atrial fibrilasyon için prediktif değeri mevcuttur.*

Anahtar Kelimeler: *Atrial fibrilasyon, koroner arter bypas greftleme, platelet-lenfosit oranı*

ABSTRACT

INTRODUCTION: *High platelet-lymphocyte ratio is an established marker of systemic inflammation and cardiac mortality, while new onset atrial fibrillation (AF) after coronary artery bypass grafting (CABG) is related with inflammatory processes. In this study, we investigated the association of platelet-lymphocyte ratio (PLR), a marker of inflammation, with new-onset atrial fibrillation after coronary artery bypass grafting.*

METHODS: *Among a total of 245 participants who underwent isolated CABG, 57 (23.1%) had postoperative atrial fibrillation (AF group) and 188 (76.7%) had normal sinus rhythm (NSR group). Clinical and laboratory parameters were compared between the two groups. The relationship between the development of postoperative AF and the study parameters was investigated by logistic regression analysis.*

RESULTS: *High density lipoprotein (HDL) and lymphocyte count were significantly higher in NSR group (p <0.05), and neutrophil- lymphocyte ratio (NLR) and PLR were significantly higher in AF group (p <0.05). In multivariate regression analysis, PLR was associated with the development of postoperative atrial fibrillation (OR: 1.05 CI: 1.01-1.09, p: 0.02).*

DISCUSSION AND CONCLUSION: *Preoperative PLR has a predictive value for new-onset atrial fibrillation after CABG.*

Keywords: *atrial fibrillation, coronary artery bypass grafting, platelet-lymphocyte ratio*

İletişim / Correspondence:

Dr. Nuray Kahraman Ay
Bezmialem Vakıf Üniversitesi Tıp Fakültesi, Kardiyoloji Kliniği, İstanbul, Türkiye.
E-mail: drnuraykahraman@hotmail.com
Başvuru Tarihi: 31.01.2019
Kabul Tarihi: 09.04.2019

INTRODUCTION

Atrial fibrillation (AF) develops in a high proportion (20% to 40%) of patients undergoing coronary artery bypass grafting(CABG) (1). This condition, referred to as post-operative AF (PoAF), is associated with increased mortality, owing to morbidities such as thromboembolic events and cardiac failure (2). Although the exact mechanism of PoAF remains unknown, the pathogenesis seems to involve both systemic and local inflammatory processes (3).

Complete blood count is a widely available and inexpensive laboratory investigation that provides quantitative information on different types of blood cells such as erythrocytes, leukocytes, and platelets. The platelet to lymphocyte ratio (PLR), which can be readily derived from a complete blood count in a single blood sample, has been recently proposed to have a predictive value for cardiac mortality and systemic inflammation (4). However, to the best of our knowledge, the association between PLR and PoAF has not been studied until now. Therefore, our objective was to investigate the association between PLR and PoAF in patients undergoing CABG.

MATERIALS AND METHODS

A total of 245 patients undergoing CABG between January 2015 and December 2018 at Bezmialem Vakif University were included. Study subjects were assigned into two groups as those who had postoperative AF (AF group) or normal sinus rhythm (NSR). The study was designed retrospectively, and the study protocol was approved by the institutional ethics committee. The data were extracted from the hospital database.

Patients undergoing isolated CABG and having normal 12-lead electrocardiography prior to surgery were included. Patients undergoing bypass surgery on a beating heart were excluded, as were those with congestive heart failure, severe cardiac valvular disease, atrial fibrillation or flatter, peripheral vascular disease, infection, severe pulmonary or neurological conditions, malignancy, hypo- or hyperthyroidism, chronic renal or hepatic disease, or chronic hematological disease.

Based on the standard protocols followed in our unit, all patients received treatment with acetylsalicylic acid and beta-blockers starting from postoperative day 1. All patients were monitored for 2 days in the intensive care unit postoperatively. Daily 12-lead ECG recordings were retrieved from patient files and were examined with regard to the basic rhythm. New-onset AF was defined as post-CABG AF developing during hospital stay in a patient with no previous history of AF.

2D Echocardiographic examination was done in left lateral de-cubitus position with GE Vivid S5 Digital ultrasound device by using 1,5-4 MHz GE 3S transducer from parasternal long and short axis and apical 2 and 4 cavity images , by a single cardiologist. Echocardiographic evaluation was based on the according the recommendation of American Echocardiography Association. The left ventricle (LV) ejection fraction measured according to the modified Simpson method .Left atrial diameter (LA ,mm), left ventricular end-diastolic diameter (LVEDD, mm), left ventricular end-systolic diameter (LVESD, mm), were measured.

All candidates for CABG underwent routine laboratory blood testing after 12 hours of preoperative fasting. Laboratory data were retrieved from patient files. EDTA tubes were used for automated blood counts, which were performed in a Sysmex XT-1800i Hematology Analyzer (Sysmex Corporation, Kobe, Japonya). Conventional methods were used for high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglyceride, C-reactive protein (CRP), and creatinine measurements. Study groups were compared in terms of clinical and laboratory results. A logistic regression model was used to examine the association between PoAF and the studied variables.

Statistical Analyses

For statistical analyses, SPSS 16.0 for Windows was used. The means were compared between groups using t-test, while the rates were compared with chi-square test. A logistic regression model was used to identify the independent predictors of AF. A p value of less than 0.05 was considered significant. Receiver-operating characteristic (ROC) curves were obtained for PLR to explore the sensitivity and

specificity. ROC curve analysis was used to determine the optimum cutoff levels of PLR level to predict the occurrence of PoAF.

RESULTS

Of the study participants, 23.2% were found to have new-onset AF after CABG. **Table 1** shows the clinical and demographic characteristics of the patients. AF and NSR patients were comparable with respect to age and gender distribution ($p > 0.05$). Also proportion of patients with preoperative risk factors (e.g. hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease) were evenly distributed between the two groups. There were no significant differences in terms of the proportion of patients receiving treatment with acetylsalicylic acid or beta-blockers. Furthermore, echocardiographic measurements of the left atrial diameter and ejection fraction as well as the cardiopulmonary bypass cross-clamp times and number of bypass grafts did not differ significantly between the groups ($p > 0.05$).

Table 1. Baseline characteristics of patients

	NSR (n=188)	AF (n=57)	p
Age	59.3±9.4	62.1±10	0.06
Female	72(38.2%)	22(38.5%)	0.96
Hypertension	125(66.4%)	36(63.1%)	0.64
Diabetes Mellitus	43(22.8%)	15(26.3%)	0.59
Hyperlipidemia	98(52.1%)	29(50.8%)	0.86
COPD	20(10.6%)	10(17.5%)	0.16
Aspirin	153(81.3%)	45(78.9%)	0.68
Betablocker	124(65.9%)	41(71.9%)	0.40
EF (%)	47.7±8.5	46.0±8.8	0.19
Left atrium dimension(mm)	39.2±6.5	40.4±7.9	0.25
Cardiopulmonary by-pass time(min)	94.3±12.1	98±9.7	0.45
Cross-clamp time(min)	63.2±8.6	61±11.2	0.56
No. of bypass grafts	2.6±0.8	2.7±0.7	0.53

NSR; Normal sinus rhythm, AF; Atrial fibrillation, COPD, Chronic obstructive pulmonary disease; EF, Ejection fraction.

While patients in two groups had similar LDL, triglycerides, creatinine, and CRP levels ($p > 0.05$), NSR patients had higher HDL ($p=0.04$). With respect to hematological parameters, no significant differences in leukocyte, neutrophil, platelet counts, or hemoglobin levels were detected ($p > 0.05$). On the other hand, NSR patients had significantly higher lymphocyte count ($p=0.03$), while patients with AF had higher neutrophil-lymphocyte (NLR) and PLR ratios ($p < 0.05$) **(Table 2).**

Table 2. Comparison of the groups with regard to labaratory data

	NSR(n=188)	AF (n=57)	p
HDL (mg/dL)	48.4±12.2	44.8±10.8	0.04
LDL (mg/dL)	94.3±28.2	98.9±30.4	0.29
Triglyceride(mg/dL)	127.4±21.7	134±38.6	0.10
White cell count ($\times 10^9$ / L)	8.9±2.5	8.7±2.3	0.52
Lymphocyte ($\times 10^9$ / L)	2.7±2.5	1.9±1.1	0.03
Neutrophil($\times 10^9$ / L)	5.8±3.6	6.3±2.9	0.42
Platelet($\times 10^9$ / L)	237.9±55.7	246.1±74.0	0.37
Hemoglobin (gr/dL)	13.8±1.8	13.6±2.0	0.63
NLR	2.9±3.3	4.5±3.8	0.004
PLR	111.9±77	167.2±116	<0.001
Creatinine(mg/dL)	1.0±0.7	0.8±0.2	0.32
CRP (mg/dL)	0.92 ±1.4	1.38±2.1	0.06

NSR; Normal sinus rhythm, AF; Atrial fibrillation, HDL, High density lipoprotein; LDL, Low density lipoprotein; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; CRP, C-reactive protein.

Univariate and multivariate regression analyses showed a significant association of PLR with PoAF (OR: 1.05 CI : 1.01-1.09, p: 0.02). **(Table 3).**

Table 3. Multivariable logistic regression analysis showing the independent predictors of in postoperative atrial fibrillation

Variables	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
NLO	0.89(0.83-0.97)	0.009	0.90(0.78-1.04)	0.18
TLO	1.0(1.0-1.0)	0.000	1.05(1.01-1.09)	0.02
CRP	0.86(0.74-1.01)	0.07	0.85(0.72-1.01)	0.07
HDL	1.02(1.0-1.05)	0.04	1.02(0.99-1.05)	0.07
LDL	0.99(0.98-1.0)	0.29		
Age	0.97(0.94-1.0)	0.06	0.97(0.94-1.0)	0.11
Sex	1.01(0.55-1.86)	0.96		
Diabetes Mellitus	0.83(0.42-1.64)	0.59		
Hypertension	1.15(0.62-2.14)	0.64		
Left atrium dimension	0.97(0.93-1.01)	0.25		
COPD	0.56(0.24-1.27)	0.16		

OR, odds ratio; CI, confidence interval;; NLR, Neutrophil to lymphocyte ratio; PLR, Platelet to lymphocyte ratio; CRP, C-reactive protein; HDL, High density lipoprotein; LDL, Low density lipoprotein; COPD, Chronic obstructive pulmonary disease.

The area under the ROC curve (95% confidence interval) for preopera-tive PLR , as a predictor of postoperative AF, was 0.68 (0.60–0.77) (p<0.001). Using a cutpoint of 121.5, the preoperative level correlated with the incidence of AF with a sensitivity of 54 % and specificity of 73% **(Figure 1).**

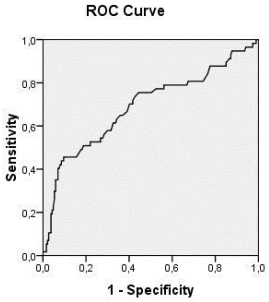

Figure 1. ROC curve analysis for prediction of postoperative atrial fibrillation by PLR

DISCUSSION

In this study, a high preoperative PLR was associated with the development of new-onset PoAF in patients undergoing CABG. Also, PoAF patients had higher preoperative NLR. On the other hand, subjects with normal sinus rhythm had higher HDL and lymphocyte measurements.

Atrial fibrillation has been reported in up to 40% of patients undergoing coronary artery bypass surgery, and it has been associated with increased morbidity and poorer long-term survival (5, 6). Identification of predictors of PoAF may assist in developing preventive strategies. Several inflammatory markers such as CRP, complement, NLR, leukocyte count, and interleukin-6(IL-6) have been reported to be associated with an increased incidence of postoperative atrial fibrillation. In addition, NLR, and (PLR, which can be derived from a complete blood count, have been reported to be markers of inflammation (7). There are not so many studies in the literature about PLR and PoAF .In 135 patients Güngör et al. found PLR is predictive for PoAF which was similar to our results, involving 245 patients.

Previously, many studies have investigated the predictors of PoAF. In a study by Anatolevna et al., left atrial dimensions as well as increased postoperative IL-6, IL-8, and superoxide dismutase were identified as predictors of PoAF (8), while advanced age, low preoperative creatinine clearance, and increased left atrial diameter were reported to be independent predictors of PoAF in the study by Ferreira et al. (9). On the other hand Hidayet Ş. et al. emphasised that LA volume index (LAVİ) and mechanical functions are better indicator than LA diameter in new onset PAF after CABG(10). Also, vitamin D deficiency was reported to be an independent predictor for PoAF in the study by Emren et al., and increased serum uric acid levels had a predictive role for PoAF in the study by Memetoglu et al. (,11,12). In the present study, we did not detect significant relationships between PoAF and clinical characteristics such as age, gender, diabetes mellitus, and hypertension as well as echocardiographic parameters.

In addition, several previous studies examined the association between inflammatory markers and PoAF. For instance, Ramlawi et al. suggested that inflammatory response (oxidative stress, complement activation) occurring after cardiopulmonary bypass results in elevation of bio-markers such as CRP and interleukin-6, which is associated with PoAF (13). Again, Lo et al. found an increased risk of AF after CABG in patients with elevated CRP (14), while Gibson et al. reported an association between AF and elevated pre- and post-operative NLR (15). Although PoAF patients had higher NLR in our study, there were no significant differences in CRP between those with or without PoAF.

Platelets play an important role in hemostasis, which represents a physiological response to vascular injury to prevent excessive blood loss. Similarly, platelets are also involved in pathological thrombus formation after the rupture of atherosclerotic plaques. Adhesion of platelets into the subendothelial tissue after intimal injury and the stimulation of the coagulation cascade and platelet aggregation by granules released upon the activation of platelets result in the formation of platelet plug and fibrin (16). Platelets also have proinflammatory and immunomodulatory activities occurring via the release of chemokines and cytokines. Therefore, platelet activation has important implications with regard to coronary artery disease , and

cardiovascular event (17). Accordingly, in the study by Nikolsky et al., an elevated platelet count was reported to be a significant predictor of mortality in patients with acute myocardial infarction (18). Again, PLR was found to be a predictor of in-hospital and long-term mortality in patients undergoing elective percutaneous coronary intervention (PCI), as well as for no-reflow, in-hospital mortality, and long-term mortality in patients undergoing PCI after a myocardial infarction (19-21). In a study by Erdem et al., the mean platelet volume , which is potentially one of the most significant bio-markers of platelet activation, was found to be a predictor of AF development after CABG (22). Also, in our multivariate analysis, PLR was found to have a predictive role for the development of PoAF.

AF is the most frequent morbidity after coronary bypass surgery, and PoAF has been reported to be associated with long-term mortality (23). Pharmacological agents such as beta-blockers and amiodarone are effective against the development of PoAF, and proper identification of the risk of PoAF may assist in the implementation of preventive strategies. PLR, which can be readily derived using a widely available and inexpensive test such as the complete blood count, can successfully predict the risk of AF after CABG.

CONCLUSION

Our results suggest that elevated pre-operative platelet to lymphocyte ratio is closely associated with new onset AFR after CABG. Therefore, pre-operative PLR may represent a simple, inexpensive, but valuable marker for predicting the risk of postoperative AFR. Our results need to be supported by prospective and randomized trials to develop evidence-based protocols.

Study limitations

The limitations of this study include the small sample size and the retrospective design. Left atrial volume index was not evaluated and no long-term noninvasive recording.

REFERENCES

1. Kaireviciute D, Aidietis A, Lip GY. Atrial fibrillation following cardiac surgery: clinical features and preventative strategies. Eur Heart J. 2009 Feb;30(4):410-25.

2. Mitchell L B ; C CS Atrial Fibrillation Guidelines Committee . Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention and treatment of atrial fibrillation following cardiac surgery. Can J Cardiol. 2011 ; 27 : 91–7

3. Kaw R , Hernandez AV , Masood I , Gillinov AM , Saliba W, Blackstone EH . Short and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2011;141:1305–12.

4. Çiçek G, Açıkgoz SK, Bozbay M, Altay S, Uğur M, Uluganyan M, et al. Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio combination can predict prognosis in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Angiology. 2015 May;66(5):441-7.

5. El-Chami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, et al. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. J Am Coll Cardiol. 2010;55:1370–6.

6. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg. 1993;56:539–49.

7. Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Res. 2018 Nov 19;271:131-5.

8. Anatoĺevna RO, Veniaminovich FO, Mikhaylovich KS. Predictors of new-onset atrial fibrillation in elderly patients with coronary artery disease after coronary artery bypass graft. J Geriatr Cardiol. 2016 Jul;13(5):444-9.

9. Ferreira AF, A Saraiva F, Moreira R, J Cerqueira R, J Amorim M, Pinho P, et al. Postoperative Atrial Fibrillation After Coronary Artery Bypass Grafting Surgery. Rev Port Cir Cardiotorac Vasc. 2017 Jul-Dec;24(3-4):129.

10. Hidayet Ş, Yağmur J, Bayramoğlu A, Taşolar MH, Kurtoğlu E, Özyalın F. Prediction of postoperative atrial fibrillation with left atrial

mechanical functions and NT-pro ANP levels after coronary artery bypass surgery: A three-dimensional echocardiography study. Echocardiography. 2018 May;35(5):661-666.

11. Emren SV, Aldemir M, Ada F. Does Deficiency of Vitamin D Increase New Onset Atrial Fibrillation after Coronary Artery Bypass Grafting Surgery? Heart Surg Forum. 2016 Aug 22;19(4):E180-4.

12. Memetoglu ME, Kehlibar T, Yılmaz M, Günay R, Arslan Y, Tuygun A, et al. Serum uric acid level predicts new-onset atrial fibrillation after coronary artery bypass graft operation. Eur Rev Med Pharmacol Sci. 2015;19(5):784-9.

13. Ramlawi B, Otu H, Mieno S, Boodhwani M, Sodha NR, Clements RT, et al. Oxidative stress and atrial fibrillation after cardiac surgery: a case-control study. Ann Thorac Surg. 2007;84:1166–72.

14. Lo B, Fijnheer R, Nierich AP, Bruins P, Kalkman CJ. C-reactive protein is a risk indicator for atrial fibrillation after myocardial revascularization. Ann Thorac Surg. 2005;79:1530-5.

15. Gibson PH, Cuthbertson BH, Croal BL, Rae D, El-Shafei H, Gibson G, et al. Usefulness of neutrophil/lymphocyte ratio as predictor of new-onset atrial fibrillation after coronary artery bypass grafting. Am J Cardiol. 2010;15:186–91.

16. Schenone M, Furie BC, Furie B. The blood coagulation cascade. Curr Opin Hematol. 2004;11:272-7.

17. Kurtul A, Yarlioglues M, Murat SN, Ergun G, Duran M, Kasapkara HA, et al. Usefulness of the platelet tolymphocyte ratio in predicting angiographic reflow after primary percutaneous coronary intervention in patients with acute ST segment elevation myocardial infarction. Am J Cardiol. 2014;114: 342–7.

18. Nikolsky E, Grines CL, Cox DA, Garcia E, Tcheng JE, Sadeghi M, et al. Impact of baseline platelet count in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction (from the CADILLAC trial). Am J Cardiol. 2007;99:1055–61.

19. Azab B, Shah N, Akerman M, McGinn JT. Value of platelet/ lymphocyte ratio as a predictor of all-cause mortality after non-STelevation myocardial infarction. J Thromb Thrombolys. 2012;34: 326–34.

20. Yildiz A, Yuksel M, Oylumlu M, Polat N, Akyuz 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 Apr;21(3):223-8.

21. Ayça B, Akin F, Çelik Ö, Yüksel Y, Öztürk D, Tekiner F, et al. Platelet to lymphocyte ratio as a prognostic marker in primary percutaneous coronary intervention. Platelets. 2015;26(7):638-44.

22. Erdem K, Ayhan S, Ozturk S, Bugra O, Bozoglan O, Dursin H, et al. Usefulness of the mean platelet volume for predicting new-onset atrial fibrillation after isolated coronary artery bypass grafting. Platelets. 2014;25(1):23-6.

23. El-Chami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, et al. New-onset atrial fibrillation predicts long-term mortality after coronary artery bypass graft. J Am Coll Cardiol. 2010 Mar 30;55(13):1370-6.