

## Are preoperative neutrophil/lymphocyte, platelet/lymphocyte, and platelet/neutrophil ratios markers in new-onset atrial fibrillation after coronary artery bypass grafting?

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### ABSTRACT

**Objectives:** This study aims to investigate the predictive value of platelet/neutrophil ratio (PNR) as a marker for postoperative atrial fibrillation (POAF) in addition to neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) measured in the preoperative period in patients who underwent coronary artery bypass grafting (CABG).

**Patients and methods:** The data of a total of 122 patients (89 males, 33 females; mean age 63.2±9.19, range, 41 to 86 years) who underwent isolated CABG in our clinic and had no prior atrial fibrillation history between May 2018 and February 2020 were reviewed retrospectively. The patients were divided into two groups as those with and without POAF. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated.

**Results:** Postoperative atrial fibrillation was detected in 36 of 122 patients. A significant difference was found in lymphocyte count ( $p=0.043$ ), NLR ( $p=0.01$ ), and PNR ( $p=0.048$ ) in the patients who developed POAF. In the univariate logistic regression model, NLR was found to be an independent predictor for POAF development with 75% sensitivity, 53% specificity, 61.5% PPV, 67.9% NPV, and 64% accuracy (AUC: 0.646,  $p=0.01$ ). In the POAF patients, the ROC analysis was performed to determine the diagnostic value of the PNR; however, no significant results were obtained.

**Conclusion:** Our study results show an independent association between baseline NLR and POAF after CABG surgery.

**Keywords:** Atrial fibrillation, coronary artery bypass grafting, platelet/lymphocyte ratio, platelet/neutrophil ratio, neutrophil/lymphocyte ratio.

The most common rhythm disorder after cardiac surgery is atrial fibrillation (AF).<sup>[1]</sup> The first three-day after surgery is the period with the highest incidence of postoperative atrial fibrillation (POAF).<sup>[2]</sup> In particular, in this period, although the etiology of POAF is multifactorial, one of the most important causes is the ongoing inflammatory and oxidative changes.<sup>[3]</sup> Neutrophils are an indicator of activated non-specific inflammatory response, and lymphopenia is an indicator of physiological stress and poor general health.<sup>[4]</sup> It has been shown that lymphocytes also regulate the immune response at all stages of progressive atherosclerosis. As the source of inflammatory mediators, platelets play an important role in the pathogenesis of AF due to their relationship with both thrombosis and inflammation.<sup>[5,6]</sup> In addition, increased platelet and decreased lymphocyte levels have been associated with poor prognosis in cardiovascular diseases.<sup>[7,8]</sup> In this context, neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have been reported

as indirect indicators of systemic inflammatory response and markers for POAF in recent years.<sup>[9,10]</sup>

There is no study using the platelet/neutrophil ratio (PNR) as an inflammatory marker, not only for POAF, but also for any other field in the literature. In the present study, therefore, we aimed to investigate the predictive value of PNR as a marker for POAF in addition to NLR and PLR measured in the preoperative period in patients who underwent coronary artery bypass grafting (CABG).

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## PATIENTS AND METHODS

The data of a total of 122 patients (89 males, 33 females; mean age  $63.2 \pm 9.19$ , range, 41 to 86 years) who underwent isolated CABG in our clinic between May 2018 and February 2020 were reviewed retrospectively. Patients who had a history of AF in the preoperative period or underwent off-pump surgery, had a valve pathology, underwent combined valve-CABG, were taken to the emergency operation, had a history of hyperthyroidism, hypothyroidism, infection, autoimmune disease in the preoperative period, and patients using steroid, amiodarone, digital, synthetic hormone preparations were excluded from the study. A written consent form was obtained from each patient. The study protocol was approved by Suleyman Demirel University, Faculty of Medicine, Ethics Committee (No. 12.03.2020/78). The study was conducted in accordance with the principles of the Declaration of Helsinki.

A detailed medical history, physical examination and routine blood tests, echocardiogram, electrocardiogram, carotid Doppler ultrasound (CDUS), chest radiograms and respiratory function tests, body mass index (BMI), European System for Cardiac Operative Risk Evaluation (EuroSCORE) were performed in all patients who were scheduled for an open heart surgery. Patients who were smoking on the date of coronary angiography were evaluated as smokers. Internal medicine consultation was requested for the patients who had a previous diagnosis of diabetes mellitus (DM) and patients who did not have a diagnosis of DM, but whose fasting blood glucose was  $>126$  mg/dL and the diagnosis of DM was confirmed. Patients who previously received antihypertensive treatment and those who had  $>130/85$  mmHg blood pressure during clinical follow-up were considered hypertensive (HT) patients. Before the operation, the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB),  $\beta$ -blocker and statin history were examined. The patients on routine hemodialysis program were evaluated as patients with chronic kidney failure. All patients who had chronic pulmonary obstructive disease (COPD) were evaluated by a chest physician with pulmonary function test or by arterial blood gas examination and those who were unable to perform pulmonary function tests were evaluated with physical examination. Those with a history of myocardial infarction (MI) within the past three months were evaluated as recent MI. The patients with dyspnea symptoms even at rest were considered

the New York Heart Association (NYHA) Class IV according to the NYHA congestive heart failure classification.

### Biochemical and hematological parameters

Blood samples were taken after 12 h of fasting. Complete blood counts, which included total white blood cells (WBCs), neutrophils, lymphocytes, and platelets were obtained using an automated blood counter, Mindray BC 6800 (Mindray, Shenzhen China). The NLR was calculated as the ratio of neutrophils ( $10^3/\mu\text{L}$ )-to-lymphocytes ( $10^3/\mu\text{L}$ ), PLR was calculated as the ratio of platelets ( $10^3/\mu\text{L}$ )-to-lymphocytes ( $10^3/\mu\text{L}$ ), and PNR was calculated as the ratio of platelets ( $10^3/\mu\text{L}$ )-to-neutrophils ( $10^3/\mu\text{L}$ ) obtained from the blood samples. C-reactive protein (CRP) levels were measured using the Siemens BN II System (Siemens Medical Solution, Malvern, PA, USA), and the preoperative glomerular filtration rate (GFR) was estimated using standard methods.

### Operative technique

Median sternotomy was applied to all patients under general anesthesia. Cardiopulmonary bypass (CPB) was performed using aortocaval cannulation technique in all patients following systemic heparin administration (300 IU/kg). Cardiac arrest was achieved using hypothermic, hyperkalemic blood cardioplegia, and topical hypothermia. Surgery was performed under moderate systemic hypothermia ( $32^\circ\text{C}$ ). The CPB flow was maintained at  $2.2\text{--}2.5$  L/min/ $\text{m}^2$ , mean perfusion pressure was maintained between 50 and 80 mmHg, and hematocrit level was maintained at 20-25% during CPB. Cardiac arrest was maintained using intermittent antegrade cold blood cardioplegia infusions. In patients who had low ejection fraction (EF), multi-vessel disease (MVD), and poor ventricular function, continuous retrograde cold blood cardioplegia was infused in addition to antegrade intermittent cold blood cardioplegia. The left internal mammary artery was used in all patients for revascularization of the left anterior descending artery. A saphenous vein graft was used for grafting other coronary arteries. Warm blood cardioplegia was given in all patients immediately before removing the cross-clamp. All proximal anastomoses were performed using side clamps. All early postoperative patient follow-ups were done in the third-degree cardiovascular surgery intensive care unit (ICU).

## POAF

All patients were monitored in the ICU after surgery with a five-lead monitoring system Philips IntelliVue MX800 (Philips, Boeblingen, Germany) using the standard lead II configuration. After discharge from the ICU, the patients were followed six to eight times daily in the ward. Following surgery, subsequent 12-lead electrocardiograms were daily obtained from each patient until discharge and also, if a patient manifested with symptoms of palpitations or an irregular pulse, a 12-lead electrocardiography Mindray Bene Heart R12 (Shenzhen Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China) was performed to diagnose the arrhythmia. New-onset POAF was described as AF according to the established Society of Thoracic Surgeons definition occurring during hospitalization after CABG in a patient with no history of AF. Episodes of AF were treated according to clinical routines which included pharmacological interventions with

intravenous amiodarone or, if contraindicated, with an oral  $\beta$ -blocker (metoprolol) and/or with electrical therapies such as cardioversion.

## Statistical analysis

Power analysis and sample size calculation were performed using the G\*Power version 9.1.2 (University of Düsseldorf, Düsseldorf, Germany). In the power analysis performed by evaluating the frequency of POAF development in the literature, the sample was calculated by taking the power value 85% and the effect size 0.75. Accordingly, the sample size for the case group was determined to be 30 patients who developed POAF and 70 patients who did not develop POAF.

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were presented in number and frequency, while continuous variables were expressed in mean  $\pm$  standard deviation (SD) or median

**Table 1**  
Baseline demographic and clinical characteristics of patients

Characteristic	POAF negative (n=86)			POAF positive (n=36)			p
	n	%	Mean $\pm$ SD	n	%	Mean $\pm$ SD	
Sex							0.223
Male	60	69.8		29	80.6		
Female	26	30.2		7	19.4		
Diabetes mellitus							0.799
No	38	44.2		15	47.7		
Yes	48	55.8		21	58.3		
Considered hypertensive							0.434
No	52	60.5		19	52.8		
Yes	34	39.5		17	47.2		
COPD							0.921
No	51	59.3		21	58.3		
Yes	35	40.7		15	47.7		
Smoker							0.420
No	66	76.7		30	83.3		
Yes	20	23.3		6	16.7		
Recent myocardial infarction							0.183
No	62	68.1		20	55.6		
Yes	29	31.9		16	44.4		
Age (year)			62.4 $\pm$ 9.6			64.5 $\pm$ 9.2	0.364
Number of bypasses (n)			3.2 $\pm$ 0.8 (3; 1; 5)			3.1 $\pm$ 0.8 (3; 1; 5)	0.661
Body mass index (kg/m <sup>2</sup> )			28.7 $\pm$ 4.3			29.9 $\pm$ 4.4	0.122
Cardiopulmonary bypass time (min)			114.7 $\pm$ 35.4			112.7 $\pm$ 30.4	0.713
POAF: Postoperative atrial fibrillation; SD: Standard deviation; COPD: Chronic pulmonary obstructive disease.							

(min-max). The consistency of continuous variables to normal distribution was tested by Kolmogorov-Smirnov test. In general, the variables were not distributed normally. Therefore, the Mann-Whitney

U test was performed for the comparison of two independent groups, and Monte Carlo exact chi-square ( $\chi^2$ ) test was used to determine the correlation between the categorical variables. A prospective progressive

Table 2 Patient data							
Characteristics	POAF negative (n=91)			POAF positive (n=36)			p
	n	%	Mean±SD	n	%	Mean±SD	
NYHA Class IV							0.841
No	83	96.5		35	92.7		
Yes	3	3.5		1	2.8		
Beta-blocker							0.186
No	12	14.0		2	5.6		
Yes	74	86.0		34	94.4		
Statin							0.345
No	73	84.9		28	77.8		
Yes	13	15.1		8	22.2		
ACEI/ARB							0.005*
No	71†	82.6		21‡	58.3		
Yes	15†	17.4		15‡	41.7		
LIMA							0.523
No	1	1.2		1	2.8		
Yes	85	98.9		35	97.2		
Ejection fraction (%)			54.2±9.4			53.9±9.0	0.813
GFR (mL/mn)			85.9±15.5			80.6±16.7	0.132
EuroSCORE			1.5±1.1 (1.13; 0.5; 7.23)			1.6±1.3 (1.25; 0.50; 7.65)	0.613
LA diameter (mm)			36.5±4.1			37.7±5.7	0.442
CRP (mg/dL)			1.1±1.5 (0.44; 0.30; 6.90)			1.0±1.1 (0.59; 0.30; 4.19)	0.753
X-clamp (min)			67.2±21.9			65.8±21.0	0.651
Hemoglobin (mg/dL)			13.4±1.6			13.5±1.5	0.395
White blood cell			7.6±2.0			7.9±2.1	0.571
Neutrophil (10 <sup>3</sup> /μL)			4.5±1.4			5.1±1.8	0.132
Lymphocytes (10 <sup>3</sup> /μL)			2.2±0.8			1.9±0.5	0.043*
Monocytes (10 <sup>3</sup> /μL)			0.5±0.2			0.5±0.2	0.659
Platelet			243.4±72.2			236.8±66.4	0.509
NLR			2.2±0.8			2.7±1.1	0.010*
PLR			116.5±33.7			130.3±45.9	0.315
PNR			58.5±21.9			51.7±20.9	0.048*
Neutrophil/CRP			8.9±5.8			8.7±5.9	0.954
Lymphocytes/CRP			4.8±3.7			4.1±2.9	0.585
Platelet/CRP			480.5±293.5			460.1±324.7	0.676
POAF: Postoperative atrial fibrillation; SD: Standard deviation; NYHA: New York Heart Association; ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; LIMA: Left internal mammary artery; GFR: Glomerular filtration rate; LA: Left atrium; CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; PNR: Platelet/neutrophil ratio; † Mann-Whitney U test. ‡ Chi-square test; * p<0.05.							

univariate logistic regression model was constructed to determine the factors affecting development of POAF. The receiver operating characteristic (ROC) curve analysis was applied for proportional scale variables which were found significant among the contributing factors. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated according to the calculated cut-off value. Type-I error value was taken as 5% in the whole study. A  $p$  value of  $<0.05$  was considered statistically significant.

## RESULTS

Of a total of 122 patients, 29.5% ( $n=36$ ) developed POAF. More than half of the cases included in the study had DM (56.6%), almost half had HT (41.8%) and COPD (41.0%). While 21.3% of the patients were smokers, 36.9% of them had a recent history of MI. While the majority of patients were using  $\beta$ -blockers (88.5%), statin use was low (17.2%) and ACEI use was 24.6% (Table 1).

Various clinical features and measurement values were compared between the patients with and without POAF. The values measured in demographic features and clinical features did not significantly differ between the groups. Age, BMI, WBC, and PLR values were higher in the patients who developed POAF. The CPB time, EF, GFR, cross-clamp time, and platelet values were lower in the patients who developed POAF, although it did not reach statistical significance. Only in hematological measurements, the lymphocyte count ( $p=0.043$ ), NLR ( $p=0.010$ ) and PNR ( $p=0.048$ ) and ACEI/ARB use ( $p=0.005$ ) significantly differed in the patients with POAF. The mean lymphocyte count, which was significantly lower in the POAF group, was found to be  $1.94 \pm 0.54 \times 10^3/\mu\text{L}$  in the patients who developed POAF, while

it was  $2.23 \pm 0.82 \times 10^3/\mu\text{L}$  in the patients without AF. The mean NLR value was found to be  $2.73 \pm 1.10$  in the patients with POAF and  $2.15 \pm 0.81$  in the patients without POAF. The mean PNR decreased in the patients with POAF ( $51.72 \pm 20.84$ ). The ratios of neutrophil, lymphocyte, and platelet counts-to-CRP values were determined. Although the rates obtained using CRP were found to be lower in the patients who developed POAF, there was no significant difference in predicting the development status of POAF (Table 2).

A univariate logistic regression model was created considering developing POAF as a dependent category and not developing it as the reference category. Drug use, comorbid diseases, demographic features, and biochemistry measurements were included in the prospective model created by the forward likelihood ratio (LR) method. The goodness-of-fit results of the model obtained as a result of the second stage were found to be significant (omnibus test  $\chi^2=15.29$ ,  $p<0.001$ ;  $-2LL=132.72$ , Nagelkerke  $R^2=0.168$ ; Hosmer-Lemeshow  $\chi^2=15.53$ ,  $p=0.052$ ). Only two variables significantly contributed to the model. It was calculated that the effect of NLR was positive and the effect of ACEI/ARB use was negative. The odds ratio (OR) was 1.833 ( $p=0.07$ ) for NLR and 0.335:2.985 ( $p=0.017$ ) for ACEI/ARB use (Table 3).

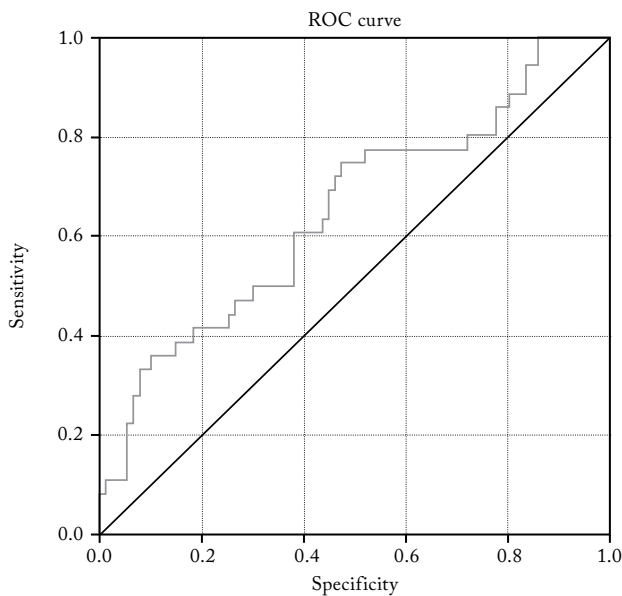
The ROC analysis was performed to test the success of NLR values in predicting POAF development (Figure 1). The area under the curve (AUC) was found to be significant ( $\text{AUC}=0.649$ ;  $p=0.010$ ). In the calculation, the cut-off value was calculated as 2.04. Accordingly, the differential diagnosis rates (95% confidence interval [CI]) were calculated as follows: sensitivity: 75% (65.3–83.1%), specificity= 53% (42.7–63.1%), PPV= 61.5% (55.7–66.9%), NPV= 67.9% (59.1–75.7%), and accuracy= 64% (56.9–70.6%).

**Table 3**  
Correlation analysis results

Factors	Model	Nagelkerke $R^2=0.168$		Hosmer & Lemeshow $\chi^2=15.531$ ( $p=0.052$ )
		Beta	$p$	OR (95% CI)
NLR		0.606	0.007*	1.833 (1.183–2.838)
ACEI/ARB	Use	-1.093	0.022*	0.335 (0.137–0.821)
				2.985 (1.218–7.299)

OR: Odds ratio; CI: Confidence interval; NLR: Neutrophil/lymphocyte ratio; ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.





**Figure 1.** Receiver operating characteristic (ROC) of neutrophil-lymphocyte ratio in postoperative atrial fibrillation.

In the POAF group, the ROC analysis was performed to determine the diagnostic value of the PNR which was found to be significantly low (AUC=0.575,  $p=0.244$ ) although the results were not found to be significant in the ROC analysis.

## DISCUSSION

In this study, a high preoperative NLR and low preoperative PNR were evaluated as risk factors for the development of new-onset POAF in patients undergoing CABG. On the other hand, lymphocyte counts, and the ACEI/ARB use were higher in the patients who were in normal sinus rhythm.

The most common arrhythmia after CABG is AF and POAF can be seen in 15 to 40% of cases following isolated CABG.<sup>[1]</sup> Atrial fibrillation can cause complications such as heart failure, thromboembolism, cerebrovascular occlusive events, and renal insufficiency. Also, it is one of the leading causes of mortality after CABG itself and, due to morbidities caused by AF, many patients have prolonged hospital stays and prolonged hospitalization increases the cost per patient.<sup>[11]</sup> New-onset POAF is associated with many factors such as age, male sex, DM, HT, recent MI, heart failure, obesity, and left atrial size.<sup>[1,10]</sup> In our study, although age and BMI

measurements were found to be higher in the POAF group, no statistically significant difference was found between those with and without POAF.

The relationship between AF following after cardiac surgery and preoperative inflammatory markers has been evaluated in many studies and demonstrated by inflammatory cell infiltration and interstitial fibrosis observed in the atrial tissues of patients developing AF. The link between oxidative stress following after cardiac surgery, complex inflammatory response.<sup>[12,13]</sup> caused by the effect of cellular inflammation, interleukin 6 and 8, increased WBC count, CRP levels, and AF development has been previously shown.<sup>[14-16]</sup> In our study, although WBC counts were found to be higher in the patient group who developed POAF, it was not statistically significant. In addition, there was no significant difference in the CRP levels in the patients with or without POAF.

The WBC count and its subtypes have been found to be markers of inflammation in various cardiovascular diseases.<sup>[4]</sup> Neutrophils represent activated non-specific inflammation.<sup>[4]</sup> In addition, neutrophil activation during CPB causes perioperative myocardial damage and, subsequently, reperfusion injury.<sup>[4,17,18]</sup> Decreased lymphocytes are associated with poorer general health, increased physiological stress, and depressed immune response.<sup>[4]</sup> Platelets play an important role in inflammation and thrombosis by secreting various mediators.<sup>[6]</sup> Therefore, we examined WBC subtypes in our study. We found lower lymphocyte counts in the patients with POAF compared to those without POAF ( $p=0.043$ ). However, we found no significant difference in the neutrophil, platelet, and basophil counts between the groups. In recent years, the NLR, PLR, and non-specific inflammatory response have been associated in many studies based on the increase in neutrophil and platelet counts and a decrease in the lymphocyte counts.<sup>[7-11,19-22]</sup>

Correlation studies between NLR and development of AF conducted by Gibson et al.<sup>[9]</sup> showed that the rate of AF development was higher in patients with a high NLR value, which is used as an inflammatory marker.<sup>[4,23]</sup> Also, in this study, preoperative NLR was independently associated with POAF with 75% sensitivity and 53% specificity.

A limited number of studies is available in the literature reporting the association between PLR and POAF after CABG surgery. Gungor et al.<sup>[10]</sup>

found a higher risk of developing POAF in patients with higher preoperative PLR. Later, this result was supported by similar studies.<sup>[24,25]</sup> In our study, we found a higher preoperative PLR in the patients with POAF. However, we found no statistically significant difference in the preoperative PLR values in the patients who did not develop POAF ( $p=0.315$ ).

To the best of our knowledge, this is the first study to evaluate PNR for inflammation and AF predictability in the literature. In our study, the PNR was found to be a significantly lower predictor for POAF, although no significant results were found in the ROC analysis (AUC: 0.575,  $p=0.244$ ). We believe that low PNR in patients who develop POAF can yield significant results in predicting the development of POAF. However, further large-scale studies are needed to confirm this hypothesis.

Although ACEI and ARB inhibit the renin-angiotensin system by targeting different sites in the pathway, clinical studies have shown that both drugs effectively lower blood pressure and reduce cardiovascular events.<sup>[26,27]</sup> They can modify atrial substrate, prevent inflammation and, thus, reduce the risk of AF.<sup>[28,29]</sup> A growing number of evidence suggests that ACEI and ARB can be used for AF prevention.<sup>[30,31]</sup> In our study, we found that ACEI/ARB use was protective against POAF development in the preoperative period in addition to NLR and PNR (OR=0.335).

The limitations of this study include its relatively small sample size, retrospective design, and relatively short follow-up period. Asymptomatic, short-term POAF episodes or new-onset POAF within the first month of control visit following discharge may not have been identified.

In conclusion, unlike many other inflammatory markers and bioassay, the PNR, NLR, and PLR are simple, inexpensive, and routinely reported tests as a part of complete blood count. In this study, we found an independent correlation between baseline NLR and POAF after CABG surgery. In addition, when studied in larger cohorts, the decrease in the PNR in patients who develop POAF can yield significant results in predicting the development of POAF and can be used as a marker. Nonetheless, further, large-scale, long-term, prospective studies using PNR, NLR, and PLR are required to evaluate long-term outcomes of POAF after CABG surgery.

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The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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