Original Article

Value of Preoperative Platelet-to-Lymphocyte and Neutrophil-to-Lymphocyte Ratios in Predicting Postoperative Atrial Fibrillation in Patients Undergoing Lung Resection

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Abstract

Background: *The aim of this study was to investigate the association between the platelet/lymphocyte ratio (PLR) and the neutrophil/lymphocyte ratio (NLR) and postoperative atrial fibrillation (POAF) after lung resection.*

Methods: *After the implementation of the exclusion criteria, 170 patients were retrospectively analyzed. PLR and NLR were obtained from fasting complete blood counts before surgery. POAF was diagnosed using standard clinical criteria. The associations between different variables and POAF, NLR, and PLR were calculated using univariate and multivariate analyses. The receiver operating characteristics (ROC) curve was used to determine the sensitivity and specificity of PLR and NLR.*

Results: *Of the 170 patients, 32 with POAF (mean age =71.28±7.27 y, 28 males and 4 females) and 138 patients without POAF (mean age =64.69±10.31 y, 125 males and 13 females) were identified, and the difference in the mean age was statistically significant (P=0.001). It was found that PLR (157.67±65.04 vs 127.52±56.80; P=0.005) and NLR (3.90±1.79 vs 2.04±0.88; P=0.001) were statistically significantly higher in the POAF group. In the multivariate regression analysis, age, lung resection size, chronic obstructive pulmonary disease, NLR, PLR, and pulmonary arterial pressure were independent risk factors. In the ROC analysis, PLR had a sensitivity of 100% and a specificity of 33% (AUC, 0.66; P<0.001), and NLR had a sensitivity of 71.9% and a specificity of 87.7% (AUC, 0.87; P<0.001). A comparison of AUC between PLR and NLR showed that NLR was statistically more significant (P<0.001).*

Conclusion: *This study showed that NLR was a stronger independent risk factor than PLR for the development of POAF after lung resection.*

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Keywords: *Atrial fibrillation; Lymphocytes, blood; Neutrophils, blood; Blood platelet count*

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Introduction

Atrial fibrillation (AF) is the most common cardiac complication after lung resection, with its prevalence ranging from 8% to 20%. It is usually observed in the first 3 postoperative days. Postoperative atrial fibrillation (POAF) is associated with increased morbidity, mortality, length of hospital stay, and thromboembolic risk.[1] Although the etiopathogenesis of POAF is not well understood, older age, high brain natriuretic peptide levels, the male sex, known heart failure, a history of peripheral artery disease, resection size, and chronic obstructive pulmonary disease (COPD) are known risk factors.[2,3]

Inflammation and oxidative stress play a fundamental role in the development of AF after cardiac and noncardiac surgery.[4] It is well known that C-reactive protein, a systemic inflammatory marker, is a risk factor for POAF, regardless of the type of surgery.[5,6] Statin therapy, which has anti-inflammatory, antioxidant, and cell membrane regulatory effects before surgery, reduces the risk of AF development by threefold after major thoracic surgery, regardless of disease severity.[7]

The platelet/lymphocyte ratio (PLR) is a novel inflammatory marker and provides more information about hemostasis and inflammatory pathways than platelet count alone. Its value in the prognosis of ST-elevation myocardial infarction, various malignancies, and chronic inflammatory diseases has also been demonstrated.[8-10] The neutrophil/lymphocyte ratio (NLR) is a long-established inflammatory marker and plays an essential role in the etiopathogenesis and prognosis of cardiovascular diseases, malignancies, and chronic inflammatory diseases.[11,12] Both NLR and PLR are recognized as predictors of AF development after cardiac surgery.[13,14]

The present study aimed to investigate the predictive value of PLR and NLR vis-a-vis POAF in patients undergoing lung resection for various reasons.

Methods

After the institutional ethics committee approved the study protocol (Adnan Menderes University Non-Interventional Clinical Research Ethics Committee permission, dated 12/10/2021 and numbered 2021/79), 750 patients who had undergone lung resection for various reasons at a single center between 2015 and 2020 were retrospectively screened in this study. The study was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria for the study were a history of lung resection for various reasons and age >18 years. The exclusion criteria were a history of thoracic surgery, paroxysmal AF, class I–III antiarrhythmic therapy, β-blocker and calcium channel blocker consumption, implanted pacemakers, steroid use, thyroid dysfunction, neoadjuvant chemotherapy, heart failure, valvular heart disease, and the absence of preoperative sinus rhythm. The treatment of patients receiving β-blockers and calcium channel blockers for coronary artery disease and/or hypertension was continued.

After the implementation of the exclusion criteria, 170 patients were enrolled in the study. The patients were divided into a non-POAF group (138 patients) and a POAF group (32 patients).

Baseline clinical data, preoperative medical treatments, echocardiographic characteristics, reasons for surgery, and type of resection were recorded for the entire study population. All the patients were questioned in detail about hypertension, hyperlipidemia, diabetes mellitus, COPD, coronary artery disease, and medications taken. Diagnostic criteria for COPD were FEV1/FEVC<70% or FEV1<70% after inhaled bronchodilators. Chronic renal failure was defined as a glomerular filtration rate <60 for more than 3 months. A diagnosis of hypertension was accepted if the patient was taking antihypertensive therapy or had at least 3 measurements above the systolic value of 160 mm Hg and the diastolic value of 90 mm Hg. Diabetes was defined as taking antidiabetic medications or having at least 2 fasting blood glucose measurements >126 mg/dL. Preoperative treatment was resumed in all the patients on the first postoperative day.

Echocardiographic examinations were performed on the patients with the iE33 Cardiac Ultrasound System (Philips Healthcare, Best, The Netherlands) with a 2.5–5 MHz probe system. Ejection fraction was measured using the modified Simpson method.

Fasting blood samples were obtained from all the patients in the morning before surgery. Leukocyte, neutrophil, lymphocyte, and platelet counts were recorded as part of the complete blood count. The ratio of PLR to NLR was calculated and recorded. The cutoff value for PLR and NLR was set at 142 and 3, respectively. Other hematologic and biochemical values were also measured and recorded.

For surgical treatment, the patients were divided into 2 groups: those who underwent standard thoracotomy and those who underwent the VATS (video-associated thoracic surgery). In all oncologic surgery patients, neoplastic material was harvested, and all lymph nodes were dissected. The VATS method was performed under general anesthesia in the lateral decubitus position after a 2–3 cm skin incision in the midaxillary of the intercostal space 7–8 with 0° rigid thoracoscopy. For the classification of lung resection size, patients with lobectomy, bilobectomy, and pneumonectomy were formed as the major operation group and segmentectomy and wedge resection as the minor operation group. After surgery, all the patients received continuous infusion analgesia with epidural anesthesia for postoperative pain control. They were followed up after an overnight stay in the intensive care unit (ICU). All the patients received prophylactic antibiotic therapy before surgery.

The entire study population was followed up 72–96 hours after surgery (Apexpro 7-lead General Electrical Medical System). The new diagnosis of AF was made in case of an irregular pulse that lasted >5 minutes. POAF was diagnosed by the absence of P waves on the 12-lead electrocardiogram obtained when patients continuously monitored during ICU or service follow-up complained of palpitations or an irregular pulse on physical examination. In addition, anticoagulant therapy was given. In case of hemodynamic instability, electrical cardioversion was performed.

SPPS 25 IBM Corp Released 2017 and IBM SPSS Statistics for Windows (version 25.0. Armonk, NY: IBM Corp) were used to analyze the data. Descriptive statistics (mean, standard deviation, median, minimum, maximum, number, and percentile) were given for categorical and continuous variables in the study. Homogeneity of variances, one of the prerequisites for the parametric tests, was checked with the Levene test. The assumption of normality was checked with the Shapiro-Wilk test. In assessing differences between the 2 groups, the Student *t* test was used if the conditions for the parametric test were met; if not, the Mann-Whitney *U* test was used. Relationships between categorical variables were analyzed using the Fisher exact test and the Pearson χ^2 test. P value <0.05 and P value <0.01 were considered statistically significant. A P value <0.05 was considered statistically significant. The variables for which the unadjusted P value was <0.05 in the logistic regression model were identified as potential risk markers and included in the full multivariate model. Backward elimination multivariate logistic regression analyses using a likelihood ratio test to eliminate variables were utilized. A 2-tailed P value <0.05 was considered statistically significant. The receiver operating characteristics (ROC) curve was used to determine the sensitivity and specificity of PLR with NLR and the optimal cutoff value for predicting POAF in individuals who had undergone surgery.

Results

POAF (mean age =71.28±7.27 y, 28 males) was observed in 32 of 170 patients, while 138 had no POAF (mean age =64.69±10.31 y, 125 males). There was no difference between the groups in terms of sex; nonetheless, a statistical difference was observed in terms of age, and the POAF group was older (P=0.001) (Table 1).

Table 1. Baseline characteristics, preoperative medications, and operation findings

	Postoperative Atrial Fibrillation		P		Postoperative Atrial Fibrillation		P
	Yes	No			Yes	No	
Demographics Features				ARB			0.393
Sex			0.601	Yes	(n=1)	(n=10)	
Male	(n=28)	(n=125)		No	(n=31)	(n=128)	
Female	(n=4)	(n=13)		β-blocker			0.230
Age	71.28±7.27	64.69±10.31	0.001	Yes	(n=3)	(n=25)	
Medical History				No	(n=29)	(n=113)	
Diabetes mellitus			0.561	CCB			0.400
Yes	(n=4)	(n=23)		Yes	(n=0)	(n=3)	
No	(n=28)	(n=115)		No	(n=32)	(n=135)	
Hyperlipidemia			0.285	ASA			0.497
Yes	(n=1)	(n=12)		Yes	(n=2)	(n=14)	
No	(n=31)	(n=126)		No	(n=30)	(n=124)	
Hypertension			0.209	Statın			0.274
Yes	(n=4)	(n=31)		Yes	(n=0)	(n=5)	
No	(n=28)	(n=107)		No	(n=32)	(n=133)	
CAD			0.473	Surgıcal Features			
Yes	(n=6)	(n=19)		Reason of resection			0.479
No	(n=26)	(n=119)		Adenoca	(n=26)	(n=109)	
COPD			0.001	Scc	(n=6)	(n=23)	
Yes	(n=17)	(n=0)		Other	(n=0)	(n=6)	
No	(n=15)	(n=138)		Surgıcal approach			0.499
Medication Use				VATS	(n=10)	(n=51)	
Ace			0.310	Open	(n=22)	(n=87)	
Yes	(n=4)	(n=28)		Operation			0.030
No	(n=28)	(n=110)		Major	(n=25)	(n=100)	
				Minor	(n=7)	(n=38)	

N, Number; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; ACE İNH, Angiotensin-converting enzyme (ACE) inhibitors; ARB, Angiotensin receptor blocker; CCB, Calcıum chanel blocker; ASA, Acetylsalicylic acid; VATS, Video-assisted thoracoscopic surgery; Adenoca, Adenocancer; Scc, Squamous cell carcinoma

When the groups were evaluated regarding risk factors and additional diseases, no difference was found in diabetes mellitus, hypertension, and coronary artery disease. The POAF group had a statistically higher rate of COPD (P=0.001). There was no difference between the groups concerning preoperative medical treatment (P>0.05). In the evaluation of surgery, there was no difference in the reason for surgery and type of surgery, but there was a difference between major and minor surgery groups regarding lung resection size. POAF was statistically significantly more frequent in the major thoracic surgery group (P=0.001) (Table 1).

In the evaluation of laboratory values, the lymphocyte count was statistically higher in the non-POAF group (2.2±1.10 vs 1.8±0.60; P=0.011). The neutrophil count was statistically higher in the POAF group (6.6±2.60 vs 4.3±1.80; P=0.001). There was no difference in other laboratory parameters. PLR (157.67±65.04 vs 127.52±56.80; P=0.005) and NLR (3.90±1.79 vs 2.04±0.88; P=0.001) were statistically higher in the POAF group (P=0.001). Echocardiography revealed statistically higher pulmonary artery systolic pressure (PAP) in the POAF group (P=0.007). There were no statistical differences in other echocardiographic parameters (P>0.05) (Table 2).

Lung resection size, age, COPD, NLR, PLR, PAP, and neutrophil count were compared in univariate and multivariate logistic regression analyses. Resection size (OR, 1.512; P=0.042; 95% CI, 1.46 to 1.81), age (OR, 2.151; P=0.012; 95% CI, 1.01 to 5.50), COPD (OR, 1.431; P=0.001; 95% CI, 1.31 to 2.67), NLR (OR, 1.005; P=0.015; 95% CI, 1.01 to 1.02), PLR (OR, 1.006; P=0.001; 95% CI, 1.00 to 1.01), and PAP (OR, 1.021; P=0.015; 95% CI, 1.01 to 1.05) were found to be independent risk factors for POAF (Table 3).

Table 2. Laboratory parameters of the patients*

	Postoperative Atrial Fibrillation		P
	Yes (n=32)	No (n=138)	
Hematological Features			
Hg (g/dL)	13.67±1.96	13.96±9.79	0.301
Hct (%)	41.75±4.98	41.33±5.25	0.581
Leucocyte (x10^9/L)	7.91±1.93	8.72±3.12	0.440
Lymphocyte (x10^9/L)	1.83±0.61	2.24±1.13	0.011
Platelet (x10^9/L)	259.12±86.23	254.21±82.11	0.624
Neutrophil (x10^9/L)	6.64±2.63	4.36±1.84	0.001
PLR (%)	157.67±65.04	127.52±56.80	0.005
NLR (%)	3.90±1.79	2.04±0.88	0.001
Renal Features			
Urea (mg/dL)	35.37±15.10	31.84±10.28	0.604
Creatinine (mg/dL)	0.93±0.21	0.87±0.21	0.226
NA (mmol/L)	139.12±2.43	138.52±10.95	0.484
K (mmol/L)	4.24±0.66	4.30±0.41	0.826
Ca (mmol/L)	9.13±0.57	9.18±0.49	0.733
Albumin (g/L)	40.53±3.74	40.34±4.14	0.739
Thyroid features			
TSH (mIU/L)	1.65±0.58	1.45±0.15	0.340
Echocardiographic Features			
LVEF (%)	60.50±8.11	62.86±5.82	0.054
Left Atrium (mm)	35.93±3.30	36.68±3.47	0.060
PAP (mm Hg)	38.87±4.91	35.32±6.80	0.007

*Data are presented as mean±SD or n (%).

Hg, Hemoglobin; Hct, Hematocrit; PLR, Platelet/lymphocyte ratio; NLR, Neutrophil/lymphocyte ratio; Na, Sodium; K, Potassium; Ca, Calcium; TSH, Thyroid-stimulating hormone; LVEF, Left ventricular ejection fraction; PAP, Pulmonary artery pressure

Table 3. Effects of various variables on postoperative atrial fibrillation in univariate and multivariate logistic regression analyses

	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P
Age	3.957	2.12-4.71	0.001	2.151	1.01-5.50	0.012
COPD	3.317	1.48-7.39	0.003	1.431	1.31-2.67	0.001
NLR (%)	1.009	1.00-1.01	0.014	1.005	1.01-1.02	0.015
PLR (%)	1.006	1.00-1.00	<0.001	1.006	1.00-1.01	0.001
PAP(mm Hg)	1.040	1.02-1.05	<0.001	1.021	1.01-1.05	0.015
Resection size	1.006	1.12-1.32	0.001	1.512	1.46-1.81	0.042
Neutrophil	1.211	1.10-1.32	0.000	1.155	0.95-1.39	0.131

COPD, Chronic obstructive pulmonary disease; NLR, Neutrophil/lymphocyte ratio; PLR, Platelet/lymphocyte ratio; PAP, Pulmonary artery pressure

Table 4. Comparison of AUC between PLR and NLR

	AUC	SE	95% CI	P
NLR	0.87	0.034	0.81 to 0.92	<0.001
PLR	0.66	0.045	0.58 to 0.73	

PLR, Platelet/lymphocyte ratıo; NLR, Neutrophıl/lymphocyte ratıo; AUC, Area under the curve, SE, Standard error

In ROC analysis, PLR had a sensitivity of 100% and a specificity of 33% (AUC, 0.66; P<0.001) (Graph 1), while NLR had a sensitivity of 71.9% and a specificity of 87.7% (AUC, 0.87; P<0.001) (Graph 1). A comparison of AUC ratios between PLR and NLR showed that NLR was statistically higher (P<0.001) (Figure 1) (Table 4).

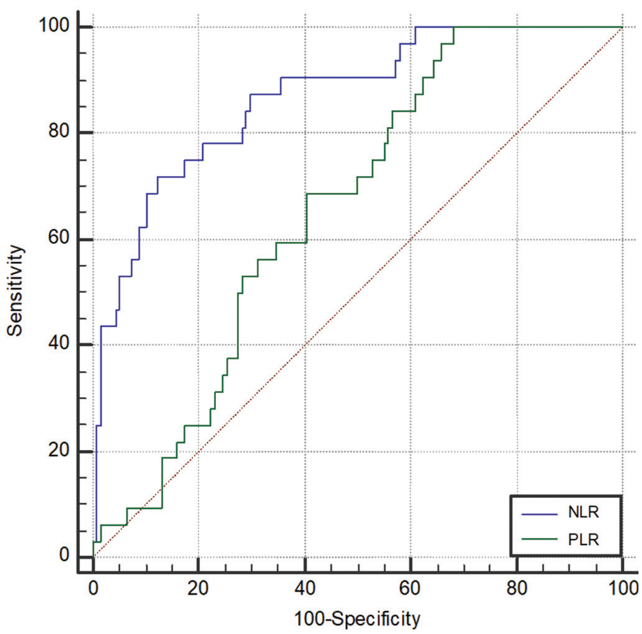

Figure 1. Comprasion of PLR and NLR AUC value
PLR, Platelet/lymphocyte ratio; NLR, Neutrophil/lymphocyte ratio; AUC, Area under the curve

Discussion

This study demonstrated that preoperative high PLR and NLR were independent risk factors for the development of POAF in patients undergoing lung resection. In the secondary analysis of the study, PLR and NLR were compared, and NLR was found to be statistically more valuable.

Similar to previous studies, we found that advanced age, COPD, PAP, and resection size were independent risk factors for AF. Many studies have shown that atrial remodeling and fibrosis occurring with advanced age are risk factors for POAF.[15-17] Law et al[19] showed that intestinal fibrous structures and fatty acids in myocytes increased in an age-dependent manner.[18] In addition, increased proinflammatory responses such as mitochondrial adaptor protein p66 and deacetylases enzyme family, sirtuins related to aging, the disruption of cyclooxygenase and NO (nitric oxide) synthetase pathways, and the occurrence of a chronic inflammatory state were the main pathophysiological reasons for AF.

COPD has been recognized as an independent risk factor for POAF. Hypoxia, hypercapnia, pulmonary hypertension, oxidative stress, changes in atrial form, and inhalation treatments occurring in COPD are among the most critical causes of POAF.[20] In a study by Sekine et al,[21] FEV1 <70% and FEV1/FVC <70% in the preoperative pulmonary function test for non-small cell lung cancer were shown to be independent risk factors for postoperative atrial tachycardia. Ishibashi et al[22] assessed 947 patients and reported that the presence of COPD was an independent risk factor for POAF after lung cancer lobectomy.

Pulmonary hypertension is considered an independent risk factor for POAF. Pulmonary hypertension is particularly associated with increased pulmonary vascular resistance and chronic right ventricular and atrial strain. The increase in sympathetic tone, in addition to dilatation and fibrosis, developing as a consequence of long-term right atrial strain, is regarded as the basic pathophysiological mechanism for AF.[23] Akça et al[24] concluded that the presence of pulmonary hypertension was an independent risk factor for POAF after coronary artery bypass grafting.

Research has shown that an increase in pulmonary resection volume is an independent risk factor for POAF. Previous investigations have also demonstrated that the incidence of POAF increases with a rise in resected lung volume.[25,26] In a study conducted by Ueka et al,[27] pneumonectomy was a major risk factor for POAF. Hemodynamic effects resulting from increased operative time, surgical stress, blood loss, and transfusion requirements associated with the resection size were accepted as major factors for POAF. Fink et al,[28] in their study on POAF following pulmonary surgery, found that pulmonary vein and atrial anatomy and electrophysiology changed significantly, particularly after pneumonectomy compared with lobectomy, and that catheter ablation was more difficult than lobectomy.

Although the underlying mechanism of POAF formation has not been fully elucidated,[29] depending on the characteristics of patients, in addition to comorbidities such as age-related fibrosis, the presence of structural heart disease, and hypertension, surgical causes can be listed as the type of surgery, intraoperative bleeding, electrolyte imbalance, hypotension, increased inflammatory state, and hypoxia.[30,31] Nakamura et al[32] showed that inflammation, oxidative stress, fibrosis, and myocyte necrosis were severe in the left atrium of patients with AF, but the anti-inflammatory mechanisms were insufficient. Further, with the release of mediators and cytokines by the occurrence of inflammation, platelet release from megakaryocytes and neutrophil proliferation increased. On the other hand, Nakamura and colleagues observed a decrease in lymphocyte count. Tselentakis et al[33] observed that action potential duration and the effective refractory period in the left atrium changed due to increased inflammatory mediators in patients who developed POAF after surgery. Ishie et al[34] reported increased inflammation in the atrium, resulting in the impaired homogenization of conduction in the atrium of POAF patients.

Previous studies have shown that PLR and NLR are independent risk factors for AF after coronary artery bypass surgery.[12,35,36] However, Walsh et al[37] found no association between NLR and the development of AF after noncardiac surgery in their study of oncology patients, which is discordant with our findings. We believe this is due to differences in the patient population and methodology between the studies. Advanced age is one of the main risk factors for AF, and this study included only patients older than 60 years. In addition, another difference between the groups is in treatment with β-blockers, one of the main drugs whose consumption can reduce the incidence of POAF. In the present study, we found that more β-blockers were taken in the non-POAF group. In addition, all patients included in the study were oncology patients, and most patients received neoadjuvant chemotherapy, which was observed as the main difference revealing the contradiction between the studies.

The current study was retrospective and conducted at a single center. The lack of comparison of inflammatory values, such as baseline C-reactive protein levels and erythrocyte sedimentation rates, between the groups, as well as the history of intraoperative or postoperative blood transfusions and the need for inotropic medications, can be considered the limitations of this study.

Conclusion

This study revealed the association between PLR and NLR and the occurrence of POAF after lung resection. Our secondary analysis showed that NLR was statistically more valuable. Our results could shed further light on the development of new treatment strategies and new studies in POAF patients after lobectomy.

Acknowledgments

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