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C-reactive protein/albumin ratio in predicting atrial fibrillation after coronary artery bypass grafting

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ABSTRACT

Objectives: In the present study, the purpose was to investigate the usability of the preoperative C-reactive protein/albumin ratio as a predictor of the development of postoperative atrial fibrillation in patients who undergo coronary artery bypass grafting.

Patients and methods: A total of 336 patients (228 males, 108 females; mean age: 58.1±8.5 years; range 35 to 88 years) who underwent isolated coronary artery bypass grafting with cardiopulmonary bypass between January 2019 and January 2021 were reviewed in the single-center, retrospective study. Those with postoperative sinus rhythm were considered Group 1 (n=258), and patients with postoperative atrial fibrillation were defined as Group 2 (n=78). Preoperative routine biochemical tests of the patient groups were evaluated.

Results: The incidence of postoperative atrial fibrillation was 23.2%. Statistically significant differences were detected between the two groups in terms of age ($p<0.001$) and previous percutaneous coronary intervention ($p=0.028$). In multivariate analysis, age, hemoglobin, mean platelet volume, neutrophil/lymphocyte ratio, and C-reactive protein/albumin ratio variables were found to be independent predictive factors of postoperative atrial fibrillation development ($p<0.001$, $p=0.005$, $p=0.002$, $p<0.001$, and $p<0.001$, respectively).

Conclusion: Preoperative hemoglobin, mean platelet volume, calculated neutrophil/lymphocyte ratio, and C-reactive protein/albumin ratio values can be used as predictors of postoperative atrial fibrillation development in patients who will undergo coronary artery bypass grafting.

Keywords: Atrial fibrillation, C-reactive protein, albumin, coronary artery bypass grafting.

One of the most common complications in the postoperative period after coronary artery bypass grafting (CABG) is cardiac arrhythmias, and the most common one is atrial fibrillation, particularly in the first 24 to 72 h.[1] Postoperative atrial fibrillation (PoAF) leads to thromboembolic events and hemodynamic disorders by impairing ventricular functions, and therefore, causes increased morbidity and mortality.[2] Inflammation plays a prominent role in the pathophysiology of PoAF. An acute systemic inflammatory response occurs due to CABG and cardiopulmonary bypass (CPB), and the patient's preoperative inflammatory status significantly affects this inflammatory response.[3,4]

C-reactive protein (CRP)/albumin ratio (CAR) is a new marker that is associated with inflammation. C-reactive protein is a nonspecific inflammation biomarker. Albumin, on the other hand, is an important protein regulating the oncotic pressure in the body with a carrier role in the blood. Low albumin levels are considered an indicator of poor prognosis.[5] Therefore, the CAR value has been associated with many cardiovascular diseases and their prognosis.[6]

In this study, the purpose was to investigate the usability of the CAR value obtained from preoperative routine biochemical tests as a predictor of PoAF development in patients who undergo CABGs.

PATIENTS AND METHODS

Patients who underwent isolated CABG with CPB by the same surgical team in the Adıyaman Training and Research Hospital, Cardiovascular Surgery Clinic

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between January 2019 and January 2021 were included in this single-center, retrospective study. The data on the patients were obtained from the electronic registry system and archive files. Patients who underwent emergency surgery, reoperations, combined cardiac surgeries, off-pump surgery, preoperative rhythm disorders, preoperative amiodarone treatment, or an acute or chronic infection, patients with a systemic inflammatory disease that requires anti-inflammatory treatment, chronic liver or renal disease, or hematological disease, and those who received steroid therapy were excluded from this study. After applying the exclusion criteria, 336 (228 males, 108 females; mean age: 58.1±8.5 years; range 35 to 88 years) patients were included in the study. Patients with postoperative sinus rhythm were considered Group 1 (n=258; mean age: 56.2±9.8 years), and patients with PoAF were defined as Group 2 (n=78; mean age: 64.3±10.3 years). Demographic characteristics of the patients, comorbidities, preoperative echocardiographic findings (left atrium diameter and ejection fraction [EF]), blood parameters, perioperative (number of distal anastomoses, cross-clamp time, CPB time) data, and postoperative (inotropic support need, total drainage amount, intensive care unit [ICU] stay, and hospital stay) data were recorded.

Preoperative routine laboratory analyzes of the patients were checked from blood samples taken from the antecubital vein at the time of admission to the clinic. Automated analyzers were used for complete blood count and biochemical measurements (CELL-DYN Ruby; Abbott Park, IL, USA, and Architect 16000; Abbott Park, IL, USA). Hemoglobin, white blood cell, neutrophil, lymphocyte, mean platelet volume (MPV), platelet, creatinine, blood urea nitrogen, CRP and albumin values were recorded, and also neutrophil/lymphocyte ratio (NLR) and CAR were calculated.

The patients were followed up with continuous electrocardiography (ECG) monitoring in the ICU in the postoperative period. Arterial blood pressure and heart rate measurements were performed routinely every 4 h, with daily 12-lead ECG control

Table 1
Preoperative variables and demographic characteristics of the patients

	Group 1 - PoAF (-) (n=258)			Group 2 - PoAF (+) (n=78)			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			56.2±9.8			64.3±10.3	<0.001*
Sex							
Male	173	67.1		55	70.5		0.567†
Hyperlipidemia	88	34.1		23	29.5		0.447†
Hypertension	142	55.0		48	61.5		0.310†
Diabetes mellitus	85	32.9		27	34.6		0.784†
CVA	18	7.0		9	11.5		0.194†
COPD	31	12.0		15	19.2		0.104†
Current smoker	65	25.2		18	23.1		0.704†
BMI (kg/m^2)			27.4±4.6			28.5±5.0	0.071‡
Previous PCI	41	15.9		21	26.9		0.028†
ACE-I/ARB use	59	22.9		21	26.9		0.461†
Beta-blocker use	77	29.8		27	34.6		0.425†
Preoperative HR (bpm)			79.1±10.0			81.0±11.1	0.170‡
Left atrial diameter (cm)			3.6±0.2			3.7±0.3	0.082*
Left ventricle EF (%)			50.5±6.2			49.0±7.1	0.189*

PoAF: Postoperative atrial fibrillation; SD: Standard deviation; CVA: Cerebrovascular accident; COPD: Chronic obstructive pulmonary disease; BMI: Body mass index; PCI: Percutaneus coronary intervention; ACE-I: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; HR: Heart rate; EF: Ejection fraction; * Mann-Whitney U test; † Chi-square test; ‡ Student-t test.

in patients transferred to the inpatient clinic after the ICU. If there were no contraindications, beta-blocker (metoprolol) treatment was administered to the patients in the preoperative period and in the postoperative period from the first day to avoid the development of PoAF. Patients with complaints such as palpitations, shortness of breath, or increased heart rate were immediately evaluated with a 12-lead ECG. According to monitor or 12-lead ECG recordings, an episode of atrial fibrillation (irregular RR intervals and distinct P waves) lasting at least 30 sec was defined as PoAF, with reference to the European Society of Cardiology definition of atrial fibrillation.[7]

Statistical analysis

Analyzes were made with the SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed as the mean ± standard deviation, and qualitative variables were presented as numbers and percentages. The normality distribution of the data was evaluated with the Shapiro-Wilk test. The chi-square test was used to evaluate the relationship between qualitative variables. Whether there were differences between the categories of the qualitative variable that had two categories in terms of a quantitative variable was evaluated with Student's t-test if normal distribution assumptions were met and with the Mann-Whitney U test if not. Receiver operating characteristic (ROC) analysis was performed for quantitative variables, and the Youden index was used to calculate the cut-off value for quantitative variables. Logistic regression analyzes were used to determine the risk factors that affected the development of PoAF. A p value of <0.05 was considered statistically significant.

Table 2
Preoperative laboratory values and perioperative/postoperative variables of the patients

	Group 1 - PoAF (-) (n=258)			Group 2 - PoAF (+) (n=78)			
Variables	n	%	Mean±SD	n	%	Mean±SD	p
Creatinine (mg/dL)			0.9±0.2			0.9±0.3	0.201*
BUN (mg/dL)			22.1±4.1			21.0±3.7	0.081*
Albumin (g/dL)			3.9±0.3			3.7±0.2	<0.001*
CRP (mg/dL)			6.4±2.5			11.5±3.1	<0.001‡
Hemoglobin (g/dL)			13.7±1.5			14.1±2.0	0.070‡
White blood cell (10^3/µL)			7.9±1.2			8.1±1.5	0.533*
Neutrophil (10^3/µL)			4.7±1.0			5.1±1.2	0.019*
Lymphocyte (10^3/µL)			2.2±0.5			1.8±0.6	<0.001*
Mean platelet volume (fL)			8.5±1.0			9.1±0.8	<0.001*
Platelet (10^3/µL)			245.0±40.3			239.0±49.4	0.575*
NLR			2.2±0.7			3.0±1.0	<0.001*
CAR			1.7±0.6			3.1±0.9	<0.001‡
CPB time (min)			90.0±14.9			94.0±27.5	0.252*
Cross-clamp time (min)			45.0±8.3			46.1±10.2	0.539*
Number of distal anastomoses			3.1±1.0			3.2±1.0	0.354*
Inotropic support	39	15.1		15	19.2		0.386†
Total drainage (mL)			610.0±154.7			580.0±168.3	0.310*
ICU stay (days)			1.9±0.6			2.3±0.8	<0.001*
Hospital stay (days)			6.3±1.3			7.9±1.2	<0.001*

PoAF: Postoperative atrial fibrillation; SD: Standard deviation; BUN: Blood urea nitrogen; CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; CAR: C-reactive protein/albumin ratio; CPB: Cardiopulmonary bypass; ICU: Intensive care unit; * Mann-Whitney U test; † Chi-square test; ‡ Student-t test.

Table 3
Logistic regression analysis to identify possible predictors of PoAF

	Univariate analysis			Multivariate analysis		
			95% CI			95% CI
Variables	*p*	OR	Lower-Upper	*p*	OR	Lower-Upper
Age	<0.001	1.083	1.053-1.113	<0.001	1.132	1.076-1.190
Previous PCI	0.030	1.950	1.069-3.558			
Left atrial diameter	0.042	2.874	1.041-7.932			
Preoperative HR	0.170	1.017	0.993-1.043			
CPB time	0.098	1.012	0.998-1.025			
Number of distal anastomoses	0.384	1.120	0.868-1.446			
White blood cell	0.220	1.129	0.930-1.371			
Hemoglobin	0.035	1.184	1.012-1.387	0.005	1.530	1.133-2.064
Mean platelet volume	<0.001	1.949	1.468-2.589	0.002	2.049	1.305-3.216
NLR	<0.001	3.482	2.393-5.066	<0.001	3.383	1.828-6.260
CAR	<0.001	13.394	7.351-24.404	<0.001	19.164	8.281-44.352

CI: Confidence interval; OR: Odds ratio; PCI: Percutaneus coronary intervention; HR: Heart rate; CPB: Cardiopulmonary bypass; NLR: Neutrophil/lymphocyte ratio; CAR: C-reactive protein/albumin ratio.

RESULTS

In the present study, which included 336 patients, PoAF developed in 23.2% (n=78). There was a statistically significant difference between the mean age of the groups (p<0.001). No statistically significant differences were found between the patient groups in terms of sex, hyperlipidemia, diabetes mellitus, hypertension, chronic obstructive pulmonary disease cerebrovascular accident, current smoking habit, body mass index, preoperative medical treatment (beta-blocker and angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker use), and preoperative heart rate. The rate of previous percutaneous coronary intervention (PCI) was significantly higher in Group 2 (p=0.028). There were no significant differences between the groups in terms of left ventricular EF and left atrium diameter parameters, which were evaluated preoperatively (Table 1).

The comparison of the preoperative laboratory values of the patient groups is given in Table 2. Albumin and lymphocyte levels were significantly lower in Group 2 (p<0.001 and p<0.001, respectively), and CRP, neutrophil, and MPV values were significantly higher (p<0.001, p=0.019, and p<0.001, respectively). The mean NLR value was 2.2±0.7 in Group 1 and 3.0±1.0 in Group 2, and the difference was statistically significant (p<0.001). The mean CAR value was 1.7±0.6 in Group 1 and 3.1±0.9 in Group 2, and the difference was statistically significant (p<0.001). Although there were no significant differences between the patient groups in terms of perioperative variables, among the postoperative variables, only ICU and hospital stay were found to be statistically significantly higher in Group 2 (p<0.001 and p<0.001, respectively; Table 2).

Age, previous PCI, left atrial diameter, hemoglobin, MPV, NLR, and CAR variables were found to be statistically significant risk factors in univariate analysis and were included in multivariate analysis to identify possible predictors of PoAF development (Table 3). According to the results of this analysis, age, hemoglobin, MPV, NLR, and CAR variables were found to be independent predictive factors for the development of PoAF (p<0.001, p=0.005, p=0.002, p<0.001, and p<0.001, respectively).

The ROC curve analysis was used to determine the predictive effects of MPV, NLR, and CAR variables on the development of PoAF (Figure 1). The cut-off value was 9.1 for MPV (area under the curve [AUC]: 0.695, 95% confidence interval [CI]: 0.634-0.756, p<0.001) with 61.5% sensitivity and 72.9% specificity. The cut-off value was 2.5 for NLR (AUC: 0.746, 95% CI: 0.679-0.812, p<0.001)

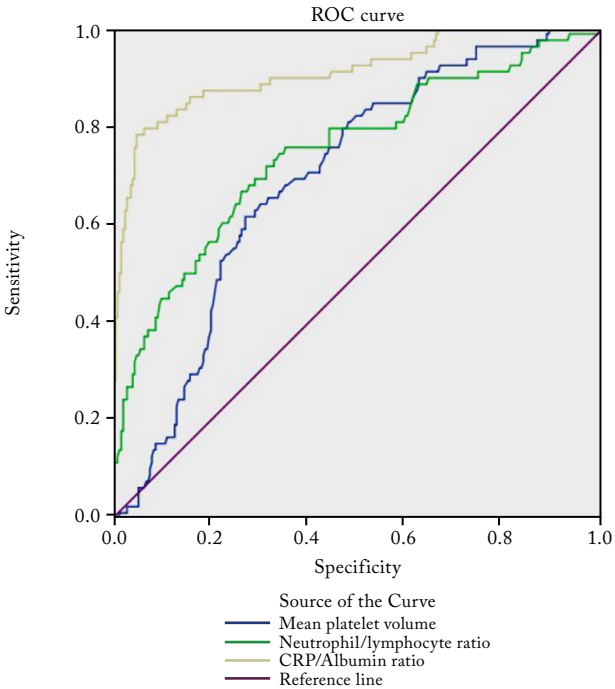

Figure 1. Receiver operation characteristic curve of MPV, NLR, and CAR for predicting PoAF.

ROC: Receiver operating characteristic; CRP: C-reactive protein; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte ratio; CAR: C-reactive protein/albumin ratio; PoAF: Postoperative atrial fibrillation.

with 71.8% sensitivity and 68.6% specificity. The cut-off value was 2.7 for CAR (AUC: 0.909, 95% CI: 0.867-0.951, p<0.001) with 78.2% sensitivity and 95% specificity (Table 4).

DISCUSSION

In this retrospective study investigating the relation between the development of PoAF and preoperative CAR value in patients who underwent CABG with CPB, it is remarkable that the NLR and CAR values of the patient group that developed PoAF were significantly higher. Additionally, age, hemoglobin, MPV, NLR, and CAR variables were found to be independent predictive factors of PoAF development.

Postoperative atrial fibrillation is a common complication of CABG, and its incidence has been reported between 6 and 40% in patients who undergo isolated CABG.[4] In the present study, the incidence was found to be 23.2%. Inflammation is an important factor in the pathophysiology of many postoperative complications in cardiac surgery. The inflammatory status of the patient in the preoperative period and the inflammatory response due to CPB in the perioperative period affect postoperative morbidity and mortality. It is considered that, in particular, the immune cells and mediators responsible for the inflammatory response affect the atrial tissue in the development of PoAF.[8]

After the role of inflammation in the pathophysiology of diseases and their associated complications were understood, many inflammatory biomarkers were associated with diseases. The NLR is a hematological parameter that is evaluated for this purpose and is also known as an indicator of subclinical inflammation.[9] Neutrophilia suggests nonspecific inflammation and is associated with atherothrombosis owing to platelet activation. Lymphopenia, however, indicates the strength of physiological stress and is considered an indicator of poor prognosis.[10,11] Neutrophilia and lymphopenia cause increased NLR levels, and therefore, high NLR values are associated with poor prognosis. Berkovitch et al.[12] calculated the NLR values at admission in their study, which included 21,118 individuals with the primary endpoint as new-onset atrial fibrillation. The results of this study demonstrate that there is a relation between high NLR and new-onset atrial fibrillation, and it was reported that a one-unit increase in NLR increases the risk of developing atrial fibrillation by 14% (95%

Table 4
Results of the ROC curve analysis

Variables	AUC	SE	*p*	95% CI Lower-Upper	Sensitivity (%)	Specificity (%)	Cut-off value
Mean platelet volume	0.695	0.031	<0.001	0.634-0.756	61.5	72.9	9.1
NLR	0.746	0.034	<0.001	0.679-0.812	71.8	68.6	2.5
CAR	0.909	0.021	<0.001	0.867-0.951	78.2	95.0	2.7

ROC: Receiver operating characteristic; CI: Confidence interval; AUC: Area under the curve; SE: Standard error; NLR: Neutrophil/lymphocyte ratio; CAR: C-reactive protein/albumin ratio.

CI: 1.06-1.23, p<0.001). In our study, it was revealed that the preoperative NLR values of our patient group with PoAF were significantly higher and a one-unit increase in NLR increased the risk of developing PoAF 3.383 times.

It is already known that there is a relation between low preoperative hemoglobin levels and increased postoperative mortality and morbidity in cardiac surgery.[13] In our study, although the preoperative hemoglobin levels were higher in our patient group who developed PoAF, hemoglobin was found to be an independent predictor of PoAF development in multivariate analyzes. Due to the inflammation in the body, the number of young and large-volume platelets increases; consequently, the MPV value, which is the indicator of platelet size, also increases.[2] In a study including 1,138 patients with isolated CABG, it was reported that the preoperative MPV value was significantly higher in the patient group that developed PoAF.[14] Consistent with the literature data, preoperative MPV values were significantly higher in the patient group with PoAF in our study, and MPV was found to be a predictor of PoAF development.

C-reactive protein is the most commonly used nonspecific inflammatory biomarker. Weymann et al.[4] reported in their meta-analysis that there is a significant relationship between the development of PoAF after cardiac surgeries and preoperative high CRP levels. In our study, it was found that there were significantly higher preoperative CRP levels in the patient group who developed PoAF. Albumin is a protein that has colloid osmotic effects, antithrombotic, anti-inflammatory, and antioxidant properties, and based on these characteristics, the decrease in albumin levels is an indicator of poor prognosis.[15,16] It exhibits antioxidant and anti-inflammatory properties by scavenging reactive oxygen species and free radicals that cause inflammation and endothelial dysfunction. It is known that increased reactive oxygen species increase the sensitivity of PoAF by affecting the atrial cells. In a published meta-analysis, it was reported that there is a negative correlation between serum albumin levels and the development of atrial fibrillation.[17] In our study, significantly lower albumin levels were noted in our patient group who developed PoAF.

The CAR is a marker defined as a predictor of the inflammatory status and prognosis and is considered more valuable than albumin or CRP alone.[6,18,19] Karabağ et al.[20] classified 403 stable angina pectoris patients according to the Syntax score and found that CAR was more significant alone than CRP and albumin in determining the severity of the disease. Park et al.[21] retrospectively reviewed 875 medical ICU patients, and found CAR to be an independent predictor of 28-day mortality (OR: 1.01, 95% CI: 1.00-1.02, p=0.001). In their study, which included 830 patients who underwent isolated CABG, Karabacak et al.[6] discovered that the preoperative CAR value was an independent predictor for the development of PoAF. In our study, the patient group that developed PoAF had significantly higher preoperative CAR values compared to the patient group with postoperative sinus rhythm, and preoperative CAR was also determined to be an independent predictor for the development of PoAF.

The main limitations of the study are its retrospective design and relatively low number of patients. Another significant limitation is that the development of PoAF was not evaluated after discharge. In addition, there may have been some patients whose PoAF development could not be evaluated as the patients were not followed up with the telemetry system in the inpatient clinic. The presence of comorbid hyperlipidemia was compared in the patient groups; however, the use of statin group drugs with dose-dependent effects for the treatment of hyperlipidemia was not evaluated, which can be considered a limitation since statins also have pleiotropic effects (antioxidant and anti-inflammatory).

In conclusion, statistically significant relations were detected between PoAF development and CAR values in patients who underwent CABG. Age, hemoglobin, MPV, NLR, and CAR variables were independent predictors for the development of PoAF in the analyzes performed. In addition, the predictive value of CAR value in the development of PoAF was higher than other parameters. Evaluation of hemoglobin, MPV, NLR, and CAR values, which can be easily obtained from preoperative routine biochemical tests, can provide early detection of patients at risk for PoAF, whose diagnosis is crucial due to the risk of increased morbidity and mortality.

Ethics Committee Approval: The study protocol was approved by the Adıyaman University Faculty of Medicine Ethics Committee (Date: 19/01/2021, no: 2021/01-10). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: Due to the retrospective nature of the study, informed consent was not obtained from the patients.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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