

Predictive Roles of Right Coronary Artery Disease Severity and Systemic Immune Inflammation Index in Predicting Atrial Fibrillation After Coronary Bypass Operations in Patients with Right Coronary Artery Disease

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ABSTRACT

Background: Postoperative atrial fibrillation (PoAF) is observed at a rate of 25-40% in the postoperative period after coronary artery bypass graft (CABG) surgery and can increase mortality, morbidity, and treatment costs. Inflammation and coronary artery disease (CAD) severity are important parameters to predict PoAF.

Methods: Patients with right coronary artery (RCA) disease who underwent isolated CABG operation between January 1, 2017 and April 15, 2020, were included in the study retrospectively. Demographic features, preoperative total Gensini score (TGS), right coronary Gensini score (RCGS), systemic immune inflammation index (SII), and postoperative characteristics were recorded.

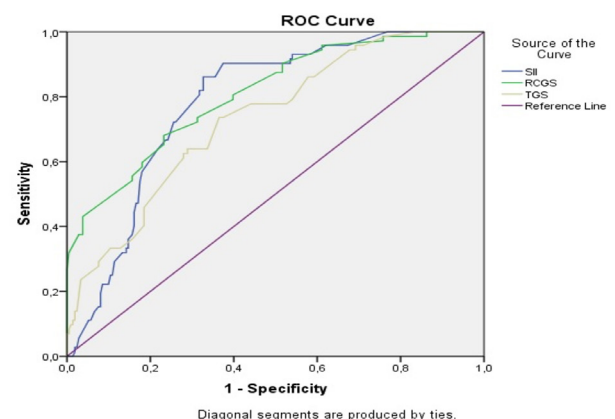
Results: A total of 283 patients were included in the study. Those who did not develop PoAF were included in Group 1 (N = 211, median age=60 (33-82) years), and those who did were included in Group 2 (N = 72, median age=68 (42-85) years). There were no statistically significant differences between the two groups, in terms of gender, hypercholesterolemia, cerebrovascular event/trans-ischemic attack history, body mass index, diabetes mellitus, smoking, beta blocker/angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, ejection fraction and left atrium diameters. As a result of multivariate analysis, advanced age (OR: 2.816 CI 95%: 1.687-3.498 $P < .001$), hypertension (OR: 0.896, CI 95%: 0.578-0.965, $P = .022$), SII (OR: 1.548 CI 95%: 1.265-2.896, $P = .003$), TGS (OR: 1.235, CI 95%: 1.096-2.424, $P = .012$), and RCGS (OR: 2.112, CI 95%: 1.665-4.156, $P < .001$) values were determined as independent predictors for predicting postoperative atrial fibrillation.

Conclusion: In this study, we showed that RCGS and SII values were independent predictors of PoAF after CABG operations in patients with right coronary artery disease.

INTRODUCTION

Coronary artery bypass graft (CABG) surgery has a prominent place in the treatment of coronary artery disease (CAD). Today, these procedures can be performed with cardiopulmonary bypass (CPB) with utmost vision and high success rates [Eris 2021]. However, as with any surgical intervention, undesirable outcomes may arise following these operations, one of the most significant being postoperative atrial fibrillation (PoAF), which occurs at a rate of 25-40% in the postoperative period, and could increase mortality, morbidity, and treatment costs, as well as prolong hospitalization [Erdolu 2020; Savran 2021].

Clinical values of various inflammatory parameters obtained from routine blood tests have been the subject of research in the cardiovascular field, as in many other medical fields. Two of the most important of these parameters in recent years are neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR). In one study, these values



Receiver operation characteristic (ROC) curve and area under the curve (AUC) for Systemic immune-inflammation index (SII), Right coronary Gensini score (RCGS) and Total Gensini score (TGS) for predicting postoperative atrial fibrillation. (SII: cutoff: 986, AUC: 0.784, 95%CI: 0.729-0.839 $P < .001$, 72.2% sensitivity and 74.4% specificity); (RCGS: cut-off: 15, AUC: 0.808, 95%CI: 0.751-0.866 $P < .001$, 74.6% sensitivity and 76.8% specificity); (TGS: cut-off: 79, AUC: 0.733, 95% CI: 0.670-0.797 $P < .001$, 63.9% sensitivity and 69.2% specificity)

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Table 1. Demographic and preoperative features of the patients

Variables	Group 1 (N = 211)	Group 2 (N = 72)	P
Age (years)	60 (33-82)	68 (42-85)	<.001‡
Female gender, n (%)	63 (29.8%)	23 (31.9%)	.868*
Hypertension, n (%)	123 (58.2%)	58 (80.5%)	<.001*
Diabetes mellitus, n (%)	44 (20.8%)	21 (29.1%)	.198*
Hypercholesterolemia, n (%)	59 (27.9%)	24 (33.3%)	.475*
Previous PCI, n (%)	58 (27.4%)	25 (34.7%)	.294*
Current smoker, n (%)	61 (28.9%)	24 (33.3%)	.574*
COPD, n (%)	21 (9.9%)	12 (16.6%)	.187*
Previous CVA	17 (7.1%)	8 (11.1%)	.441*
BMI (kg/m ²)	28.9 (24-38.8)	29.6 (24-40.1)	.357
Ejection fraction (%)	50 (35-65)	50 (35-60)	.114‡
β- Blocker therapy, n (%)	175 (82.9%)	62 (86.1%)	.394*
ARB/ACE-I therapy, n (%)	63 (29.8%)	19 (26.3%)	.414*
Left atrial diameter, mm	30 (25-50)	32 (24-50)	.258‡
TGS	70 (39-119)	85 (54-144)	<.001‡
RCGS	12 (8-21)	17 (7-48)	<.001‡

*Chi-square test, ‡Mann Whitney U test (Data is expressed as median (minimum-maximum) ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; TGS, Total Gensini Score; RCGS, Right Coronary Gensini Score

were preoperatively high in patients who developed PoAF after CABG operations [Çelik 2020]. The systemic immune inflammation index (SII), which is obtained from the parameters of these two ratios, has been investigated especially in gastrointestinal diseases and found to have more prognostic value than NLR and PLR values alone [Geng 2016]. In a recent study, SII value was reported as an independent predictor of poor outcomes after off-pump CABG operations [Dey 2020].

CAD severity may differ in patients undergoing coronary bypass. Studies have shown that the extent of atherosclerotic coronary artery disease is a predictor for PoAF [Karacaglar 2019]. Accordingly, it has been stated that right coronary artery disease may also predict PoAF [Mendes 1995].

In this study, we aimed to investigate the roles of preoperative SII value and right coronary artery disease severity in predicting PoAF after isolated CABG operations.

MATERIALS AND METHODS

Patients with right coronary artery (RCA) disease who underwent isolated CABG operation with CPB in our clinic between January 1, 2017 and April 15, 2020, were included in the study retrospectively. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices and was approved by the local ethics committee. The demographic features, preoperative routine blood parameters and postoperative characteristics of

all patients were recorded from patient files, intensive care follow-up cards, and hospital registry. Reoperations, emergency operations, combined surgeries, patients with autoimmune and inflammatory diseases, end-stage renal failure, known arrhythmias, those with left atrium diameters greater than 50mm, patients receiving preoperative amiodarone therapy, and patients with rudimentary or normal right coronary artery were excluded from the study. After the implementation of the exclusion criteria, 283 consecutive patients were included in the study. The patients who did not develop PoAF during hospitalization constituted Group 1, and those who did were included in Group 2.

Postoperative rhythm monitoring: All patients were transported to the cardiovascular surgery intensive care unit postoperatively, where electrocardiography (ECG) follow ups were performed continuously for at least two days. Twelve-lead ECG records were obtained daily, and routine ECG monitoring continued after the patients were transferred to the ward, during their bedrest. In this period, 12-lead ECG records were obtained from the patients, who had palpitations, shortness of breath, and chest pain. Based on European Society of Cardiology guidelines, atrial fibrillation was defined as the presence of irregular or fibrillatory waves or the absence of p waves on ECG, and these lasting more than 30 seconds indicated PoAF [Kirchhof 2016].

Calculation of Gensini score: Evaluations were made with a council of cardiovascular surgeons and cardiologists. According to the degree of stenosis in the coronary artery

Table 2. Preoperative laboratory variables of the patients

Variables	Group 1 (N = 211)	Group 2 (N = 72)	P‡
White blood cell (10 ³ /μL)	8.2 (4.6-14.2)	8.5 (5-14.6)	.294
Hematocrit (%)	41 (32.8-51.7)	39 (32-50.6)	.312
Platelet (10 ³ /μL)	248.2 (132-479)	251.4 (138-482)	.198
Neutrophil (10 ³ /μL)	4.5 (1.7-10.2)	4.7 (2.5-10.9)	.089
Lymphocyte (10 ³ /μL)	2.1 (0.9-4.3)	1.8 (0.8-3.5)	.002
Creatinine, mg/dL	0.98 (0.6-2)	0.95 (0.7-2)	.545
Urea, mg/dL	18 (16-38)	16 (14-42)	.324
Potassium, mmol/L	4.22 (4.05-4.4)	4.24 (4.02-4.5)	.598
Albumin (g/L)	39.8 (36.4-53.2)	39.2 (35.8-54.6)	.279
Free T3 (pg/mL)	2.5 (2.2-5.1)	2.7 (2.1-5.3)	.412
Free T4 (ng/dL)	0.8 (0.7-1.2)	0.9 (0.7-1.4)	.356
TSH (μIU/L)	1.9 (0.9-4.1)	2.1 (0.9-4.3)	.514
C Reactive protein (mg/dL)	8.7 (0.5-50.3)	9.1 (0.6-51.6)	.107
NLR	2.3 (1.2-7.8)	2.8 (1.4-8.9)	.021
PLR	149.6 (119.6-254.2)	152.4 (128.5-244.6)	.114
SII	878 (380-2134)	1034 (560-2496)	<.001

‡Mann Whitney U test; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; TSH, thyrotropin-stimulating hormone; T3, Triiodothyronine; T4, thyroxine

detected in angiography, for each lesion, 1 point was appointed for 1-25% stenosis; 2 points for 26-50% stenosis; 4 points for 51-75% stenosis; 8 points for 76-90% stenosis; 16 points for 91-99% stenosis; and 32 points for total occlusion. The calculated values then were multiplied by the pre-determined coefficients, as follows: Five for left main coronary artery, 2.5 for proximal left anterior descending artery (LAD), 1.5 for mid LAD, 1 for distal LAD, 2.5 for proximal circumflex artery (CX), and 1 for mid-distal CX and right coronary artery [Neeland 2012]. The total Gensini score (TGS) was the sum of the scores in all three coronary arteries, while right coronary Gensini score (RCGS) comprised the score for the right coronary lesion.

Evaluation of blood parameters: Preoperative blood samples of all patients were obtained from the superficial antecubital veins. An automated hematological analyzer was used for assessing hematological parameters (Coulter LH 780 Analyzer, CA, USA).

Statistical analysis: In our study, the SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) program was used to analyze the data. Means and standard deviations were calculated for mediational, continuous and ordinal data, using descriptive analysis methods. The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used for normality distribution analysis. While the Student's t test was used for the data presenting normal distribution, the Mann-Whitney U test was used for data that did not conform to normal distribution. This data was shown as mean ±sd or as mean (minimum-

maximum). Categorical variables were shown as frequency and percentage, and the Chi Square test was used for analysis. Univariate and multivariate binary logistic regression analysis was used to analyze PoAF predictors. *P*-values less than 0.05 were accepted as statistically significant. In predicting PoAF, receiver operating characteristics (ROC) curve analysis was performed for SII, TGS, and RCGS values, and the areas under the curve (AUC) were calculated.

RESULTS

A total of 283 patients were included in the study. Those who did not develop PoAF were included in Group 1 (N = 211, median age = 60 (33-82) years), and those who did were included in Group 2 (N = 72, median age = 68 (42-85) years). There were no statistically significant differences between the two groups, in terms of gender, hypercholesterolemia, cerebrovascular event/trans-ischemic attack history, body mass index, diabetes mellitus, smoking, beta blocker/angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, ejection fraction and left atrium diameters. Rates of hypertension (HT), age, TGS and RCGS values were significantly higher in Group 2 compared with Group 1 (*P* < .001 for all these parameters). Demographic characteristics and preoperative data of all patients are presented in Table 1.

Preoperative blood values of the patients are shown in Table 2. The two groups were similar, in terms of white blood cell, hematocrit, platelet, neutrophil counts, creatinine,

Table 3. Perioperative features of the patients

Variables	Group 1 (N = 211)	Group 2 (N = 72)	P‡
Total perfusion time	98 (60-190)	102 (58-185)	.218
Cross-clamp time	68 (36-92)	72 (35-94)	.310
Total chest tube drainage (ml)	650 (300-1400)	700 (400-1500)	.198
Total ICU stay (days)	2 (2-7)	4 (2-21)	<.001
Total hospital stay (days)	7 (6-15)	12 (10-25)	<.001

‡Mann-Whitney U test

C- reactive protein, PLR, and thyroid function values. In Group 2, while NLR and SII values were significantly higher, lymphocyte values were significantly lower ($P = .021$, $P < .001$, and $P = .002$, respectively).

Perioperative features of the patients are shown in Table 3. There was no statistically significant difference between the two groups, in terms of cross-clamp times, cardiopulmonary bypass times, and drainage amounts. Intensive care stay and total hospital stay days were statistically significantly higher in Group 2 ($P < .001$).

Logistic regression analysis was performed to evaluate the predictive value of certain parameters, in terms of postoperative atrial fibrillation. In univariate analysis; advanced age (OR [odds ratio] 3.768, 95% CI [confidence interval]: 1.854-4.284, $P < .001$), hypertension (OR: 1.954, 95% CI: 1.256-2.116, $P < .001$), low lymphocyte count (OR: 1.312 95% CI: 1.104-1.665, $P = .003$), NLR (OR: 0.897, 95% CI: 0.687-0.912, $P = .003$), SII (OR: 2.175, 95% CI: 1.214-2.978, $P < .001$), TGS (OR: 1.965, 95% CI: 1.748-2.894, $P < .001$), and RCGS (OR: 2.594, 95% CI: 1.864-3.3114, $P < .001$) values were found to be significantly correlated with the development of PoAF. As a result of multivariate analysis, advanced age (OR: 2.816 CI 95%: 1.687-3.498 $P < .001$), HT (OR: 0.896, CI 95%: 0.578-0.965, $P = .022$), SII (OR: 1.548 CI 95%: 1.265-2.896, $P = .003$), TGS (OR: 1.235, CI 95%: 1.096-2.424, $P = .012$), and RCGS (OR: 2.112, CI 95%: 1.665-4.156, $P < .001$) values were determined as independent predictors for predicting postoperative atrial fibrillation (Table 4).

Receiver operation characteristic curve analysis was performed to evaluate SII, TGS, and RCGS in predicting atrial fibrillation after coronary bypass operations. The cut-off value of SII was 986 (area under the curve: 0.784, confidence interval: 0.729-0.839, $P < .001$, with 72.2% sensitivity and 74.4% specificity), that of TGS was 79 (area under the curve: 0.733, confidence interval: 0.670-0.797, $P < .001$, with 63.9% sensitivity, 69.2% specificity), and RCGS was 15 (area under the curve: 0.808, confidence interval: 0.751-0.866, $P < .001$, with 74.6% sensitivity, 76.8% specificity).

DISCUSSION

PoAF that occurs after coronary bypass operations is undesirable and can lead to cerebrovascular events and heart

failure. For this reason, many studies have focused on possible risk factors, and further studies will be conducted. In this current study, we identified SII, TGS, and RCGS values as independent predictors of PoAF after CABG operations, in addition to known risk factors, such as age and hypertension. In our study, the severity of right coronary disease, calculated by the Gensini score, was determined as a predictor for PoAF for the first time.

Inflammation is a crucial factor in the pathogenesis and progression of many diseases, including atrial fibrillation. Neutrophils, lymphocytes, thrombocytes, and their ratios have been explored in many areas, primarily because they are easily obtainable and cheap. Among them, NLR and PLR values frequently are investigated. Inflammatory response occurs due to the cellular immune system after cardiac surgery, which is activated by lymphocytes, thus increasing neutrophil counts [Laffey 2002]. Lymphocyte count decreases, according to the severity of this activation [Yamanaka 2007]. Platelets play a prominent role in the production and release of various inflammatory substances, which partake in vascular wall inflammation. Especially in inflammatory processes, megakaryocyte proliferation and thrombocyte production increase [Langer 2008]. Considering all these mechanisms, NLR and PLR values emerge as notable prognostic markers.

Twelve studies involving 9,262 patients were included in a recent meta-analysis by Liu et al, investigating the relationship between NLR and PoAF, in which high preoperative NLR was correlated with PoAF (OR: 1.42, 95% CI 1.16-1.72). However, conditions such as HT and congestive heart failure were predictors for PoAF in multivariate analyses. The authors found that high preoperative NLR was associated with PoAF but concluded that novel studies were needed in large patient series, due to the heterogeneity of the groups [Liu 2020]. In another recent study, preoperative NLR and PLR values were associated with PoAF [Altinbas 2019], though in a recent study with a larger patient series ($N = 1,457$), there was no difference found in PoAF rates between patient groups with high and low PLR values (cut-off = 86) [Navani 2020]. In our study, increased NLR was correlated with PoAF, while PLR value was not.

The systemic immune inflammation index is obtained by multiplying the platelet count with the NLR value and has been the subject of studies on various malignant disease prognoses and gastrointestinal diseases [Geng 2016;

Table 4. Logistic regression analysis to identify factors affecting development of postoperative atrial fibrillation

Variables	P	Univariate analysis		P	Multivariate analysis	
		Exp (B) Odds ratio	95% CI Lower Upper		Exp (B) Odds ratio	95% CI Lower Upper
Age	<.001	3.768	1.854- 4.284	<.001	2.816	1.687- 3.498
Hypertension	<.001	1.954	1.256-2.116	.022	0.896	0.578- 0.965
Diabetes mellitus	.224	0.856	0.667-1.080	-	-	-
COPD	.198	0.769	0.494- 1.112	-	-	-
Total perfusion time	.224	1.018	0.978- 1.432	-	-	-
Lymphocyte	.003	1.312	1.104- 1.665	-	-	-
NLR	.024	0.897	0.687- 0.912	.128	1.254	0.768- 1.448
PLR	.116	1.010	0.854- 1.120	-	-	-
SII	<.001	2.175	1.214- 2.978	.003	1.548	1.265- 2.896
TGS	<.001	1.965	1.748- 2.894	.012	1.235	1.096- 2.424
RCGS	<.001	2.594	1.864- 3.114	<.001	2.112	1.665- 4.156

COPD, chronic obstructive pulmonary disease; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; TGS, Total Gensini Score; RCGS, Right Coronary Gensini Score

Tang 2018]. In a study, SII was a mortality predictor in patients with infective endocarditis [Agus 2020], while in another, among patients who received cardiac resynchronization therapy, those with low SII values showed a better response [Karauzum 2020]. In a retrospective observational study conducted by Dey et al, the predictivity of SII value for adverse outcomes after off-pump CABG operations was investigated. The authors reported that high SII value was an independent predictor of adverse outcomes, such as death, prolonged mechanical ventilation, sepsis, and renal failure, and concluded that SII value alone was more predictive than NLR and PLR values [Dey 2020]. In this study, we found that SII value was an independent predictor for PoAF, which is an important postoperative problem.

The dominance of the coronary artery circulatory system is determined by the artery from which the right posterior interventricular artery branches. Approximately 80% of the entire population has right or co-dominant circulation [Veltman 2012]. Accordingly, we included the patients who constitute the majority of those with CABG to our study. In addition, all patients had right coronary artery disease. A study showed that coronary artery complexity may be a predictor for PoAF in patients undergoing CABG [Geçmen 2016]. In another study in which coronary artery complexity was calculated by Gensini score, high Gensini score was an independent predictor for PoAF after CABG operations [Karacaglar 2019].

One of the most important risks for PoAF, which is the most common postoperative arrhythmia, is atrial ischemia. Ischemia due to right coronary artery disease can lead to atrial arrhythmias [Rechavia 1992]. In a study by Mendes et al, patients who underwent CABG were divided into those with and without severe RCA disease (> 70%) and factors affecting PoAF were investigated. The frequency of PoAF was higher

in patients with severe RCA lesions [Mendes 1995]. In our study, we showed that the RCGS value was an independent predictor for PoAF. In addition, contrary to this study, we determined RCA disease with the Gensini score, rather than a specific percentage of lesions in the artery.

The other two independent predictors of PoAF in our study were advanced age and HT. The wear on the structural elements of the heart due to advanced age, and especially atrial fibrosis, may pose a risk for PoAF [Mariscalco 2006]. Hypertension denotes increased shear stress in the vascular bed and leads to an inflammatory process. Tissue perfusion also may be impaired due to HT [Hogue 2005]. Atrial ischemia also will pose a risk for PoAF. Like ours, the association between HT, advanced age, and PoAF have been shown in numerous other studies [Savran 2021; Engin 2020].

The main limitations of our study are its retrospective, single center design as well as the sparse number of patients. Also, SII, NLR and PLR were calculated only before the surgery, the changes in these parameters after surgery may have an additional limited predictive value.

CONCLUSION

In this study, we showed that RCGS and SII values were independent predictors of PoAF after CPB-guided CABG operations in patients with right coronary artery disease, for the first time in the literature. PoAF is of great significance for clinicians, as it increases treatment costs and can lead to morbid consequences. Based on our study, patient risk groups can be identified. However, our results need to be supported by further, multi-center prospective studies in various patient groups.

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