








Systemic immune-inflammation index as a novel predictor of atrial fibrillation after off-pump coronary artery bypass grafting

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SUMMARY

OBJECTIVE: This study aims to examine the predictive role of systemic immune-inflammation index on postoperative new-onset atrial fibrillation in patients undergoing off-pump coronary artery bypass grafting.

METHODS: A total of 722 patients undergoing elective off-pump coronary artery bypass grafting between January 2017 and September 2021 were included in this study and divided into two groups as the atrial fibrillation group (n=172) and the non-atrial fibrillation group (n=550). Both groups were compared in terms of patients' baseline clinical features, operative and postoperative variables, and preoperative hematological indices derived from the complete blood count analysis. Multivariate logistic regression and receiver-operating characteristic curve analyses were performed to detect the independent predictors of postoperative new-onset atrial fibrillation.

RESULTS: The median age and length of hospital stay in the atrial fibrillation group were significantly higher than those in the non-atrial fibrillation group. The median values of white blood cell, platelet, neutrophil, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic immune-inflammation in the atrial fibrillation group were significantly greater than in those in the non-atrial fibrillation group. Logistic regression analysis demonstrated that age, platelet, platelet/lymphocyte ratio, and systemic immune-inflammation were independent predictors of postoperative new-onset atrial fibrillation. receiver-operating characteristic curve analysis revealed that systemic immune-inflammation of $706.7 \times 10^3/\text{mm}^3$ constituted cut-off value to predict the occurrence of new-onset atrial fibrillation with 86.6% sensitivity and 29.3% specificity.

CONCLUSION: Our study revealed for the first time that systemic immune-inflammation predicted new-onset atrial fibrillation after off-pump coronary artery bypass grafting.

KEYWORDS: Atrial fibrillation. Off pump coronary artery bypass.

INTRODUCTION

Atrial fibrillation (AF) is the most frequent dysrhythmia after coronary artery bypass grafting (CABG) and its incidence has been reported as 10–40% in the literature¹. New-onset AF following CABG has been demonstrated to be associated with serious morbidity, mortality, and increased financial burden². To reduce this increased morbidity, mortality, and financial burden, it is important to determine the patients with a higher risk of postoperative AF and thereby to take necessary precautions so that AF does not occur. Therefore, simply available, inexpensive, and reliable biomarkers that can be utilized in daily clinical practice are required for these purposes.

For the pathogenesis of new-onset AF after CABG, many factors such as surgical trauma, intraoperative cardiopulmonary bypass usage and cardioplegia administration, perioperative

discontinuation or inappropriate use of beta-blocker agents, hypoxia, and electrolyte imbalance are held responsible. Nevertheless, less information is available about the electrophysiological molecular mechanisms and factors leading to postoperative AF. In contrast, the inflammatory process is also known to be one of the contributing pathophysiological factors in AF occurrence^{3,4}. Various inflammatory biomarkers such as C-reactive protein, interleukins, and tumor necrosis factor- α have been extensively studied in relation to AF. In addition to these markers, hematological indices obtained from complete blood count (CBC) test such as white blood cell (WBC)⁵, red cell distribution width (RDW)⁶, mean platelet volume (MPV)⁶, neutrophil/lymphocyte ratio (NLR)⁷, and platelet/lymphocyte ratio (PLR)⁸ have been investigated as potential prognostic and predictive biomarkers for postoperative new-onset AF.

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Systemic immune-inflammation index (SII) is a novel biomarker that develops based on platelet count and NLR ($SII = \text{platelets count} \times \text{NLR}$) and demonstrates patients' inflammatory and immune statuses simultaneously. It was shown that high SII levels were related to poor outcomes and the index was an important prognostic marker in various types of cancers⁹. SII was also reported to independently predict the major adverse cardiovascular events such as nonfatal myocardial infarction (MI), nonfatal stroke, heart failure, and cardiac death in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention¹⁰. Moreover, a recent study demonstrated that high SII levels were associated with poor outcomes after elective off-pump CABG¹¹. In contrast, to the best of our knowledge, a relationship between SII and new-onset AF in patients undergoing off-pump CABG has never been examined. Thus, we designed this study to examine whether a potential relationship between SII and new-onset AF was present in patients undergoing elective isolated off-pump CABG. Additionally, we also investigated other possible predictive factors and perioperative outcomes of the new-onset AF after off-pump CABG.

METHODS

Study population and design

The study was started once approval was obtained from the local ethics committee. This was a retrospective observational cohort study and conducted on patients undergoing elective isolated off-pump CABG at a tertiary referral center in Turkey between January 2017 and September 2021. The study population consisted of a total of 722 patients, and patients were divided into two groups, namely, AF group (n=172) and non-AF group (n=550), according to the occurrence of new-onset AF during the postoperative period. Patients' preoperative baseline clinical characteristics, comorbid conditions, laboratory parameters obtained from the CBC analysis, intraoperative data, postoperative outcomes, and complications were screened through the computerized medical database of the hospital, recorded, and compared between the groups. Thus, the predictive risk factors and perioperative results of new-onset AF after off-pump CABG were determined. Patients with a history of previous AF or other cardiac dysrhythmias, those undergoing emergency, reoperative or on-pump CABG, and concomitant cardiac operation such as mitral valve surgery were excluded from the study.

In approximately past 7 years, we preferred and routinely performed the "off-pump technique" for patients undergoing

CABG to avoid the detrimental effects of cardiopulmonary bypass. All patients undergoing off-pump CABG were informed about the operation and perioperative process, and their verbal and written consents were obtained before the operation. They were operated via a standard median sternotomy under general anesthesia. Internal thoracic artery and vena saphena magna were used as primary bypass grafts in most of the patients.

Postoperative monitoring

During the postoperative first 48 h in ICU, electrocardiogram (ECG), invasive central venous and arterial pressures, and oxygen saturation of the patients were continuously monitored, and arterial blood gas analyses were performed regularly every 2–4 h. Cardiac rhythms of patients were assessed by obtaining standard 12-lead ECGs every day for the remaining days until discharge. In addition, heart rate and rhythm were assessed by palpation of the radial pulse at least once in every 4 h. An additional 12-lead ECG was obtained and analyzed in case of tachycardia, palpitation, or a suspicion of an irregular cardiac rhythm. New-onset AF was diagnosed with the existence of an irregular RR interval and an absence of P wave on the ECG.

Laboratory analysis

Blood samples were taken from a peripheral vein after a 6–8-h fasting period. The samples were placed into sterile tubes containing a standard amount of anticoagulant and were quickly delivered to the laboratory for the analysis. To determine preoperative values of the parameters of the CBC test, the samples were studied in an automatic CBC analysis device (Beckman Coulter Inc., CA, USA). The studied and derived CBC parameters for this study were hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), platelet (PLT), neutrophil (NEU), lymphocyte (LYM), platelet distribution width (PDW), plateletcrit (PCT), WBC, RDW, MPV, NLR, PLR, and SII. The SII was calculated using the formula "platelet count \times neutrophil/lymphocyte ratio."

Statistical analysis

The Shapiro-Wilk test was used to evaluate the normality of variables. Continuous variables were presented as median (min–max) values, while categorical variables were expressed as numbers (percentages). Continuous variables were analyzed using the Mann-Whitney U-test, while categorical variables were analyzed using the chi-square test. Multiple explanatory variable logistic regression analysis was performed to determine the risk factors/covariates for AF. Receiver-operating characteristic (ROC) curve analysis was performed to determine the cut-off values of selected variables, via logistic regression, for

AF from area under the curve (AUC). The ROC curve analysis was performed using the “Optimal Cutpoints” library of R software¹². The R software was used to perform the statistical analyses (R Core Team, 2021)¹³. A p-value <0.05 was regarded as statistically significant for all analyses.

RESULTS

Patients with new-onset AF were significantly older than those without AF, and the median ages were 69 (38–85) and 62 (35–87) years for the AF group and the non-AF group, respectively ($p=0.001$). There were no significant differences with regard to other baseline clinical characteristics and comorbidities between the groups. When the laboratory parameters were compared between the groups, it was detected that the median values of WBC, PLT, NEU, NLR, PLR, and SII in the AF group were significantly greater than those in the non-AF group (Table 1).

When operative and postoperative data were considered, we found that the median length of hospital stay in the AF group was significantly longer than that in the non-AF group (6 [5–24] days

for the AF group vs. 5 [4–39] days for the non-AF group; $p=0.001$). In terms of other operative and postoperative variables, the groups were similar and no significant differences were detected (Table 2).

Following the determination of the potentially significant risk factors, a multivariate logistic regression analysis was performed to assess the relationship between the occurrence of new-onset AF and independent predictors by adjusting for significant variables. According to multivariate logistic regression analysis, age, PLT, PLR, and SII were detected to be independent predictors of new-onset AF.

The ROC curve analysis demonstrated that age of 66 years constituted cut-off value for predicting the occurrence of new-onset AF with 57.5% sensitivity and 64.7% specificity, PLT of $177 \times 10^3/\text{mm}^3$ constituted cut-off value for predicting the occurrence of new-onset AF with 88.9% sensitivity and 21.1% specificity, PLR of 14.52 constituted cut-off value for predicting the occurrence of new-onset AF with 61.0% sensitivity and 51.1% specificity, and SII of $706.7 \times 10^3/\text{mm}^3$ constituted cut-off value for predicting the occurrence of new-onset AF with 86.6% sensitivity and 29.3% specificity (Figure 1).

Table 1. Preoperative clinical characteristics and laboratory parameters.

	Non-AF group (n=550)	AF group (n=172)	p-value
Age (year)	62 (35–87)	69 (38–85)	0.001
Gender (male) (%)	351 (63.8)	112 (65.1)	0.568
Weight (kg)	77 (50–130)	77 (55–122)	0.253
Height (cm)	170 (145–190)	168 (145–190)	0.170
BMI (kg/m ²)	27.2 (18.5–44.1)	27.0 (18.4–39.4)	0.658
Obesity (%)	134 (24.4)	36 (20.9)	0.410
LMCA disease (%)	100 (18.2)	27 (15.7)	0.527
LVEF level	55 (25–70)	50 (25–70)	0.201
LA diameter (cm)	3.7 (2.5–6.5)	3.9 (2.7–6.3)	0.185
Beta blocker usage (%)	223 (40.5)	68 (39.5)	0.883
Hypertension (%)	356 (64.7)	105 (61.0)	0.432
Diabetes mellitus (%)	208 (37.8)	73 (42.4)	0.319
Hyperlipidemia (%)	215 (39.1)	67 (39.0)	1.000
Myocardial infarction	195 (35.5)	66 (38.4)	0.546
Chronic renal dysfunction (%)	43 (7.8)	9 (5.2)	0.399
Chronic liver disease (%)	2 (0.4)	0 (0.0)	1.000
Peripheral arterial disease (%)	50 (9.1)	20 (11.6)	0.404
COPD (%)	47 (8.5)	18 (10.5)	0.585
Previous PCI (%)	68 (12.4)	28 (16.3)	0.234
Previous CVE (%)	43 (7.8)	11 (6.4)	0.651
Smoking (%)	155 (28.2)	43 (25.0)	0.362
HGB (g/dL)	13.5 (8.3–19.2)	13.3 (8.4–19.0)	0.329

Continue...

Table 1. Continuation.

	Non-AF group (n=550)	AF group (n=172)	p-value
HCT (%)	39 (24.8–57.6)	40 (24.0–57.0)	0.212
MCV (fL)	87.5 (63.2–105.0)	87.7 (65.9–103.3)	0.147
RDW (%)	16 (11.0–34.0)	16 (13.0–24.2)	0.598
WBC (u/mm ³)	8 (3.0–23.0)	9 (4.0–23.0)	0.049
PLT (10 ³ /mm ³)	232 (61–729)	247 (97–787)	0.016
NEU (%)	69.9 (23.5–96.2)	72.7 (28.8–94.2)	0.001
LYM (%)	17 (4.4–50.5)	14.6 (5.0–43.4)	0.128
MPV (fL)	8 (2.0–16.0)	8 (5.8–17.0)	0.875
RDW (%)	17.5 (13.3–22.4)	17.5 (14.8–22.4)	0.598
PCT (%)	0.17 (0.04–1.05)	0.17 (0.04–0.92)	0.581
NLR	4.04 (0.86–16.02)	4.68 (1.45–17.66)	0.011
PLR	14.35 (2.72–67.60)	16.61 (3.06–65.66)	0.006
SII (10 ³ /mm ³)	991.4 (175.0–4895.4)	1150.1 (199.2–5594.3)	0.001

AF: atrial fibrillation; BMI: body mass index; LMCA: left main coronary artery; LVEF: left ventricular ejection fraction; LA: left atrium; COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; CVE: cerebrovascular event; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; RDW: red cell distribution width; PCT: plateletcrit; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index. Data were expressed as median (minimum-maximum) for continuous variables or number (%) for categorical variables. Continuous variables were compared using independent samples t-test or Wilcoxon rank sum test. Categorical variables were reported as frequency (percent) and compared using Pearson's χ^2 test. Bold values indicate statistical significance at the p<0.05 level.

Table 2. Intraoperative and postoperative variables.

	Non-AF group (n=550)	AF group (n=172)	p-value
LITA usage (%)	516 (94.0)	162 (94.2)	0.841
Complete revascularization (%)	519 (94.4)	156 (90.7)	0.128
Number of distal bypass	3 (1–7)	4 (1–6)	0.499
Extubation time (h)	6 (2–30)	6 (2–19)	0.204
Length of ICU stay (h)	24 (24–360)	30 (24–288)	0.113
Length of hospital stay (day)	5 (4–39)	6 (5–24)	0.001
Inotrope requirement (%)	103 (18.7)	29 (16.9)	0.660
IABP requirement (%)	25 (4.5)	12 (7.0)	0.287
Low cardiac output syndrome (%)	25 (4.5)	12 (7.0)	0.287
Myocardial infarction (%)	18 (3.3)	6 (3.5)	1.000
Cerebrovascular event (%)	17 (3.1)	6 (3.5)	0.999
Reintubation (%)	20 (3.6)	6 (3.5)	1.000
Pneumonia (%)	19 (3.5)	8 (4.7)	0.623
Mediastinitis (%)	19 (3.5)	7 (4.1)	0.493
Reexploration for bleeding (%)	23 (4.2)	7 (4.1)	1.000
ARD requiring hemodialysis (%)	15 (2.7)	4 (2.3)	0.989
Gastrointestinal bleeding (%)	5 (0.9)	2 (1.2)	1.000
In-hospital mortality (%)	12 (2.2)	2 (1.2)	0.597

AF: atrial fibrillation; LITA: left internal thoracic artery; ICU: intensive care unit; IABP: intraaortic balloon pump; ARD: acute renal dysfunction. Data were expressed as median (minimum-maximum) for continuous variables or number (%) for categorical variables. Continuous variables were compared using independent samples t-test or Wilcoxon rank sum test. Categorical variables were reported as frequency (percent) and compared using Pearson's χ^2 test. Bold value indicates statistical significance at the p<0.05 level.

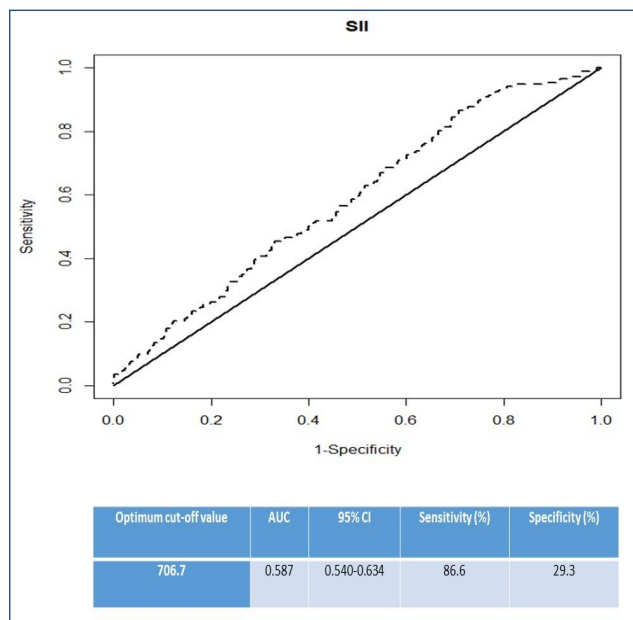


Figure 1. Receiver-operating characteristic curve for systemic immune-inflammation index.

DISCUSSION

Our study revealed that patients in the AF group were significantly older and had a longer length of hospital stay compared with those in the non-AF group. Although among hematological indices, WBC, PLT, NEU, NLR, PLR, and SII levels in the AF group were significantly greater than those in the non-AF group, according to multivariate analysis, only PLT, PLR, and SII were gained significantly and considered the associated predictive indices for postoperative new-onset AF. In our opinion, the most intriguing finding of the study was that SII independently predicts new-onset AF after off-pump CABG for the first time in the existing literature.

Determining the predictive risk factors of new-onset AF following the cardiac surgery is critical because it allows for the development of preventive measures and necessary prompt management. The use of several medications, such as β -blockers, statins, and steroids, for prophylaxis against postoperative AF should be considered in the preoperative period. In contrast, although numerous potential risk factors for postoperative new-onset AF have been identified in different studies, “advanced age” is the most known predictive variable that has been identified practically in every study found in the literature¹⁻⁴. Our study confirmed that advanced age was a substantial and independent risk factor for postoperative new-onset AF as previously reported in the literature.

Studies investigating hematological indices obtained from a simple CBC test for prediction of new-onset AF after cardiac

surgery have increased recently, and these hematological indices have become the focus of attention on this topic. The CBC test is inexpensive, easily and quickly accessible in many centers, and includes many different reliable indices. Among the indices, WBC, RDW, PLT, and MPV as well as NLR and PLR are the most studied and identified predictive variables for new-onset AF¹⁴. Although various indices derived from the CBC test have been reported to predict new-onset AF after CABG in different studies, the results are often inconclusive and inconsistent with each other. In contrast, a recent systematic review and meta-analysis including a total of 6,098 patients from 22 studies that fit the eligibility criteria showed that preoperative PLT, MPV, WBC, NLR, and RDW were associated predictive hematological indices with new-onset AF after cardiac surgery¹⁵. In our study, we detected PLT as well as PLR as predictive hematological indices for new-onset AF following off-pump CABG.

SII is a novel hematological marker that is observed using the CBC test by bringing together three inflammatory peripheral cell counts (platelet, neutrophil, and lymphocyte), which reflects patients’ inflammatory and immune statuses simultaneously. SII has been widely studied in patients with cancer and it emerged as a significant hematological prognostic indicator in many types of cancer⁹. SII has also been examined in many different cardiovascular diseases, such as CAD¹⁰, severe calcific aortic stenosis¹⁶, infective endocarditis¹⁷, and pulmonary embolism¹⁸. Additionally, in a large-scale cohort study on 13,929 middle-aged and older Chinese adults who were free of cardiovascular disease and cancer, the relationship of SII with incident cardiovascular diseases including stroke and CAD was examined, and a high SII level was detected to be significantly associated with the cardiovascular diseases¹⁹. Moreover, Bağcı et al.²⁰ recently investigated the predictive capacity of SII for the detection of new-onset AF in patients with ST-elevation MI and showed that SII predicted new-onset AF following ST-elevation MI. In contrast, the predictive role of SII on postoperative outcomes in patients undergoing cardiac surgery has also been recently studied. Yoon et al.²¹ assessed the prognostic implications of preoperative SII on 213 patients undergoing isolated tricuspid valve surgery and demonstrated that high SII levels were independently associated with the major early-term perioperative complications. Dey et al.¹¹ conducted a retrospective single-center risk-prediction study on 1,007 patients undergoing elective off-pump CABG, and revealed that the SII cut-off value of $878.06 \times 10^3/\text{mm}^3$ predicted poor outcomes, such as major adverse cardiovascular events, renal failure, sepsis, and death, with 97.6% sensitivity and 91% specificity. In this study, we revealed that the SII cut-off value of $706.7 \times 10^3/\text{mm}^3$ predicted postoperative new-onset AF with 86.6% sensitivity and 29.3% specificity.

Our study had several limitations. The major limitations of our study were its single-centered design and retrospective nature. Another important limitation was the lack of a correlation analysis with other inflammatory markers such as C-reactive protein and interleukins. Additionally, heart rhythm monitoring could not be performed on a continuous basis following an ICU stay. Although in the following days, after ICU heart rhythm was routinely monitored with standard ECGs at least twice a day and an additional ECG was obtained in all cases when any rhythm abnormality was suspected, there was a possibility of unnoticed short-time and transient attacks of asymptomatic AF.

CONCLUSION

Our study demonstrated that age, PLT, PLR and SII were independent predictive risk factors of new-onset AF following off-pump CABG. Among these aforementioned factors, SII was detected to predict postoperative new-onset AF for

the first time in the literature, and to the best of our knowledge, our study is the first clinical research to examine the predictive role of SII on new-onset AF in patients undergoing off-pump CABG. Nonetheless, further well-designed studies with larger patient participation are needed to support the results of our study and obtain more evident scientific information.

AUTHORS' CONTRIBUTIONS

DT: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **UTKK:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **YV:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **AY:** Conceptualization, Data curation, Formal Analysis, Writing – original draft. **ID:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **ERU:** Data curation, Writing – review & editing. **SAK:** Formal Analysis, Writing – review & editing.

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