

Inflammatory prognostic index predicts new-onset atrial fibrillation and mortality after on-pump coronary artery bypass grafting

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SUMMARY

OBJECTIVE: This study aimed to analyze its predictive role in incipient postoperative atrial fibrillation by constructing an inflammatory prognostic index based on hematological and biochemical parameters in patients undergoing elective isolated coronary artery surgery accompanied by cardiopulmonary bypass.

METHODS: The data of 343 patients who underwent coronary bypass surgery between May 2021 and July 2022 were evaluated. Multivariate logistic regression and recipient study characteristic curve analyses were studied by comparing the patients' hematological indices and basic clinical features between the two groups.

RESULTS: Logistic regression analysis showed that age ($p<0.001$), hypertension ($p=0.01$), and inflammatory prognostic index ($p<0.001$) were independent predictors of new-onset postoperative atrial fibrillation. To predict the development of postoperative atrial fibrillation, a cutoff value of 0.25 (77.8% sensitivity and 69.3% specificity) was determined for inflammatory prognostic index in the receiver-operating characteristic curve analysis (area under curve=0.798, 95% confidence interval 0.752–0.840).

CONCLUSION: Inflammatory prognostic index can be a noninvasive, easily available marker for predicting new-onset atrial fibrillation after coronary artery bypass surgery.

KEYWORDS: Atrial fibrillation. Coronary artery disease. Inflammation.

INTRODUCTION

Coronary artery bypass graft (CABG) operations are the most commonly performed cardiac surgery procedure all over the world, and atrial fibrillation (AF) is the most common arrhythmia after coronary artery surgery. The incidence of postoperative atrial fibrillation (POAF) after CABG varies between 20 and 50%¹. Many factors are held responsible for the development of POAF after CABG. Use of cardiopulmonary bypass (CPB), cardioplegic agents used, inappropriate use of preoperative antiarrhythmic agents, surgical trauma, hypoxia, and electrolyte disturbances are some of these¹. Inflammatory reactions that begin after surgical stress are predicted to trigger arrhythmogenic events^{2,3}. In many studies, the development of POAF has been shown to be associated with higher costs and increased morbidity and mortality rates due to longer hospital stays⁴. Predicting the risk of developing POAF and identifying high-risk patients are important in terms of taking necessary prophylactic measures. Therefore, there is a need for simple,

inexpensive, and reliable biomarkers that can be used in daily clinical practice for the prediction of POAF.

Potential predictive biomarkers for POAF after CABG have been studied and have been shown to predict POAF. White blood cell (WBC)⁵, neutrophil/lymphocyte ratio (NLR)⁶, platelet/lymphocyte ratio (PLR)⁷, C-reactive protein (CRP)³, and interleukins³ are frequently used biomarkers. The inflammatory prognostic index (IPI): CRP, NLR, and serum albumin (ALB) levels are evaluated together, and it is a new hematological biomarker that shows the inflammatory and immune status of patients ($IPI=CRP \times NLR/ALB$). This new biomarker has been shown to provide important information about prognosis in oncologic patients, and its high levels are associated with poor outcomes⁸⁻¹⁰. To the best of our knowledge, there is no study in the literature showing the role of IPI in predicting the risk of new-onset POAF in patients after CABG. Therefore, we investigated the possible role of IPI in predicting new-onset POAF after CABG.

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METHODS

Study population and design

For the study, approval was obtained from the local ethics committee of our hospital (No: 2022-10/9, Date: 16.09.2022). We retrospectively evaluated 343 adult patients who underwent elective isolated CABG operations using CPB between May 2021 and July 2022 in our hospital. The patients were classified into two groups: those who did not develop as group 1 POAF (72.3%, n=248) and those who developed as group 2 POAF (27.7%, n=95). The groups were compared in terms of demographic, clinical, and preoperative blood parameters. Preoperatively, the patients' complete blood count parameters (hemoglobin, WBC, thrombocyte, neutrophil, and lymphocyte), biochemical parameters (serum CRP, albumin, urea, creatinine, glomerular filtration rate (GFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), electrocardiographic, and echocardiographic (ECHO) findings) were recorded. The incidence of POAF in electrocardiography was determined by electrocardiography (ECG) and rhythm monitoring from the day of operation until discharge, considering new-onset POAF in cases of urgent intervention due to an AF rhythm lasting longer than 10 min or an unstable hemodynamic condition. The ECHO findings were determined by measuring left ventricular ejection fraction and left anteroposterior atrial diameter on a parasternal long-axis view. In the intraoperative and postoperative periods, CPB duration, cross-clamp time and number of bypass grafts, infection status, stroke development, intensive care unit (ICU) and hospitalization time, reintubation, reoperation, low cardiac output, and mortality rates were investigated.

Patients who received emergency surgery, reoperative surgery, valve surgery, permanent pacemaker and implantable cardioverter defibrillator, malignancy, sepsis, autoimmune and inflammatory disease, AF history, and preoperative amiodarone treatment were excluded from the study as they were thought to adversely affect the statistical results.

After the operation, ECG, arterial blood pressure, central venous pressure, oxygen saturation, and urine output were continuously monitored in all patients. The cardiac rhythms of the patients were evaluated by taking a standard 12-lead ECG every day. Additionally, radial pulse control was performed four times a day to check for rhythm changes.

Statistical analysis

Data were entered into the Statistical Package for the Social Sciences (IBM® SPSS Statistics for Windows, Version 23.0, Armonk, NY, USA) software package. Whether the distributions were normal or not was determined by Kolmogorov-Smirnov

analysis. Student's t-test was used for comparisons between groups. Pearson's chi-square test was used for comparative analysis of qualitative variables; however, Fisher's exact test was used if the sample size was small (≤ 5). Interquartile range (IQR) results were also given for the values recorded as median. A p-value < 0.05 was considered statistically significant. Multivariate analysis was performed using variables that were found to have a statistically significant effect on AF in the univariate analysis ($p < 0.05$). In the univariate analysis, only a single variable was included in the multiple logistic regression analysis when there were confounders (e.g., albumin, CRP, NLR, and IPI, or neutrophils, lymphocytes, and NLR) among the variables found to statistically affect the development of AF. Whether IPI predicted AF was analyzed by performing ROC analysis, and the area under the curve (AUC) was calculated.

RESULTS

Group 2 patients were statistically significantly older than group 1 patients, and the median age was 59 (35–78) and 70 (39–86) years for groups 1 and 2, respectively ($p < 0.001$). The number of patients with HT and COPD, left atrial size, neutrophil, lymphocyte, hemoglobin, NLR, PLR, CRP, urea, GFR, albumin, ALT, and albumin levels were found to be higher in group 1 compared to group 2. HT, COPD, left atrial size, neutrophils, NLR, PLR, CRP, urea, and IPI were found to be statistically significantly higher in group 2 compared to group 1. The groups were similar in terms of other preoperative variables, and no significant difference was found (Table 1).

In the postoperative follow-ups, the length of stay in the ICU and hospital was found to be longer in the POAF group. It was observed that patients who developed POAF had a statistically higher rate of re-intubation, more low cardiac output syndrome, and a higher rate of surgery-related infection. The mortality rate in patients who developed POAF was found to be higher, close to statistical significance, than that of those who did not develop POAF (Table 1).

A multivariate logistic regression analysis was performed to explore the link between POAF occurrence and independent predictors by controlling relevant variables. Age, HT, and IPI were found to be independent variables determining the development of POAF in multivariate logistic regression analysis (Table 2).

The effectiveness of IPI in predicting the development of AF was examined by performing ROC analysis. IPI was found to have an adequate AUC value (AUC 0.798, 95%CI 0.745–0.852). The threshold value was determined as 0.25 according to the best sensitive and specificity values for IPI (Figure 1).

Table 1. Comparison of demographic, clinical, and laboratory values of group 1 and group 2 patients.

Variable	Group 1 (n=248)	Group 2 (n=95)	p-value
Age (years), median (IQR)	59 (12)	70 (15)	<0.001
Gender, n (%)			
Male	191 (77.0)	68 (71.6)	0.295
Woman	57 (23.0)	27 (28.4)	
BMI (kg/m ²), median (IQR)	26.8 (4.7)	27.6 (4.9)	0.09
DM, n (%)	98 (39.5)	44 (46.3)	0.253
HT, n (%)	104 (41.9)	61 (64.2)	<0.001
COPD, n (%)	18 (7.3)	22 (23.1)	0.03
Smoke, n (%)	86 (34.7)	40 (42.1)	0.202
CABG graft count, median (IQR)	4 (1)	3 (1)	0.644
EF (%), median (IQR)	50 (15)	55 (15)	0.975
Left atrium size, median (IQR)	3.9 (0.3)	4.0 (0.2)	0.009
CPD time (min), median (IQR)	88 (38)	88 (45)	0.492
Cross time, median (IQR)	57 (25)	60 (21)	0.449
WBC (10 ³ /μL), median (IQR)	8.8 (3.2)	8.8 (3.0)	0.491
Neutrophil (10 ³ /μL), median (IQR)	5.6 (2.7)	7.3 (3.7)	<0.001
Lymphocyte (10 ³ /μL), median (IQR)	2.2 (1.1)	2.0 (1.2)	0.02
NLR, median (IQR)	2.4 (1.5)	4.3 (3.0)	<0.001
Monocyte (10 ³ /μL), median (IQR)	0.6 (0.3)	0.7 (0.2)	0.292
Eosinophil (10 ³ /μL), median (IQR)	0.1 (0.2)	0.1 (0.1)	0.931
Hb (g/dL), median (IQR)	13.6 (2.4)	13.0 (2.7)	0.03
RDW-SD (fL), median (IQR)	40.1 (4.5)	40.2 (4.4)	0.256
PCT (%), median (IQR)	0.26 (0.10)	0.26 (0.10)	0.922
MPV (fL), median (IQR)	10.2 (1.4)	10.2 (1.4)	0.975
PDW (fL), median (IQR)	11.6 (3.1)	11.6 (2.5)	0.788
Platelet (10 ³ /μL), median (IQR)	246.5 (97.8)	256.0 (91.0)	0.300
PLR, median (IQR)	113.5 (58.6)	138.3 (89.2)	0.002
CRP (mg/L), median (IQR)	2.6 (3.2)	4.7 (6.1)	<0.001
Urea (mg/dL), median (IQR)	32.6 (18.3)	35.5 (18.6)	0.01
Creatinine (mg/dL), median (IQR)	0.8 (0.2)	0.9 (0.3)	0.08
GFR (mL/min/1.73 m ²), median (IQR)	90.0 (26.2)	80.0 (29.6)	<0.001
Albumin (g/L), median (IQR)	42.0 (5.4)	35.8 (5.6)	<0.001
AST (IU/L), median (IQR)	21.0 (15.8)	20.0 (11.0)	0.06
ALT (U/L), median (IQR)	20.0 (13.8)	17.0 (12.0)	0.01
Potassium (mmol/L), median (IQR)	4.3 (0.6)	4.3 (0.6)	0.650
IPI, median (IQR)	0.15 (0.21)	0.53 (0.95)	<0.001
Reoperation, n (%)	4 (1.6)	4 (4.2)	0.224
ICU stay, day, median	2.5 (1.0)	4.0 (2.0)	<0.001
Hospital stay, day, median	7.0 (1.0)	9.0 (3.0)	<0.001
Mortality, n (%)	7 (2.8)	7 (7.4)	0.05
Re-intubation, n (%)	18 (7.3)	14 (14.7)	0.03
Low cardiac output, n (%), n (%)	9 (3.6)	12 (12.6)	0.002
Stroke, n (%)	4 (1.6)	3 (3.2)	0.401
Infection, n (%)	11 (4.4)	14 (14.7)	0.001

Bold p-values indicate statistical significance. The p-values indicated in italics are values close to statistical significance. Alb: albumin; ALT: alanine transaminase; AST: aspartate aminotransferase; BMI: body mass index; CABG: coronary artery bypass grafting; COPD: chronic obstructive lung disease; CPD: cardiopulmonary bypass; CRP: C-reactive protein; DM: diabetes mellitus; EF: ejection fraction; GFR: glomerular filtration rate; Hb: hemoglobin; HT: hypertension; ICU: intensive care unit; IPI: inflammatory prognostic index; IQR: interquartile range; MPV: mean platelet volume; n: number; NLR: neutrophil lymphocyte ratio; PCT: plateletcrit; PDW: platelet distribution width; Plt: platelet; PLR: platelet lymphocyte ratio; RDW-SD: red blood cell erythrocyte distribution width; WBC: white blood cell.

Table 2. Investigation of independent risk factors affecting the development of atrial fibrillation by multivariate analysis*.

Variable	Odds ratio	95%CI	p-value
Age (for each year)	1.132	1.085–1.184	<0.001
HT presence	2.089	1.138–3.834	0.01
COPD presence	1.427	0.521–3.515	0.489
Left atrium size (for each unit)	2.636	0.714–9.733	0.146
Hb (for each unit)	1.055	0.885–1.259	0.550
Urea (for each unit)	0.996	0.983–1.010	0.419
GFR (for each unit)	1.001	0.983–1.020	0.877
AST (for each unit)	0.998	0.981–1.016	0.865
IPI (for each unit)	10.880	4.810–24.610	<0.001

*In univariate analysis, only a single variable was included in the multivariate analysis when there were confounders (e.g., albumin, CRP, NLR and their IPI, or neutrophils, and lymphocytes and their NLR) that were found to statistically affect the development of AF. Bold p-values indicate statistical significance. AST: aspartate aminotransferase; CI: confidence interval; COPD: chronic obstructive; GFR: glomerular filtration rate; Hb: hemoglobin; HT: hypertension; IPI: inflammatory prognostic index.

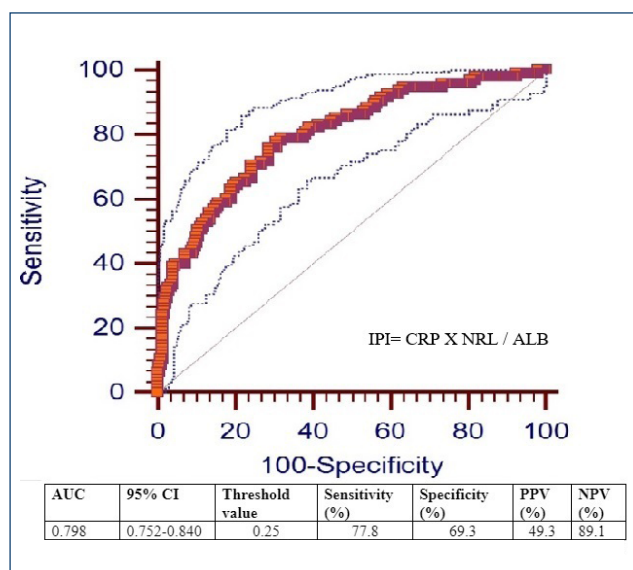


Figure 1. Receiver operating characteristic curve for inflammatory prognostic index. AUC: area under the curve; CI: confidence interval; IPI: inflammatory prognostic index; NPV: negative predictive value; PPV: positive predictive value.

DISCUSSION

Our study revealed that the patients in the group developing POAF were statistically significantly older than the other group, and the number of patients with HT and COPD was higher. Considering the hematological and biochemical parameters, hemoglobin, lymphocyte, GFR, ALT and albumin values were found to be lower in the POAF group compared to the other group. In addition, the left atrial size, neutrophil, NLR, PLR, CRP, urea, and IPI values were found to be statistically significantly higher in the group with POAF compared to the other

group. Age, HT, and IPI values were found to be statistically significant in multivariate analysis. In our study, it was determined that each unit increase in IPI increased the probability of AF 10.8 times, age 1.1 times, and HT 2.08 times. It was concluded that these parameters independently predicted POAF after CABG. The most valuable finding in our study was that, for the first time in the available literature, IPI independently predicted POAF after CABG.

The exact mechanisms of AF after CABG are still unclear. There are studies reporting that systemic inflammation is associated with the occurrence and recurrence of AF in patients undergoing CABG surgery¹¹⁻¹³. POAF occurs most frequently 2–4 days after surgery, and it is estimated that 96% of cases occur within the first 1 week after surgery¹⁴.

A systematic review and meta-analysis, including 6,098 patients and 22 studies, was conducted to evaluate the relationship between POAF developing after CABG and hematological indices. In this study, it was shown that platelet count, mean platelet volume (MPV), WBC, NLR, and red blood cell distribution width can predict the risk of POAF¹⁵. In the univariate analysis of our study, in addition to this meta-analysis, we determined that the amounts of neutrophils, lymphocytes, hemoglobin, and PLR would be the predictive hematological index for POAF.

In the prediction of patients at risk of POAF, some clinical scoring methods (CHA2DS2-VASc Score, HATCH Score, etc.) can be used in addition to inflammation and immune-based prognostic scoring methods (systemic immune inflammatory index, etc.)¹⁶⁻¹⁸.

In some studies in the literature, inflammation and immune-based effects of hematological parameters such as CRP, NLR,

and PLR have been shown to predict mortality and morbidity after cardiac surgery^{3,11,13}. In addition, a meta-analysis examining 42 studies evaluating its association with POAF following CABG showed that perioperative inflammation is involved in the pathogenesis of POAF³. In these studies, it was concluded that the perioperative evaluation of inflammatory markers, especially CRP, would help clinicians in predicting and monitoring POAF. In a study focusing on new-onset POAF after CABG, it was shown that low preoperative albumin levels are a risk factor for the development of POAF¹⁹. In our study, we showed that IPI composed of CRP, NRL, and albumin predicted POAF more strongly in patients undergoing elective isolated CABG operations.

IPI has clinical importance in predicting prognosis and is a new inflammatory prognostic marker based on CRP, NRL, and serum albumin. IPI was developed for the first time from hematological and biochemical parameters by Dirican et al. to determine the prognosis of patients with non-small cell lung cancer⁸. IPI is a noninvasive, inexpensive, accessible, and easily formulated parameter to determine prognosis. It has been used as an important new marker to determine survival in many studies on oncological patients⁸⁻¹¹. To the best of our knowledge, there is no published study investigating the relationship between IPI and POAF. We found in our study that IPI predicted POAF and survival in patients who underwent CABG for the first time in the literature. We demonstrated that the cutoff value of IPI was 2.5 in patients who developed POAF after CABG. It estimated incipient POAF with a sensitivity of 77.8% and a specificity of 69.3%.

There are many studies showing that it is associated with POAF developing after CABG, hemodynamic instability, prolonged hospital stay, increased risk of stroke, and increased mortality²⁰⁻²². In our study, it was concluded that, similar to the literature, it increased reintubation rates, development of

low cardiac output syndrome, rates of surgery-related infection, and length of stay in the ICU and hospital. Therefore, identifying patients with a high risk of POAF is considered critical for taking the necessary precautions in the preoperative period.

Our study had a few limitations. The most important limitations of our study were that it was single-center and retrospective. Another important limitation is the relatively small number of patients and the limited number of parameters examined. In addition, the lack of correlation analysis with other predictive markers of inflammatory response is an important limiting factor.

Studies on indices derived from hematological parameters in the literature have gained importance recently^{3,11,13,15,23,24}.

CONCLUSION

Our study revealed that age, HT, and IPI are independent predictive risk factors for POAF developing after elective isolated CABG. The most valuable finding in our study was that, for the first time in the available literature, IPI independently predicted POAF after CABG. To the best of our knowledge, there is no published study investigating the relationship between IPI and POAF. To support our study's findings and provide more precise scientific data, better structured trials with higher patient participation are required.

AUTHORS' CONTRIBUTIONS

SB: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **AP:** Conceptualization, Data curation, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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