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Preoperative Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio for prediction of major complications following Coronary Artery Bypass Grafting

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Original Article

Abstract

INTRODUCTION: The Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) have recently been reported as potentially useful indicators of inflammation. In this study, the authors investigated their predictive role for postoperative complications of Coronary Artery Bypass Graft (CABG).

METHOD: This study was conducted on the medical records of patients who had undergone isolated CABG in 2019-2020 in Isfahan, Iran. The baseline clinical characteristics were obtained from medical records. The diagnosis of postoperative Acute Kidney Injury (AKI) was defined based on the Kidney Disease Improving Global Outcomes guideline. The postoperative bleeding amount was measured from the total chest tube output during the Intensive Care Unit (ICU) admission after surgery. NLR and PLR were measured by dividing the neutrophil and platelet counts by the lymphocyte count, respectively. All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 24.

RESULTS: Of 356 patients, data of 280 patients, including 219 males and 61 females, were recruited. The mean age among all patients was 63.78±9.07 years. There were no significant differences between the bleeding group and non-bleeding group regarding NLR (2.33(1.89-2.73) vs. 2.20(1.63-3)) and PLR (119.26(94.41-146.39) vs. 110.26(82.13-136.34)) (p=0.742, p=0.228 respectively). NLR and PLR were significantly higher in AKI-positive patients (P< 0.001 and P=0.002, respectively). Only NLR showed the potential ability to predict postoperative AKI in the crude model (P<0.001) based on the regression tests. Moreover, no significant correlation was seen between both NLR and PLR and hospital stay time, ICU stay time, and in-hospital mortality.

CONCLUSION: The authors found that an increased NLR is associated with a higher risk for AKI after CABG. The authors also found no significant correlations between NLR and PLR with bleeding, hospital stay, ICU stay, and mortality.

Keywords: Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio, Coronary Artery Bypass Graft, NLR, PLR, CABG

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Introduction

Coronary Artery Bypass Graft (CABG) is a significant surgical revascularization procedure that can elicit a systemic inflammatory response by initiating the release of certain mediators contributing to the inflammation process [1]. These mediators trigger a cascade of events

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that promote inflammation due to the release of other mediators from platelets and White Blood Cells (WBC), such as neutrophils and lymphocytes [2]. Therefore, patients undergoing this procedure are potentially predisposed to major organ-related complications postoperatively. Acute Kidney Injury (AKI) is one of the frequent complications after CABG, which increases morbidity and mortality and leads to prolonged hospital stay and the need for intensive care. The incidence of AKI following cardiac surgery has been reported to be approximately 5-42%, of which 1-2% might require renal replacement therapy [3, 4]. Thus, predicting such a critical complication and making appropriate efforts regarding prevention and early treatment seem necessary. Bleeding is another significant complication of cardiac surgery, which requires blood transfusion and is associated with a high mortality rate [5, 6]. During Cardiopulmonary Bypass (CPB), there is a substantial stress on the coagulation system, resulting in coagulation factor depletion, fibrinolysis, and platelet dysfunction [7].

The Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) have recently been reported as clinically useful indicators associated with inflammation and stress, which are predisposing factors for major postoperative complications such as AKI and bleeding [8, 9]. Therefore, they might be potentially useful as predictors to identify patients more susceptible to these medical conditions in advance.

Considering the dearth of literature regarding the performance of these inflammation indicators in the cardiac surgery field, this study aimed to investigate the predictive role of preoperative NLR and PLR for the common postoperative complications of CABG, including AKI, bleeding, length of hospital and ICU stay, and in-hospital mortality.

Materials and Methods

This retrospective cross-sectional study was conducted in 2021 on the medical records of 356 patients who had consecutively undergone isolated CABG by the same surgical team between January 2019 and December 2020 at Milad Hospital, Isfahan, Iran. The study protocol complied with the Declaration of Helsinki, and full approval was granted by the Research and Ethics Committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1399.967).

The inclusion criteria were undergoing elective isolated CABG with no history of previous sternotomy. The exclusion criteria included having an implantable cardioverter defibrillator; patients previously diagnosed with thyroid malfunction, impaired renal function (serum creatinine more than 1.5), systemic inflammatory diseases, and the use of steroids and chemotherapeutic agents before surgery. Patients whose medical records had missing data needed for this study were also excluded.

The demographic and baseline clinical characteristics were obtained by investigating the patients' medical records. Age; Body Mass Index (BMI); gender; history of hypertension and diabetes mellitus; history of smoking and consumption of alcohol and opioids; previous medications, such as aspirin and statins; preoperative Left Ventricular Ejection Fraction (LVEF); pre and postoperative laboratory results, such as WBC, lymphocyte and neutrophil and platelet counts, hemoglobin levels, and creatinine; operation information including the number of grafts, CPB time, aortic cross-clamping time; hospital and ICU length of stay, and in-hospital death were recorded from patients' records.

The diagnosis of postoperative AKI was defined as an increased serum creatinine level 1.5 times the baseline serum creatinine concentration within the previous seven days or more than 0.3 within 48 hours after the operation according to the Kidney Disease Improving Global Outcomes guideline [10].

The postoperative bleeding amount was measured from the total chest tube output during the ICU admission after surgery. Based on the needed amount of blood transfusion, patients were categorized as bleeders (who needed more than four units of pack cells) and non-bleeders (who needed less than four units of pack cells).

Moreover, preoperative NLR and PLR were measured by dividing the neutrophil count and platelet count by the lymphocyte count, respectively.

Statistical Analysis

Data for normally and non-normally distributed continuous variables are expressed as mean ± SD and median (IQR), respectively. Categorical variables are presented as n (%). The normality of distribution in numerical variables was assessed by the Kolmogorov-Smirnov test. The Independent t-test or Mann-Whitney U test were used for comparison of continuous variables between subgroups of patients. To compare the categorical variables between subgroups, the chi-square test was used. The predictive value of NLR and PLR was assessed using separate univariate binary logistic regression tests. In addition, a multiple logistic regression test was used to adjust the effect of possible confounders, including age, sex, diabetes, hypertension, CPB time, preoperative LVEF, hospital stay, and ICU stay. Moreover, Receiver Operating Characteristic (ROC) analysis and Youden index were used to determine the sensitivity, specificity, and cut-off point of predictive biomarkers. All data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows (version 24.0; SPSS Inc., Chicago, IL, USA).

Results

Out of 356 patients, data from 280 patients (76 patients were excluded due to missing data in their medical records), including 219 males and 61 females, were analyzed after applying the exclusion criteria. The mean age among all patients was 63.78±9.07 years.

Patients were divided into two groups based on the amount of bleeding after the operation. Baseline demographic and clinical characteristics of patients are shown and compared between the two groups in Tables 1 and 2. Based on our data, the ICU stay was significantly higher in the bleeding group (median=68, IQR [54.75-85]) compared to the non-bleeding group (median=49, IQR [46-70]) (P=0.026). However, there was no significant difference between the bleeding and non-bleeding groups regarding age (p=0.331), sex (p=0.906), hospital length of stay (p=0.305), postoperative AKI (p=0.794), and in-hospital mortality (p=0.189).

Furthermore, there were no significant differences between the two groups regarding NLR (2.33(1.89-2.73) vs. 2.20(1.63-3)) and Platelet to Lymphocyte Ratio (PLR) (119.26(94.41-146.39) vs. 110.26(82.13-136.34)) (p=0.742, p=0.228 respectively).

Table 1. Comparison of qualitative variables between bleeding and non-bleeding groups

Variables		Bleeders [N (%)] N=24	Non-bleeders [N (%)] N=256	P-Value
Sex	Male	19(79.2)	200(78.1)	0.906
	Female	5(20.8)	56(21.9)	
Diabetes Mellitus		16(66.7)	122(47.7)	0.075
Hypertension		19(79.2)	159(62.1)	0.097
Hyperlipidemia		17(70.8)	143(55.9)	0.156
Smoking		7(29.2)	74(28.9)	0.979
Alcohol consumption		0(0)	14(5.5)	0.618
Opium use		4(16.7)	37(14.5)	0.763
Postoperative AKI[1]		9(37.5)	103(40.2)	0.794
In-hospital mortality		2(8.3)	8(3.1)	0.189

[1] Acute Kidney Injury

*Statistical analysis: Chi-squared test was done for all categorical variables

Table 2. Comparison of quantitative variables between bleeding and non-bleeding groups

Variables	Bleeders [Mean ± SD] [Median(IQR)] N=24	Non-bleeders [Mean ± SD] [Median(IQR)] N=256	P Value
Age	65.58 ± 8.67	63.71 ± 9.10	0.334
BMI[1]	25.58(23.05-27.81)	26.50(24.07-29.06)	0.203
Preoperative EF[2]	55(37.5-60)	55(45-60)	0.376
Aortic clamp time (minutes)	54(43-67)	49.5(42.25-55.75)	0.130
CPB[3] time (minutes)	95.50(76-108)	87(75-98)	0.750
ICU[4] stay (hours)	68(54.75-85)	49(46-70)	0.026
Hospital stay (days)	8(7-9)	7(7-8)	0.305
Bleeding amount (cc)	1075(575-1962.5)	650(450-950)	0.002
NLR[5]	2.33(1.89-2.73)	2.20(1.63-3)	0.742
PLR[6]	119.26(94.41-146.39)	110.26(82.13-136.34)	0.228

[1] Body Mass Index, 2- Ejection Fraction, 3- Cardiopulmonary Bypass, 4- Intensive Care Unit, 5-Neutrophil to Lymphocyte Ratio, 6- Platelet to Lymphocyte Ratio
*Statistical analysis: independent t test (for normally distributed variables) and Mann-Whitney U test (for variables without normal distribution).

The authors also divided the patients into two groups based on AKI incidence after the operation and compared these variables between AKI positive and AKI negative patients. Based on the results, patients with AKI had a lower prevalence of diabetes mellitus (P= 0.013) and a higher prevalence of hypertension (P= 0.013) (Table 3).

Table 3. Comparison of qualitative variables between patients with or without AKI after CABG

Variables		AKI positive [N (%)] N=112	AKI negative [N (%)] N=168	P Value
Sex	Male	97(86.6)	122(72.6)	<0.001
	Female	15(13.4)	46(27.4)	
Diabetes Mellitus		45(40.2)	93(55.4)	0.013
Hypertension		81(72.3)	97(57.7)	0.013
Hyperlipidemia		58(51.8)	102(60.7)	0.139
Smoking		34(30.4)	47(28)	0.667
Alcohol consumption		4(3.6)	10(6)	0.370
Opium use		15(13.4)	26(15.5)	0.629
In-hospital mortality		4(3.6)	6(3.6)	>0.99

*Statistical analysis: Chi-squared test was done for all categorical variables

Lower pre-operative Ejection Fraction (EF) (P= 0.016), higher Cardiopulmonary Bypass (CPB) time (P= 0.004), longer ICU stay (P< 0.001), longer hospitalization duration (P< 0.001), and age (P= 0.018) are significantly different between the two groups. NLR and PLR were significantly higher in AKI-positive patients compared to AKI-negative patients (P< 0.001 and P=0.002, respectively) (Table 4).

Table 4. Comparison of quantitative variables between patients with or without AKI after CABG

Variables	AKI positive [Mean ± SD] [Median(IQR)] N=112	AKI negative [Mean ± SD] [Median(IQR)] N=168	P Value
Age	65.53 ± 10.32	62.77 ± 7.96	0.018
BMI[1]	26.89(24.71-29.30)	25.95(23.87-29.00)	0.146
Pre-operative EF[2]	55(40-60)	55.5(50-60)	0.016
Aortic cross clamp time (minutes)	50(45-57.75)	48.5(42-55)	0.152
CPB[3] time (minutes)	91(76-104.50)	82.5(74-96.75)	0.004
ICU[4] stay (hours)	63.5(48-85)	48(44-69)	<0.001
Hospital stay (days)	8(7-9)	7(6-8)	<0.001
Bleeding	725(462.5-1100)	650(450-950)	0.207
NLR[5]	2.77(1.96-3.87)	1.97(1.51-2.50)	<0.001
PLR[6]	125.22(92.04-148.22)	101.80(80.78-130.05)	0.002

[1] Body Mass Index, 2- Ejection Fraction, 3- Cardiopulmonary Bypass, 4- Intensive Care Unit, 5-Neutrophil to Lymphocyte Ratio, 6- Platelet to Lymphocyte Ratio
*Statistical analysis: independent t test (for normally distributed variables) and Mann-Whitney U test (for variables without normal distribution)

Based on the separate binary logistic regression tests for NLR and PLR, only NLR showed the potential ability to predict postoperative AKI in both crude and adjusted models. PLR showed a slightly protective predictive ability for AKI after adjustment for possible confounding variables; however, the results cannot be interpreted and comprehended clinically. These findings are indicated in Table 5.

Table 5. Assessments of predictive ability of NLR1 and PLR2 for postoperative acute kidney injury

Variable	Crude model		Model 1		Model 2	
	OR(95%CI)	P-value	OR(95%CI)	P-value	OR(95%CI)	P-value
NLR[1]>2.48	1.596(1.301-1.959)	<0.001	1.568(1.275-1.930)	<0.001	1.860(1.395-2.479)	<0.001
PLR[2]>124.33	1.002(0.999-1.005)	0.311	1.002(0.998-1.005)	0.319	0.994(0.989-0.998)	0.006

1 Neutrophil to Lymphocyte Ratio,
2 Platelet to Lymphocyte Ratio,
Model 1: Adjusted for age and sex
Model 2: further adjusted for diabetes, hypertension, Cardiopulmonary Bypass time, preoperative Ejection Fraction, hospital stay and Intensive Care Unit stay.
Statistical analysis: Univariate logistic regression tests were done for the crude model. Multiple logistic regression test was used for the adjusting the possible confounders.

In addition, according to the (ROC) analysis, 2.48 and 124.33 were determined as the optimal cut-off points of NLR and PLR in predicting post-CABG AKI, respectively. Moreover, the analysis results indicate that an NLR of more than 2.48 predicts the post-CABG AKI with a sensitivity and specificity of 58.04% and 75%, respectively (area under the ROC curve: 0.714) (Figure 1).

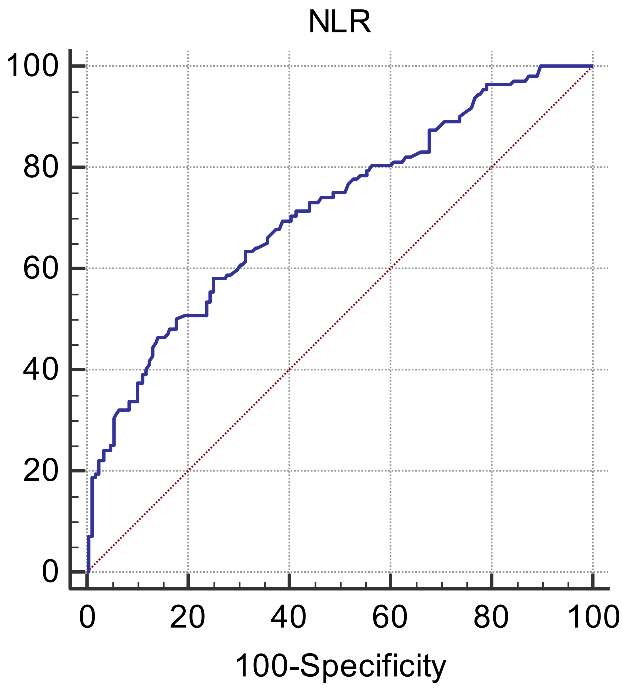

Figure 1. ROC curve analysis for NLR
Area under the ROC curve (AUC) = 2.48

Discussion

So far, various predictive and preventive strategies have been investigated to decrease the main complications after CABG, such as AKI, bleeding, and mortality, but more efforts are required in this regard. In the present study, the authors evaluated the predictive value of NLR and PLR for preoperative, perioperative, and postoperative complications in 280 patients. The findings showed no significant difference between the bleeding and non-bleeding groups regarding NLR and PLR. However, patients who experienced AKI after the operation had significantly higher NLR and PLR. Only preoperative NLR showed the predictive ability for postoperative AKI. The authors also showed that the Cardiopulmonary Bypass (CPB) time, hospital, and ICU length of stay were longer in patients with AKI compared to non-AKI patients.

The mentioned data emphasized the predictive role of inflammatory indices such as NLR and PLR for the complications in patients undergoing CABG, similar to the previous works in the literature. In 2018, a study was performed by Parlar and colleagues on 311 candidates of CABG. They assessed the relation of NLR and PLR with various CABG complications. Based on this study, increased NLR and PLR were directly related to AKI development in the early postoperative period [11]. Seropian et al. [12] also assessed the use of NLR and PLR as predictors of survival after heart transplantation surgery. After assessing 111 patients, they showed that increased NLR and PLR could predict the need for postoperative renal replacement therapy due to AKI; however, only high NLR (OR= 3.4) was correlated with a one-year mortality rate.

Another study in 2020 by Dey and colleagues showed that increased NLR and PLR could be useful in predicting some complications, including AKI, atrial fibrillation, and intra-aortic balloon pump requirement after CABG [13]. The authors' findings were in line with the results of these studies, showing the importance of NLR and PLR in predicting complications of CABG.

The present study demonstrated that the NLR could be useful in predicting AKI after CABG. The Platelet to Lymphocyte Ratio (PLR) was significantly higher in AKI-positive patients, but it did not predict AKI in our patients. It appears that by using these ratios, physicians could take appropriate therapeutic measures to protect high-risk patients from these dangerous complications. Recent studies have also shown that in cardiac and other major surgeries, increased NLR and decreased platelet levels are associated with early postoperative AKI and mortality [2, 14]. The authors also showed an increased risk (OR=1.59) of AKI in patients with higher NLR. In 2020, Parlar and colleagues assessed the use of NLR and PLR in predicting AKI after CABG. It was shown that increased postoperative NLR and PLR were associated with an increased risk of AKI (OR= 1.14, OR= 1.01 respectively) [15]. However, they mentioned that further research should be performed in this regard. These data are also consistent with the findings of our study, but here the authors aimed to assess the relation between NLR and PLR with other CABG complications as well. In addition, based on our results, the predictive value of PLR for AKI was not significant.

Some evidence has also claimed that combining NLR and PLR with other blood parameters could increase their predictive power, resulting in a better postoperative prognosis for patients undergoing CABG. It has also been declared that increased NLR and PLR could contribute to the atherosclerosis process, another explanation for worse outcomes in these patients [16, 17].

Although the authors' findings suggest that NLR could be used in predicting AKI following CABG, they believe that more studies on larger populations should be conducted in the future.

Conclusion

Taken together, the authors indicated that patients with AKI after CABG have higher NLR and PLR, and increased NLR is associated with a higher risk for AKI after CABG. The authors also found no significant correlations between NLR and PLR with bleeding or other complications. These results were in line with the findings of previous studies.

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