

# Association between Neutrophil-to-Lymphocyte Ratio and the Systemic Inflammatory Immunologic Index and the Angiographic SYNTAX Score and the TIMI Flow Grade in Acute STEMI: A Cohort Study

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## Abstract

**Background:** In patients with ST-segment-elevation myocardial infarction (STEMI), it is essential to determine the complexity of coronary lesions on presentation and predict the risk of no-reflow after primary percutaneous coronary intervention (pPCI). Given that inflammation plays an important role in the pathogenesis of atherosclerosis, using inflammatory indices might be helpful in this setting.

**Methods:** This prospective cohort study recruited 200 consecutive patients with STEMI who underwent pPCI. The presentation neutrophil-to-lymphocyte-ratio (NLR) and the systemic inflammatory immunologic index (SII), calculated using the formula platelets  $\times$  neutrophils/lymphocytes, were recorded. Study outcomes included the SYNTAX score and the TIMI flow grade before and after pPCI. The associations between the NLR and the SII and the study outcomes were investigated using univariate and multivariate logistic regression analyses.

**Results:** Among 200 patients at a mean age of  $59.85 \pm 11.23$  years, 160 (80.0%) were male and 40 (20.0%) were female. The NLR and SII values were not statistically different between the 3 SYNTAX subgroups. While the mean NLR and SII values were similar between the patients with preprocedural TIMI flow grades 0/1 and 2/3, the mean NLR and SII were significantly lower in the group with a postprocedural TIMI flow grade 3. After adjustments for age and sex, the NLR and the SII were independent predictors of postprocedural no-reflow.

**Conclusion:** In patients with STEMI, the presentation NLR and SII are useful for predicting the risk of no-reflow after pPCI. However, the NLR and the SII are not predictors of the SYNTAX score and the preprocedural TIMI flow grade.

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**Keywords:** Myocardial infarction, No-reflow phenomenon, Coronary artery disease, Percutaneous coronary intervention, Neutrophils, Lymphocytes, Blood platelets

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## Introduction

Primary percutaneous coronary intervention (PCI) is the standard therapeutic method for the management of patients with ST-segment-elevation myocardial infarction (STEMI).<sup>1</sup> Nonetheless, no-reflow in the infarct-related artery (IRA) may compromise the results and lead to adverse complications and mortality.<sup>2</sup> Preprocedural factors, including preprocedural IRA patency and coronary lesion complexity, may be predictive of the outcomes in patients.<sup>3</sup> The SYNTAX score is a scoring system by which the complexity of patients' coronary lesions and possible responses to angiographic interventions are evaluated.<sup>4-6</sup> The determination of preprocedural IRA patency and SYNTAX score needs coronary artery angiography, hence the significance of finding prognostic factors that are readily available on patient presentation.

The pathophysiological mechanisms of the development and underlying causes of atherosclerosis for the occurrence of an acute episode of MI, including STEMI, involve complex pathways of systemic and local inflammatory, immunologic, and thrombotic systems. Consequently, there is increasing interest in incorporating factors of these pathways into risk stratification models of patients with a diverse range of cardiovascular diseases.<sup>7, 8</sup> Some investigations have assessed the predictive role of these inflammatory markers for the complexity of coronary lesions, IRA patency before primary PCI, and the no-reflow rate after primary PCI in IRA. Nevertheless, studies exclusively conducted on patients with STEMI have demonstrated varying results for each inflammatory component.<sup>9-12</sup> On the other hand, there is also a newly investigated index, termed "the systemic inflammatory immunologic index (SII)", which has been used in patients with various neoplastic diseases. This index combines the 3 main circulating blood components: neutrophils, lymphocytes, and platelets.<sup>13-17</sup> Still, the role of the SII in patients with cardiovascular diseases has yet to be elucidated.<sup>18</sup>

Accordingly, we designed this prospectively recruited cohort study on patients with STEMI treated with primary PCI to investigate the association between the presentation neutrophil-to-lymphocyte ratio (NLR) and the SII and our study outcomes, consisting of the SYNTAX score<sup>5, 19</sup> and preprocedural and postprocedural thrombolysis in myocardial infarction (TIMI) flow grades.<sup>20</sup>

## Methods

This prospective observational cohort study recruited 200 consecutive patients with a diagnosis of STEMI who underwent primary PCI in the first 6 hours of symptom onset in our cardiovascular hospital. Patients with a history of cancer, hepatic cirrhosis, autoimmune diseases, hematologic

disorders, and recent infectious diseases were excluded. Pregnant patients, patients with severe valvular diseases, and patients who had received thrombolytic or glycoprotein IIb/IIIa inhibitors were also excluded from this study. The institutional ethics and research committee reviewed and approved the study protocol. The descriptive nature of the study precluded the necessity of obtaining informed consent; however, complete patient privacy was protected in all steps of the study. All the procedures performed were in accordance with the Helsinki Declaration of 1975, as revised in 2013.

A trained physician recorded the patients' demographics, past medical history, laboratory data, and angiographic findings in prepared questionnaires. A different trained interventional cardiologist reviewed the digital angiographic recording.

Venous blood samples were collected via standard venipuncture procedures on patient admission to the emergency department. Blood samples were collected in tubes containing potassium ethylenediaminetetraacetic acid (EDTA) as an anticoagulant and were analyzed by the central laboratory of the hospital with an automated and daily-calibrated Coulter CBCH1 counter. The total white blood cell (WBC), neutrophil, lymphocyte, and platelet counts and hemoglobin levels were documented from laboratory reports. The NLR was calculated as the absolute neutrophil count per mm<sup>3</sup> of blood divided by the absolute lymphocyte count per mm<sup>3</sup> of blood. The platelet-to-lymphocyte ratio (PLR) was determined as the platelet count per mm<sup>3</sup> divided by the lymphocyte count per mm<sup>3</sup>. The SII was calculated from peripheral platelet ( $\times 10^9/L$ ), neutrophil ( $\times 10^9/L$ ), and lymphocyte ( $\times 10^9/L$ ) blood counts by using the formula  $SII = \text{platelets} \times \text{neutrophils} / \text{lymphocytes}$ .<sup>14</sup>

Primary PCI was performed via the standard femoral approach with a 7F guiding catheter. With the aid of the digital records of angiographic procedures for each patient, the SYNTAX score and the TIMI flow grade<sup>20</sup> before and after primary PCI were evaluated by an experienced interventional cardiologist, who was blind to the clinical and laboratory findings of the patients. Preprocedural IRA patency was defined as a TIMI flow grade 2 or 3 (TIMI-2/3). Postprocedural no-reflow was defined as a TIMI flow grade of 0 or 1 or 2 (TIMI-0/1/2). The Syntax score<sup>5</sup> was calculated by using the standard SYNTAX scoring algorithm by the same interventional cardiologist. The patients were classified into 3 groups based on the SYNTAX score: the low SYNTAX score group ( $\leq 22$ ), the intermediate SYNTAX score group (23–32), and the high SYNTAX score group ( $> 32$ ).<sup>19</sup>

The data were analyzed by IBM SPSS Statistics for Windows, version 22.0. Categorical variables were stated as frequencies and percentages and compared by using the  $\chi^2$  or the Fisher test as appropriate. Continuous variables were stated as the mean  $\pm$  the standard deviation or the



median 25% to 75% interquartile range (IQR<sub>25-75%</sub>). The Kolmogorov–Smirnov test was used to determine normal distribution. Continuous variables with a normal distribution were compared between the groups by using the independent *t* test or the ANOVA test, and continuous variables without a normal distribution were compared by using the Mann–Whitney test or the Kruskal–Wallis test as appropriate. Receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC), as well as the cutoff values, was calculated. Based on the cutoff points, the patients were divided into 2 groups and compared. Logistic regression analysis was employed to assess the independent role of the study variables on the study outcomes. Two-tailed significance tests were reported, and a *P* value of less than 0.05 was considered statistically significant.

## Results

The study population consisted of 200 patients, including 160 men (80.0%), at a mean of 59.85±11.23 years. The mean SYNTAX score was 18.71±8.66. Regarding the distribution of the SYNTAX score subgroups, low, intermediate, and high SYNTAX scores were present in 63.0%, 31.0%, and 6.0% of the study patients, respectively. Preprocedural TIMI-2/3 was reported in 43 patients (21.5%) and postprocedural TIMI-0/1/2 in 34 patients (17.0%). The mean NLR was 4.65±3.62, and the median (IQR<sub>25-75%</sub>) NLR was 3.62 (2.0–5.67). The mean PLR was 125.10±81.66, and the median (IQR<sub>25-75%</sub>) PLR was 107.70 (75.37–153.04). The mean SII was 1022.96±921.51, and the median (IQR<sub>25-75%</sub>) SII was 776.60 (458.87–1267.33).

Table 1 presents the comparisons of baseline characteristics and angiographic and hematological findings between the 3 SYNTAX subgroups. Demographic information and cardiovascular risk factors were similar in the 3 subgroups. The left ventricular ejection fraction was significantly different in the 3 subgroups (38.97±7.08% vs 35.89±7.87% vs 35.00%±5.64% in the low-, intermediate-, and high-risk subgroups, respectively; *P*=0.010).

Patients in the higher-risk SYNTAX score group were more likely to experience anterior MI than inferior MI (51.6% vs 69.4% vs 75.0% in the low, intermediate, and high-risk subgroups, respectively; *P*=0.033). The mean WBC count was significantly different between the 3 subgroups. The post hoc analysis revealed significant differences in the WBC count between the high-risk and moderate-risk groups, as well as the high-risk and low-risk groups. The neutrophil count and the platelet count were also significantly different between the 3 SYNTAX subgroups (Table 1). The post hoc analysis also demonstrated that the difference in the platelet count was significant between the high-risk and low-risk SYNTAX subgroups. The post hoc analysis on the neutrophil count showed a significant difference between the

high-risk and moderate-risk SYNTAX subgroups, as well as the high-risk and low-risk SYNTAX groups. The NLR, PLR, and SII values were not statistically different between the 3 SYNTAX risk subgroups (Table 1).

As is presented in Table 2, there were no differences between the patients with a preprocedural TIMI-0/1 and those with a preprocedural TIMI-2/3 regarding the baseline characteristics, cardiovascular risk factors, angiographic findings, and hematological values. The median (IQR<sub>25-75%</sub>) NLR was 3.81 (2.00–5.63) in the group with a preprocedural TIMI-0/1 and 3.33 (2.11–5.71) in the group with a preprocedural TIMI-2/3 (*P*=0.892). The median PLR (IQR<sub>25-75%</sub>) was 99.67 (73.72–162.18) in the preprocedural TIMI-0/1 group and 113.72 (77.40–137.16) in the preprocedural TIMI-2/3 group (*P*=0.421). The median SII (IQR<sub>25-75%</sub>) was 805.0 (424.67–1280.00) in the preprocedural TIMI-0/1 group and 680.0 (483.24–1096.67) in the preprocedural TIMI-2/3 group (*P*=0.754).

As is presented in Table 2, demographic information, cardiovascular risk factors, and angiographic findings were not significantly different between the patients with postprocedural TIMI-0/1/2 and those with the complete postprocedural flow. However, the WBC count, the neutrophil count, the NLR, and the SII were all significantly higher in the group with a postprocedural TIMI-0/1/2. The median (IQR<sub>25-75%</sub>) NLR was 4.72 (2.33–8.50) in the group with a postprocedural TIMI-0/1/2 and 3.50 (2.00–5.33) in the group with the complete postprocedural flow (*P*=0.036). The median (IQR<sub>25-75%</sub>) SII was 973.95 (617.03–1608.70) in the group with a postprocedural TIMI-0/1/2 and 697.25 (408.25–1216.0) in the group with the complete postprocedural flow (*P*=0.010).

The ROC curve of the SII for the prediction of postprocedural no-reflow (TIMI-0/1/2) is depicted in Figure 1. The ROC analysis revealed a cutoff point of 458.87 for the SII with an AUC of 0.640 (95% confidence interval (CI), 0.54–0.74; *P*=0.010). An SII of greater than 458.87 had 94.12% sensitivity and 28.92% specificity in predicting the development of no-reflow after primary PCI.

Figure 2 illustrates the ROC curve of the NLR for the prediction of postprocedural no-reflow. The ROC analysis revealed a cutoff point of 7.08 for the NLR with an AUC of 0.615 (95% CI: 0.51–0.72; *P*=0.035). An NLR of greater than 7.08 had 41.18% sensitivity and 85.54% specificity in predicting the development of no-reflow after primary PCI.

Table 3 presents the comparisons of the study variables between the low and high NLR groups, as well as low and high SII groups. The prevalence of a postprocedural TIMI-0/1/2 was significantly higher than that of a postprocedural TIMI-3 in the high NLR group (12.6% vs 34.1%; odds ratio [OR], 3.60; 95% CI: 1.62 to 8.00; *P*=0.002). The analysis was repeated after adjustments for age and sex, which were previously reported as influential factors for the NLR in a healthy population. The results of the

multivariate regression analysis revealed the independent role of the NLR in predicting postprocedural no-reflow (OR, 3.47; 95% CI: 1.55–7.76; P=0.002). The prevalence of a postprocedural TIMI-0/1/2 was significantly higher than that of a postprocedural TIMI-3 in the high SII group (4.0% vs 21.3%; OR, 6.51; 95% CI: 1.50–28.23; P=0.012). The results of the multivariate regression analysis after adjustments for age and sex revealed the independent role of the SII in predicting postprocedural no-reflow (OR, 6.02; 95% CI: 1.37–26.41; P=0.017).

## Discussion

According to the results of our study, in patients with STEMI who underwent primary PCI, the presentation NLR and the presentation SII were both independently associated with the postprocedural TIMI flow. While the SII had a higher sensitivity for determining the postprocedural no-reflow, the NLR had a higher specificity for predicting no-reflow after primary PCI. In addition, the NLR and the SII were not linked with the SYNTAX score or the preprocedural TIMI flow.

Table 1. Comparison of the study variables according to the subgroups of the SYNTAX score\*

	SYNTAX Score Subgroups			P
	Low	Moderate	High	
Age (y)	58.46±10.90	61.98±10.91	63.50±14.59	0.066
Sex (male)	101 (80.2)	49 (79.0)	10 (83.3)	
Diabetes	19 (15.1)	14 (22.6)	4 (33.3)	0.181
Hypertension	51 (40.5)	25 (40.3)	6 (50.0)	0.807
Hyperlipidemia	8 (6.3)	3 (4.8)	1 (8.3)	0.864
Smoking	50 (39.7)	30 (48.4)	4 (33.3)	0.430
Family history	10 (7.9)	1 (1.6)	1 (8.3)	0.261
Ejection Fraction (%)	38.97±7.08	35.89±7.87	35.00±5.64	0.010
White blood cell (10 <sup>9</sup> /L)	10.02±3.08	10.83±3.86	14.16±4.47	<0.001
Neutrophil (10 <sup>6</sup> /L)	7300.29±2951.02	8040.12±3671.20	10507.93±4383.68	0.004
Lymphocyte (10 <sup>6</sup> /L)	2212.72±1237.29	2188.59±1117.11	2646.27±1173.62	0.462
Hemoglobin (g/dL)	14.71±2.01	14.86±2.35	14.79±1.53	0.900
Platelets (10 <sup>9</sup> /L)	211.95±64.19	224.24±67.14	264.92±62.83	0.021
NLR	3.35 (2.00-5.43)	4.17 (2.00-6.67)	4.42(2.17-6.21)	0.710
PLR	103.43 (77.17-148.57)	112.28 (68.78-162.18)	102.37 (69.10-153.57)	0.828
SII	693.93 (441.18-1128.30)	900.89 (390.86-1460.0)	826.67 (594.61-1786.42)	0.251
Location of Myocardial Infarction				
Anterior MI	65 (51.6)	43 (69.4)	9 (75.0)	
Inferior MI	61 (48.4%)	19 (30.6)	3 (25.0)	0.033
Number of Involved Arteries				
Single-vessel disease	63 (50.0)	16 (25.8)	0	
Double-vessel disease	50 (39.7)	23 (37.1)	4 (33.3)	
Triple-vessel	13 (10.3)	23 (37.1)	8 (66.7)	<0.001
Infarct-Related Artery				
LMCA	0	2 (3.2)	0	
LAD	66 (52.4)	41 (66.1)	9 (75.0)	
LCX	15 (11.9)	7 (11.3)	0	
RCA	45 (35.7)	12 (19.4)	3 (25.0)	0.070
Hospital mortality	2 (1.6)	3 (4.8)	1(8.3)	0.252

\*Data are presented as mean±SD, IQR<sub>25-75%</sub>, or n (%)

LAD, Left anterior descending; LCX, Left circumflex artery; LMCA, Left main coronary artery; MI, Myocardial infarction; NLR, Neutrophil-to-lymphocyte ratio; PCI, Percutaneous coronary intervention; PLR, Platelet-to-lymphocyte ratio; RCA, Right coronary artery; SII, Systemic immune inflammation index; TIMI, Thrombolysis in myocardial infarction; WBC, White blood cell



Table 2. Comparison of the study variables with regard to pre- and postprocedural TIMI flow grades\*

	Preprocedural TIMI Flow Grade		P value	Postprocedural TIMI flow Grade		P
	TIMI-0/1	TIMI-2/3		TIMI-0/1/2	TIMI-3	
Age (y)	59.80±11.29	60.05±11.20	0.900	60.68±10.91	59.69±11.33	0.641
Sex (male)	126 (80.3)	34 (79.1)	0.863	24 (70.6)	136 (81.9)	0.132
Diabetes	28 (17.8)	9 (20.9)	0.643	8 (23.5)	29 (17.5)	0.407
Hypertension	62 (39.5)	20 (46.5)	0.407	17 (50.0)	65 (39.2)	0.242
Hyperlipidemia	9 (5.7)	3 (7.0)	0.761	4 (11.8)	8 (4.8)	0.120
Smoking	68 (43.3)	16 (37.2)	0.473	11 (32.4)	73 (44.0)	0.211
Family history	10 (6.4)	2 (4.7)	0.674	3 (8.8)	9 (5.4)	0.447
Ejection fraction (%)	37.36±7.33	39.30±7.53	0.127	35.74±7.60	38.19±7.31	0.077
Neutrophil (10 <sup>6</sup> /L)	7806.55±3370.46	7413.74±3332.85	0.403	9333.82±4088.11	7391.98±3100.32	0.008
Lymphocyte (10 <sup>6</sup> /L)	2274.76±1253.17	2072.40±957.28	0.436	2139.49±1097.84	2250.05±1217.90	0.645
WBC (10 <sup>9</sup> /L)	10.66±3.56	10.01±3.53	0.292	12.08±4.42	10.20±3.27	0.037
Hemoglobin (g/dL)	14.69±2.01	15.03±2.35	0.710	14.53±1.92	14.81±2.13	0.482
Platelet (10 <sup>9</sup> /L)	217.45±64.12	224.37±72.98	0.562	243.21±76.26	213.97±62.79	0.060
NLR	3.81(2.0-5.63)	3.33 (2.11-5.71)	0.892	4.72 (2.33-8.5)	3.50 (2.00-5.33)	0.036
PLR	99.67 (73.72-162.18)	113.72 (77.4-137.16)	0.421	120.92 (71.92-182.92)	104.61 (75.46-145.74)	0.172
SII	805.0 (424.67-1280.0)	680.0 (483.24-1096.67)	0.754	973.95 (617.03-1608.70)	697.25 (408.25-1216.0)	0.010
Location of Myocardial Infarction						
Anterior	88 (56.1)	29 (67.4)		25 (73.5)	92 (55.4)	
Inferior	69 (43.9)	14 (32.6)	0.179	9 (26.5)	74 (44.6)	0.051
Number of Involved Vessels						
Single-vessel disease	61 (38.9)	18 (41.9)		13 (38.2)	66 (39.8)	
Double-vessel disease	59 (37.6)	18 (41.9)		9 (26.5)	68 (41.0)	
Triple-vessel disease/ LMCA	37 (23.6)	7 (16.3)	0.591	12 (35.3)	32 (19.3)	0.089
Culprit Vessel						
LMCA	2 (1.3)	0		1 (2.9)	1 (0.6)	
LAD	87 (55.4)	29 (67.4)		24 (70.6)	92 (55.4)	
LCX	19 (12.1)	3 (7.0)		0	22 (13.3)	
RCA	49 (31.2)	11 (25.6)	0.466	9 (26.5)	51 (30.7)	0.062
In-hospital mortality	6 (3.8)	0	0.193	2 (5.9)	4 (2.4)	0.280

\*Data are presented as mean±SD, IQR<sub>25-75%</sub>, or n (%)

TIMI, Thrombolysis in myocardial infarction; LAD, Left anterior descending; LCX, Left circumflex artery; LMCA, Left main coronary artery; MI, Myocardial infarction; NLR, Neutrophil-to-lymphocyte ratio; PCI, Percutaneous coronary intervention; PLR, Platelet-to-lymphocyte ratio; RCA, Right coronary artery; SII, Systemic immune inflammation index; WBC, White blood cell

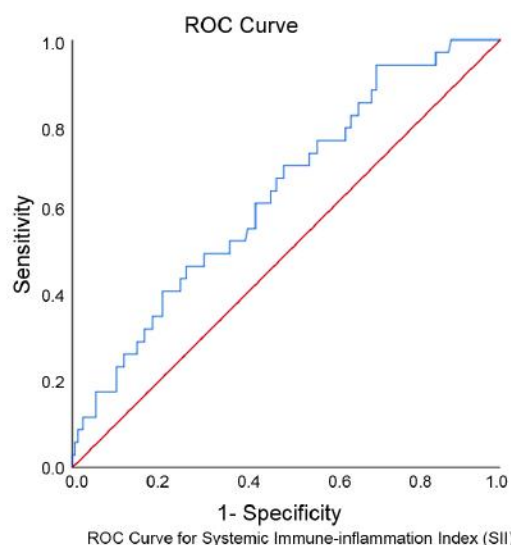


Figure 1. The image depicts the receiver operating characteristic (ROC) curve for evaluating the sensitivity and specificity of the systemic inflammatory immunologic index (SII) for the prediction of postprocedural no-reflow.

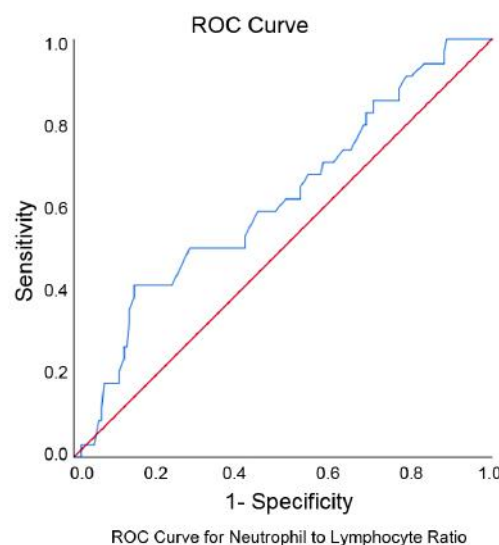


Figure 2. The image illustrates the receiver operating characteristic (ROC) curve for evaluating the sensitivity and specificity of the neutrophil-to-lymphocyte ratio (NLR) for the prediction of postprocedural no-reflow.



Table 3. Comparison of the study variables based on the SII and NLR cutoff points\*

	NLR		P value	SII		
	Low	High		Low	High	P
Age (y)	59.84±11.15	59.90±11.71	0.978	58.66±10.46	60.25±11.49	0.378
Ejection fraction (%)	38.02±6.91	36.83±9.07	0.437	39.40±6.67	37.23±7.56	0.073
Sex						
Male	130 (81.8)	30 (73.2)		47 (94.0)	113 (75.3)	
Female	29 (18.2)	11 (26.8)	0.314	3 (6.0)	37 (24.7)	0.008
Diabetes	26 (16.4)	11 (26.8)	0.189	9 (18.0)	28 (18.7)	0.916
Hypertension	60 (37.7)	22 (53.7)	0.095	15 (30.0)	67 (44.7)	0.097
Hyperlipidemia	8 (5.0)	4 (9.8)	0.443	2 (4.0)	10 (6.7)	0.734
Smoking	68 (42.8)	16 (39.0)	0.798	21 (42.0)	63 (42.0)	0.999
Family history	11 (6.9)	1 (2.4)	0.479	6 (12.0)	6 (4.0)	0.077
Anterior MI	92 (57.9)	25 (61.0)		29 (58.0)	88 (58.7)	
Inferior MI	67 (42.1)	16 (39.0)	0.855	21 (42.0)	62 (41.3)	0.934
Number of involved Vessels						
Single-vessel disease	63 (39.6)	16 (39.0)		24 (48.0)	55 (36.7)	
Double-vessel disease	60 (37.7)	17 (41.5)		15 (30.0)	62 (41.3)	
Triple-vessel disease/LMCA	36 (22.6)	8 (19.5)	0.876	11 (22.0)	33 (22.0)	0.291
SYNTAX Score Group						
Low	100 (62.9)	26 (63.4%)		33 (66.0)	93 (62.0)	
Moderate	50 (31.4)	12 (29.3)		16 (32.0)	46 (30.7)	
High	9 (5.7)	3 (7.3)	0.905	1 (2.0)	11 (7.3)	0.388
Hospital mortality	2 (1.3)	4 (9.8)	0.017	0	6 (4.0)	0.340
Before Primary PCI						
TIMI flow grade 2/3	34 (21.4)	9 (22.0)		9 (18.0)	34 (22.7)	
TIMI flow grade 0/1	125 (78.6)	32 (78.0)	0.937	41 (82.0)	116 (77.3)	0.619
After Primary PCI						
TIMI flow grade 0/1/2	20 (12.6)	14 (34.1)		2 (4.0)	32 (21.3)	
TIMI flow grade 3	139 (87.4)	27 (65.9)	0.002	48 (96.0)	118 (78.7)	0.002

\*Data are presented as mean±SD or n(%)

SII, Systemic immune inflammation index; NLR, Neutrophil-to-lymphocyte ratio; LMCA, Left main coronary artery; MI, Myocardial infarction; PCI, Percutaneous coronary intervention; TIMI, Thrombolysis in myocardial infarction

In our study, patients with lower NLR values were more likely to experience complete blood flow after undergoing primary PCI in the setting of STEMI. Although most studies have evaluated the association between the NLR in adverse outcomes of patients and acute coronary syndromes, several studies have exclusively investigated the association between the NLR and the postprocedural flow in the IRA after primary PCI in patients with STEMI. Similar to our findings, in a recent paper, Karabağ et al<sup>21</sup> reported an independent association between the presentation NLR and postprocedural no-reflow in patients with STEMI. In their study, WBC, neutrophils, and lymphocytes were also associated with no-reflow. We too found the association of WBC and neutrophils in our study; nonetheless, our results failed to show a significant association with the lymphocyte count. Our findings also did not show a statistically significant association between the platelet count and no-reflow after primary PCI, which chimes in with the findings of the study by Karabağ et al.<sup>21</sup> In another study, Lee et al<sup>22</sup> reported an association between the presentation NLR and IRA patency before and after primary PCI in patients with STEMI. Our findings are similar concerning the postprocedural TIMI flow; nevertheless, we found no association between the presentation NLR and preprocedural IRA patency. It should be noted that Lee et

al<sup>22</sup> did not include patients with a postprocedural TIMI-0/1. Kaya et al<sup>10</sup> demonstrated an association between the NLR and no-reflow following primary PCI in univariate analysis. In their multivariate analysis for the prediction of major adverse cardiovascular events, the NLR was an independent predictor after adjustments for no-reflow. In a study by Akpek et al,<sup>7</sup> the NLR was independently associated with no-reflow after primary PCI, but WBC and platelet counts were similar between patients with reflow and those without reflow following primary PCI. In contrast to our finding, the NLR was not associated with no-reflow after primary PCI in patients with STEMI in a study by Karahan et al,<sup>23</sup> who compared a postprocedural TIMI-0/1 with a TIMI-2/3, which may have contributed to the different results. The discrepancies between studies regarding the role of hematological indices in predicting postprocedural no-reflow may partially be explained by different inclusion criteria and the definition of IRA patency by TIMI flow grading.

Our results revealed no significant association between the NLR and a preprocedural TIMI-2/3 in comparison with a preprocedural TIMI-0/1. These findings are consistent with the results of a study by Sen et al,<sup>24</sup> who reported that preprocedural TIMI flow grades were not significantly different between NLR tertiles. Lee et al<sup>22</sup> found higher



NLR levels in lower TIMI flow grades before primary PCI in univariate analysis, but not in multivariate analysis. In contrast, there are other studies reporting the NLR as an independent predictor of the preprocedural TIMI flow.<sup>11, 25, 26</sup>

We also studied the association between the NLR and the SYNTAX score. According to our results, the NLR was not significantly associated with SYNTAX score subgroups. Still, WBC, neutrophil, and platelet counts were significantly higher in our higher SYNTAX subgroups. In a study by Sahin et al,<sup>9</sup> the NLR was an independent predictor of the SYNTAX score in patients with STEMI who underwent primary PCI. In a univariate analysis, they also found an association between a higher SYNTAX score and WBC, neutrophil, and lymphocyte counts, but not with the platelet count.

While the roles of inflammatory and thrombotic pathways in the pathogenesis of atherosclerosis and coronary artery diseases are well known, the incorporation of presentation blood counts into risk stratification models, which may potentially change therapeutic plans, has become challenging due to the diverse nature of coronary artery diseases and different study samples, including a diverse range of patients with coronary atherosclerosis.<sup>27-29</sup>

More recently, the SII, which combines the 3 types of cells, namely platelets, neutrophils, and lymphocytes, has been shown as a reliable marker for the prediction of outcomes in various neoplasms.<sup>15, 16</sup> However, the role of this index in coronary artery diseases, in which all 3 cell types are potentially involved, is not known yet. As the SII is calculated from the counts of 3 blood cell types that are readily available in all patients on presentation, we decided to investigate its role in predicting the SYNTAX score and pre- and postprocedural TIMI flow grades in patients with STEMI who underwent primary PCI. While the SII on presentation was not associated with the TIMI flow grade before primary PCI or the SYNTAX score, a higher SII predicted the increased possibility of no-reflow in IRA after primary PCI with a higher sensitivity and a lower specificity than the NLR.

An increase in the NLR and the SII is indicative of an acute inflammatory response in the setting of an ongoing MI. Despite the fact that acute inflammation leads to an increased number of circulating neutrophils and platelets, cortisol secretion can decrease the lymphocytes in circulation in the course of an MI.<sup>30, 31</sup> Our findings showed no association between the NLR and the SII and the extent of coronary involvement assessed by SYNTAX score or preprocedural TIMI flow grade, but they showed a significant association between impaired flow after primary PCI and an increased NLR and SII on presentation. Although the adverse outcome of patients without a final TIMI-3 during PCI is well established,<sup>32</sup> the complex underlying pathophysiological mechanism is not entirely known. Vasospasm, distal thromboemboli, cellular and endothelial

injury, and edema as a result of ischemia and reperfusion injury are all involved in the pathogenesis of impaired reflow and microvascular stagnation after PCI.<sup>33</sup> The ischemia-induced local inflammation may become augmented by systemic inflammatory cells and released mediators, which flow to the site after the recanalization of the epicardial artery. Furthermore, enhanced systemic platelet activation and aggregation, which may persist even with double antiplatelet therapies, contribute to this process.<sup>34</sup> Platelet and leukocyte aggregation in coronary capillaries may further increase microvascular resistance and decrease the flow.<sup>35</sup> Additionally, endothelial dysfunction and local inflammatory state may trigger the formation of microvascular thrombosis and the formation of platelet-neutrophil complexes,<sup>36</sup> which in turn exacerbates the severity of inflammatory tissue injury. This veracious cycle, as well as the resultant no-reflow after the recanalization of the epicardial artery, may adversely influence the clinical benefit of primary PCI in the setting of STEMI. It should be noted that ongoing research regarding the pharmacological and non-pharmacological adjunctive treatments for preventing no-reflow after primary PCI show controversial results, partly due to the heterogeneous nature of patient populations.<sup>37</sup> Accordingly identifying susceptible patients and targeting the at-risk population may help identify potential treatments.

Future multicenter investigations with larger samples are needed to explain the discrepancy of results regarding the role of presentation blood cells in predicting the SYNTAX score and the preprocedural TIMI flow. There might be other unmeasured confounding factors that could potentially affect the findings. In addition, experimental studies are required to better understand the underlying mechanism by which inflammatory cells contribute to the pathophysiology of impaired reflow and reperfusion injury.

## Conclusion

In patients with STEMI, the presentation NLR and SII are both useful for predicting the risk of no-reflow after primary PCI. While the NLR has a higher specificity for predicting no-reflow following primary PCI, the SII has a higher sensitivity for detecting the risk of no-reflow. Nonetheless, the NLR and the SII are not associated with SYNTAX risk groups and preprocedural TIMI flow grades in STEMI.

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