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Assessment of systemic immune-inflammation index as an independent surrogate biomarker of no-reflow phenomenon in acute coronary syndrome patients with coronary artery bypass grafting undergoing percutaneous coronary intervention of saphenous vein graft

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Abstract. – OBJECTIVE: Numerous mechanisms have been proposed for the no-reflow phenomenon (NRP) in the literature including leukocyte intravascular plugging, microembolisms, and extrinsic coagulation pathway activation. Some of the more recent studies suggested a relationship between NRP and systemic immune-inflammation index (SII) in different contexts. To this end, the objective of this study was to investigate the relationship between NRP and SII in acute coronary syndrome (ACS) patients with coronary artery bypass grafting (CABG) who underwent percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI) of saphenous vein graft (SVG).

PATIENTS AND METHODS: The sample of this retrospective study consisted of 124 ACS patients with CABG who underwent PTCA/PCI of SVG.

RESULTS: The incidence of NRP in the study group was 30.6% (n=38). The results of the multivariate logistic regression analysis indicated that ST-elevation myocardial infarction (STEMI) and SII were independent predictors for NRP ($p<0.05$). The receiver operating characteristic (ROC) curve analysis revealed that the optimal cut-off value of SII in predicting the development of NRP in patients undergoing PTCA/PCI of SVG and the sensitivity and specificity values thereof are 975, 74%, and 80%, respectively [Area under the curve (AUC): 0.84, 95% confidence interval (CI): 0.76-0.91, p-value <0.001].

CONCLUSIONS: The study findings indicated that SII, which can be easily calculated from a single complete blood count test, is an independent predictor of the development of NRP in ACS patients undergoing PTCA/PCI of the SVG.

Key Words:
Acute coronary syndrome, Coronary artery bypass grafting, No-reflow phenomenon, Systemic immune-inflammation index, Percutaneous coronary intervention, Saphenous vein grafts.

Introduction

Coronary artery bypass grafting (CABG) is a revascularization method used as an alternative to percutaneous transluminal coronary angioplasty (PTCA) or percutaneous coronary intervention (PCI) in patients with high SYNTAX (Synergy between PCI with taxus and cardiac surgery) scores or particular patient groups[1,2]. Saphenous vein grafts (SVGs) are the most commonly used grafts in CABG, given that they are easily accessible in daily clinical practice and do not have a major impact on venous circulation. However, 10-15% of SVGs are occluded during the first year after CABG[3], and SVG patency rates due to degenerative and/or occlusive disease are halved in the first decade[4]. PTCA/PCI of SVGs present many challenges, including slow or no-reflow and distal embolization[5]. The no-reflow phenomenon (NRP) is a common complication of PTCA/PCI of SVG. NRP may develop during PTCA/PCI of native vessels or, more commonly, of SVGs[6]. Although the incidence of NRP in PTCA/PCI of SVGs has been reported around at 4% in previous publications[6], it reaches 15% in more recent publications[7].

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Many recent studies[8,9] demonstrated the relationship between NRP and inflammatory markers in the context of different patient groups. Low neutrophil counts were associated with NRP in patients with ST-elevation myocardial infarction (STEMI) who do not have a history of CABG[10].

The systemic immune-inflammation index (SII), which is based on neutrophil, lymphocyte, and platelet counts, has been developed as a novel inflammatory marker during the last decade. The three inflammatory parameters that make up SII can easily be measured within the scope of the complete blood count test. SII is a sensitive parameter that can effectively estimate a patient's inflammatory state.

In parallel, it has been proven[11,12] to be a strong and independent prognostic indicator of adverse outcomes in most types of cancer. Some studies[13,14] have shown that SII is superior to other inflammatory markers, including neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), in determining the incidence of inflammation-based coronary artery disease (CAD). However, there is no study in the literature on the relationship between SII levels and the development of NRP in patients undergoing PTCA/PCI of SVG. Additionally, there is a demand in clinical practice for a parameter that can predict the risk of NRP before it develops or even before the surgical procedure. In this context, the objective of this study is to investigate the relationship between NRP and SII in acute coronary syndrome (ACS) patients with CABG who underwent PTCA/PCI of SVG.

Patients and Methods

Population and Sample

The population of this retrospective study consisted of 216 consecutive patients with CABG who presented with ACS and subsequently underwent PCI/PTCA of SVG at Ankara City Cardiovascular Hospital and Ankara Yüksek Ihtisas University Training and Research Hospital. Seventy-six patients were excluded from the study due to severe kidney disease, anemia, infection, and use of steroids or anticoagulants. An additional 16 patients were excluded from the study due to missing data (Figure 1).

The study sample consisted of the remaining 124 patients, which were divided into two groups as patients with NRP (n=38) and patients with normal flow (n=86). The study was carried out in accordance with the principles set forth in the Declaration of Helsinki.

No-Reflow Phenomenon

The term "no-reflow" was first used about half a century ago to describe the experimental signs of brain ischemia observed in animals[15]. The clinical reports[16] on the observation of NRP during PCI in humans are more recent. NRP is defined as insufficient myocardial tissue perfusion after a transient period of ischemia without evidence of mechanical obstruction such as dissection, spasm, or thrombus in the epicardial artery[6]. The concept of NRP also covers the slow-flow phenomenon[6]. Numerous mechanisms have been proposed for the NRP in the literature including cellular edema[17], ischemia-reperfusion injury, microvascular spasm, intravascular leukocyte plugging, microembolisms[18], and extrinsic coagulation pathway activation[19]. NRP is an independent predictor of in-hospital mortality related to myocardial infarction. The long-term effects of NRP include an increase in the incidence of heart failure, long-term mortality, and major cardiac events[20-23]. A prolonged no-reflow/slow-flow has a poor prognosis[24]. NRP occurs in approximately 2-5% of the total PCI/PTCA cases[23]. In patients with ACS, the incidence of NRP is reported between[20-22] 10-30%. NRP poses a serious challenge for interventional cardiologists, since there is still no treatment developed specifically for NRP. Current procedural and pharmacological strategies have limited success in preventing NRP and managing it in the event of occurrence[25]. The procedural strategies used to prevent NRP include direct stenting without predilation and the use of short stent, embolism protection devices, and excimer laser[26], whereas the pharmacological strategies involve the use of adenosine to the distal bed[27], nicardipine[28], and nitroprusside[29]. For the purposes of this study, NRP was defined as a flow grade of less than 3 in thrombolysis in myocardial infarction (TIMI) without clear evidence of dissection, stenosis, or vasospasm[30].

Systemic Immune-Inflammation Index (SII)

Blood samples were taken from the patients at the time of admission. Complete blood count included measurement of hemoglobin level as well as platelet, white blood cell, and total neutrophil and lymphocyte counts.

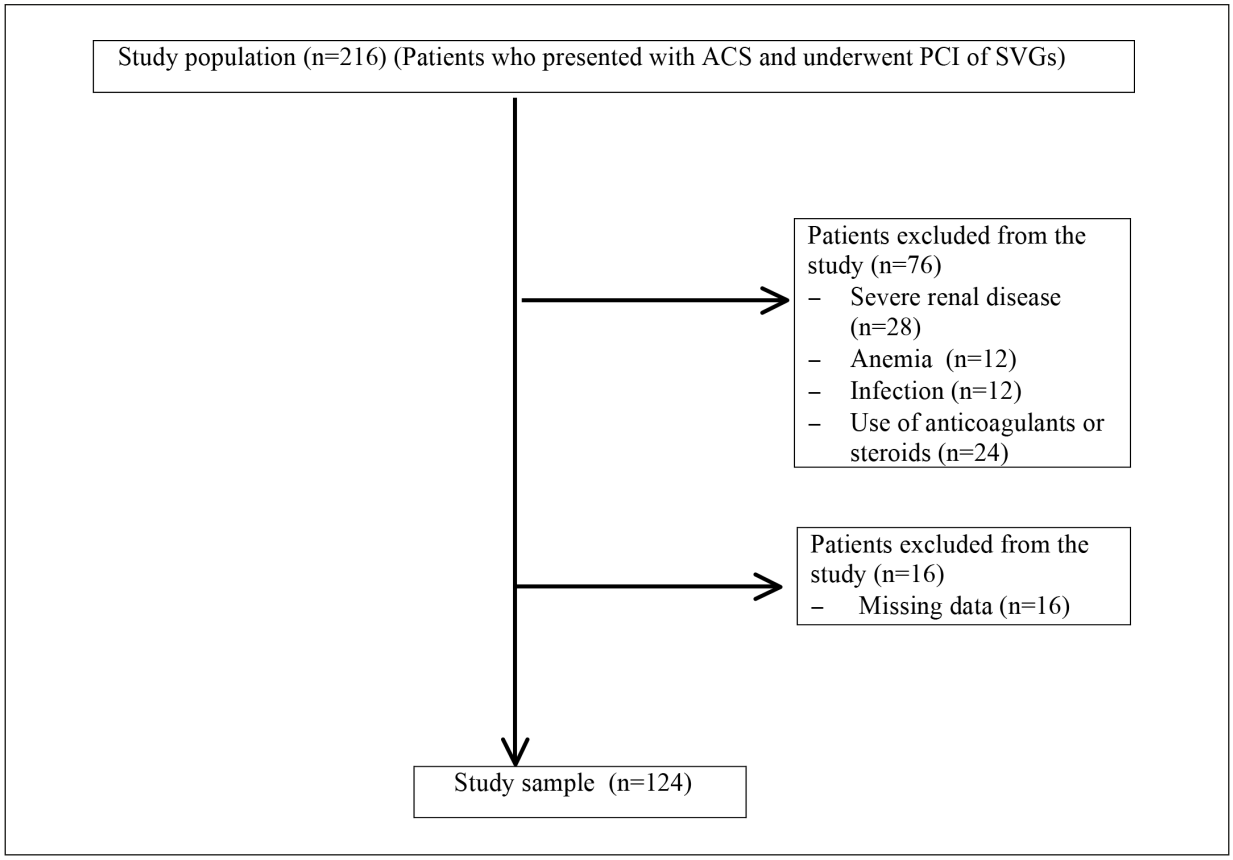

Figure 1. Flow chart of the study. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; SVG, saphenous vein graft.

NLR was calculated as the ratio of total neutrophil to lymphocyte count. SII was calculated as the ratio of the product of the total neutrophil count and the total platelet count to the lymphocyte count[31,32].

Statistical Analysis

The research data were analyzed using SPSS 24.0 for MacOS (Statistical Package for Social Sciences, IBM Corp., Armonk, NY, USA) software package. Normal distribution characteristics of the numerical variables were evaluated by the Kolmogorov-Smirnov test. Pearson's Chi-squared test was used to compare independent categorical variables, which were presented as percentage (%) values, between the groups. Fisher's exact test was used in cases where the Pearson's Chi-squared test could not be applied. The Student's *t*-test was used to compare independent numerical variables that were determined to conform to the normal distribution, which were presented as mean±standard deviation (SD) values, between the groups. The Mann-Whitney U test was used to compare the independent numerical variables that were determined not to conform to the normal distribution, which were presented as median values and 25th and 75th percentiles, between the groups. Receiver operating characteristic (ROC) curve analyzes were performed to determine the cut-off, sensitivity and specificity values of SII in predicting NRP.

Univariate and multivariate logistic regression analyses were performed to determine the variables significantly correlated with NRP, and results were expressed as odds ratios (OR) within 95% confidence interval (CI). The clinical, demographic, and laboratory parameters that could be associated with NRP were analyzed within the scope of the univariate logistic regression analysis. The variables with a p-value < 0.10 in the univariate logistic regression analysis were further analyzed within thescope of the multivariate logistic regression analysis. A two-way alpha value < 0.05 was deemed to indicate statistical significance in all analyses.

Results

One The study sample included a total of 124 ACS patients. Of these patients, 38 (30.6%) had NRP. Demographic, clinical, and laboratory characteristics of the patients with and without NRP were compared (Table I). The mean ages of the NRP and normal reflow groups were calculated as 64±12 and 67±11 years, respectively. Compared to 73.6% of the NRP group, 77.9% of the normal reflow group consisted of males. There was no significant difference between the groups in terms of age and gender (p=0.247 and p=0.609, respectively). There was also no significant difference between the groups in terms of ACS type (p=0.086).

On the other hand, there was a significant difference between the groups in terms of glucose levels [134 (min. 106, max. 226) *vs.* 118 (min. 94, max. 174) mg/dL, p=0.040)], creatinine [0.9 (min. 0.7, max. 1.1) *vs.* 1.0 (min. 0.9, max. 1.2) mg/dL, p=0.034)], and C-reactive protein (CRP) levels [10.8 (min. 3.4, max. 18.2) *vs.* 4.4 (min. 2.1, max. 10.7) mg/dL, p=0.022]. There was no significant difference between the groups in urea, albumin, total protein, and troponin levels, and lipid panel. There was a significant difference between the groups in neutrophil count [8.7 (3.9-15.8) *vs.* 7.3 (2.7-14.0) x $10^3/mm^3$, p=0.005], and lymphocyte count [2.1 (0.6-9.0) *vs.* 3.9 (1.1-8.9) x $10^3/mm^3$, p=<0.001] parameters of the complete blood count. There was no significant difference between the groups in terms of erythrocyte sedimentation rate (ESR), another anti-inflammatory marker. Hemoglobin levels and platelet counts (257±72 *vs.* 218±60 x $10^3/mm^3$, p=0.066) levels were similar between the groups. There was also no significant difference between the groups in left ventricular ejection fraction (LVEF) values calculated by echocardiography.

Among the periprocedural outcomes, stent length was significantly higher in the NRP group than in the normal reflow group [25 (min. 19, max. 36) mm *vs.* 18 (min. 15, max. 27) mm, p=0.018]. There was also a significant difference between the groups in terms of TIMI score. Accordingly, 55% of patients who developed NRP had Grade 5 thrombus score (p=0.002). There was no significant difference between the groups in number and type of stents, graft number, and saphenous graft target. Patients who had predilatation could not be evaluated due to missing data. The duration of the pain was higher, albeit not significantly, in the NRP group than in the normal reflow group [2 (min. 1, max. 5) hours *vs.* 1 (min. 0.8, max. 5.5) hours, p=0.220]. In terms of clinical outcomes, in-hospital mortality was significantly higher in the NRP group than in the normal reflow group [3 (8%) *vs.* 0 (0%), p=0.027]. In addition, there was a significant difference between groups in terms of 1-year survival (p=0.042). Accordingly, the number of patients who died from any cause was 21% for the NRP group, compared to 8% rate in the normal reflow group. There was no significant difference between the groups in the length of hospital stay and Killip classification. The periprocedural outcomes are shown in Table II.

Parameters that may act as risk factors for NRP in patients with ACS undergoing saphenous PCI were evaluated by logistic regression analysis. To this end, parameters such as age, gender, ACS type, presence of diabetes mellitus, hypertension, and heart failure, location of the saphenous graft, number, type and length of the stent, TIMI score, creatinin, low density lipoprotein (LDL) cholesterol, and CRP levels, LVEF, and SII were analyzed in the context of whether they were correlated with NRP. The risk factors found to be correlated with NRP as a result of the univariate logistic regression analysis, i.e., ACS type, TIMI score, LDL cholesterol, LVEF, and SII were further analyzed with multivariate logistic regression analysis in the context of a single model. Accordingly, a high SII score (OR: 1.001, 95% CI: 1.001-1.002, p<0.001) was found to be an independent predictor for NRP in saphenous vein PCI (Table III).

The ROC curve analysis revealed that the optimal cut-off value of SII in predicting the development of NRP in patients undergoing PTCA/PCI of SVG and the sensitivity and specificity values thereof are 975, 74%, and 80%, respectively [Area under the curve (AUC): 0.84, 95% CI: 0.76-0.91, p<0.001] (Figure 2).

Discussion

A thorough review of the literature did not reveal any study on the relationship between NRP and SII in patients who underwent saphenous PCI for ACS. Hence, this is the first study to date that investigated the said relationship. Consequently, SII was found to be an independent predictor for NRP in ACS patients with CABG.

In parallel with the increase in the patient population diagnosed with CAD, there has been an

Table I. Basal demographic and laboratory characteristics.

	Normal reflow (n=86)	No-reflow (n=38)	*p*-value
Demographic characteristics			
Age (years)	67 ± 11	64 ± 12	.247
Gender (male)	67 (77.9%)	28 (73.6%)	.609
ACS type			.086
STEMI	10 (12%)	9 (24%)	
NSTEMI	76 (88%)	29 (76%)	
Comorbidites			
Diabetes mellitus	40 (46%)	23 (60%)	.150
Hypertension	55 (64%)	23 (60%)	.716
Heart failure	22 (26%)	12 (33%)	.404
Smoking	28 (34%)	10 (29%)	.555
Embolism	0	1 (3%)	.306
iCVA	0	0	NA
Atrial fibrillation	1 (1%)	0	1.00
Treatments			
GIIb-IIIa inhibitors	11 (13%)	15 (40%)	.001
Statin	81 (94%)	32 (84%)	.072
Acetyl salicylic acid	86 (100%)	34 (89%)	.002
Clopidogrel	70 (81%)	28 (78%)	.647
Ticagrelor	10 (12%)	6 (17%)	.452
Prasugrel	4 (5%)	2 (6%)	.833
RAAS inhibitors	74 (86%)	34 (97%)	.074
Beta-blockers	84 (98%)	34 (97%)	.865
Biochemical tests			
Glucose (mg/dL)	118 (94-174)	134 (106-226)	.040
Urea (mg/dL)	37 (29-45)	34 (27-52)	.646
Creatinin (mg/dL)	1.0 (0.9-1.2)	0.9 (0.7-1.1)	.034
Albumin (g/dL)	3.7 (3.5-3.9)	3.7 (3.5-3.9)	.908
Total protein (g/dL)	6.5 (6.1-7.0)	6.8 (6.2-6.9)	.975
Troponin* (ng/L)	0.3 (0.1-1.3)	0.7 (0.1-3.1)	.074
Peak CK MB (ng/mL)	25 (17-44)	42 (20-78)	.119
Sedimentation	16 (7-30)	30 (10-62)	.091
LDL-C (mg/dL)	109 (84-140)	113 (87-176)	.339
Triglyceride (mg/dL)	130 (87-201)	146 (86-229)	.282
HDL-C (mg/dL)	37 (32-44)	39 (30-42)	.674
Total cholesterol (mg/dL)	172 (142-206)	181 (154-252)	.118
CRP (mg/dL)	4.4 (2.1-10.7)	10.8 (3.4-18.2)	.022
Complete blood count			
WBC (10^3/mm^3)	11.0 ± 3	11.2 ± 2.2	.200
Neutrophil (10^3/mm^3)	7.3 (2.7-14.0)	8.7 (3.9-15.8)	.005
Lymphocyte (10^3/mm^3)	3.9 (1.1-8.9)	2.1 (0.6-9.0)	<.001
Platelet (10^3/mm^3)	218 ± 60	257 ± 72	.066
Hemoglobin (g/dL)	13.4 ± 1.8	13.4 ± 1.8	.952
Hematocrit (%)	41 ± 5	40 ± 5	.741
Monocytes (10^3/mm^3)	0.7 (0.6-0.8)	0.6 (0.5-0.7)	.056
MPV (fL)	9.5 ± 1.3	9.3 ± 1.0	.398
SII x10^3	472 (268-826)	1,649 (775-2,811)	<.001
LVEF (%) ± SD	46 ± 10	42 ± 10	.064

*At admission. ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; RAAS, renin-angiotensin-aldosterone system; iCVA, ischaemic cerebrovascular accident; CK MB, creatine kinase myocardial band; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; WBC, white blood cell; MPV, mean platelet volume; LVEF, left ventricular ejection fraction; SII, systemic immune-inflammation index; SD, standard deviation.

Table II. Angiographic and procedural characteristics and clinical outcomes.

	Normal reflow (n=86)	No-reflow (n=38)	*p*-value
Location of the saphenous graft			.502
RCA	30 (35%)	18 (47%)	
Diagonal	12 (14%)	2 (5%)	
Cx	11 (13%)	6 (16%)	
LAD	5 (6%)	2 (5%)	
Obtuse marginalis	28 (33%)	10 (26%)	
Procedural data			
Number of grafts	3 (2-3)	3 (2-3)	.524
Number of stents	1 (1-1)	1 (1-2)	.083
Stent type			.478
DES	37 (43%)	12 (36%)	
BMS	48 (57%)	21 (64%)	
Stent length (mm)	18 (15-27)	25 (19-36)	**.018**
TIMI score			**.002**
Grade 0	4 (5%)	0	
Grade 1	2 (2%)	1 (3%)	
Grade 2	4 (5%)	0	
Grade 3	13 (15%)	5 (13%)	
Grade 4	47 (55%)	11 (29%)	
Grade 5	16 (19%)	21 (55%)	
Duration of pain	1 (0.8-5.5)	2 (1-5)	.220
Clinical outcomes			
Killip classification			.071
I-II	84 (98%)	34 (89%)	
III-IV	2 (2%)	4 (10%)	
In-hospital mortality	0	3 (8%)	**.027**
Length of hospital stay	3 (2-6)	3 (3-5)	.377
1-year mortality	7 (8%)	8 (21%)	**.042**

RCA, right coronary artery; Cx, circumflex artery; LAD, left anterior descending artery; DES, drug-eluting stent; BMS, bare-metal stent; TIMI, thrombolysis in myocardial infarction

Table III. Analysis of independent predictors of NRP by logistic regression analyses.

	Univariate logistic regression analysis		Multivariate logistic regression analysis*,†	
	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value
Age	0.98 (0.94-1.01)	.229		
Gender	1.26 (0.52-3.05)	.609		
ACS type	0.42 (0.16-1.15)	.092	4.32 (1.24-15.1)	.022
Diabetes mellitus	0.57 (0.26-1.23)	.152		
Hypertension	1.16 (0.53-2.54)	.716		
Heart failure	0.70 (0.30-1.63)	.406		
Location of the saphenous graft	0.90 (0.72-1.13)	.378		
Number of stents	1.70 (0.85-3.41)	.132		
Stent type	1.35 (0.59-3.10)	.479		
Stent length	1.02 (0.99-1.04)	.121		
TIMI score	2.11 (1.25-3.56)	.005	1.4 (0.82-2.54)	.201
Creatinin	0.37 (0.10-1.42)	.146		
LDL-C	1.01 (1.00-1.02)	.047	1.01 (0.99-1.02)	.207
C-reactive protein	1.01 (0.99-1.03)	.115		
Left ventricular ejection fraction	0.96 (0.92-1.01)	.062	0.97 (0.91-1.02)	.217
SIIcontinous	1.001 (1.001-1.002)	<.001	1.001 (1.001-1.002)	<.001

*Nagelkerke R square= 0.513; -2 Log Likelihood= 85; *p*-value <.001
†Hosmer-Lemeshow test's Chi-square value= 7.0; *p*-value= .532

ACS, acute coronary syndrome; TIMI, thrombolysis in myocardial infarction; LDL-C, low density lipoprotein cholesterol; SII, systemic immune-inflammation index; CI, confidence interval.

increase in the number of patients revascularized by CABG. The development of coronary imaging methods in recent years provided the opportunity to diagnose more patients with coronary diseases on time and thereby to intervene earlier. However, there have been some drawbacks in patients with CABG such as more complex and undesirable saphenous interventions due to longer intervention times, more opaque delivery compared to native vein PCI, and incompatibility of grafts and catheters. Interventions of SVGs have increased the incidence of negative and undesirable situations such as NRP[6].

NRP is observed in 2-5% of all PCI patients[23]. However, the major risk group is the patient group presenting with ACS, where the risk for NRP reaches 30%[33]. As a matter of fact, the rate of patients with NRP in the sample of this study was found to be approximately 31%. Both ACS and saphenous vein interventions are risk factors for NRP[33]. In a study conducted by Eid-Lidt et al[34] with 127 patients, NRP was observed in 15% of the unselected saphenous PCI cases. Similarly, in another study[35], 18% of the 205 unselected saphenous PCI cases had NRP.

It has been emphasized in the literature[36] that NRP is an independent predictor of increased in-hospital mortality and is associated with heart failure and malignant arrhythmias due to prolonged acute ischemia. The fact that NRP is associated with mortality after postprocedural cardiovascular interventions and the lack of a curative treatment has driven cardiologists to learn more about the pathogenesis of NRP. Thus a number of studies[8,17-19,37-40] has been carried out to that effect. Some of these studies[17-19,37,38] on the mechanisms that may cause NRP are mentioned above. The impact of ACS on the development of NRP is still unknown. In parallel, NRP has been associated with different inflammatory mediators in various studies[8,39,40] conducted with different patient groups. In one of these studies[8], which was conducted by the authors of this study, NRP was found to be associated with the CRP to albumin ratio in patients who underwent PCI of SVGs.

Wang et al[10] found the neutrophil count an independent predictor of NRP in patients with STEMI. Dogan et al[41] reported that low lymphocyte count is an independent predictor of NRP. Kocas et al[9] demonstrated that NLR is an independent predictor of high TIMI frame count.

As new inflammatory predictors of abnormal coronary flow emerge, further studies are being conducted on novel predictive markers with new patient groups. The immunothrombosis model, which consists of two parts of the immune system and the hemostasis system, has provided new evidence[42,43] in that regard as a model considered to reflect inflammation better. On the other hand, SII, an inflammation marker that has emerged in recent years, reportedly assesses patients' inflammatory and immunothrombotic status simultaneously.

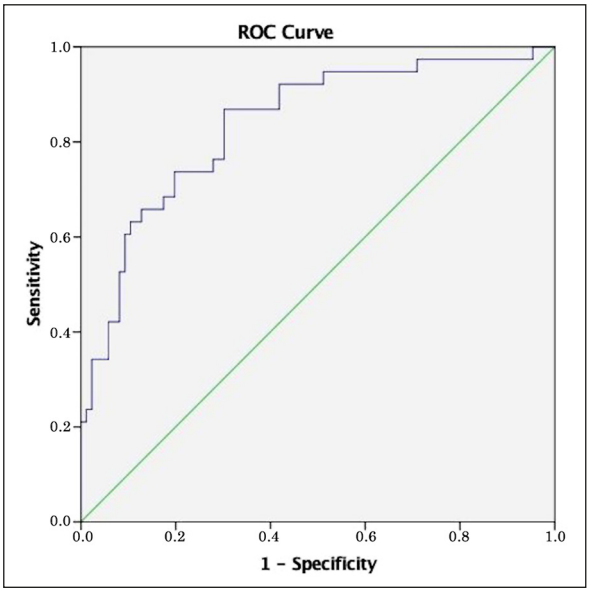

Figure 2. ROC curve analysis of the prognostic power of SII in predicting NRP. AUC: 0.84 [95% CI: (0.76-0.91)], (0.76-0.91), *p*-value <0.001. ROC, The receiver operating characteristic; SII, systemic immune-inflammation index; NRP, no-reflow phenomenon.

The SII was initially thought to be a prognostic indicator for a variety of malignancies[11,12]. However, as an index that provides information about the prognosis of the NRP via a single blood test, it has attracted the attention of interventional cardiologists. Hence, several dozens of studies have been published in the literature consecutively in the last 5 years on the relationship between SII and NRP.

Erdogan et al[14] study on fractional flow reserve (FFR) in patients with chronic coronary syndrome revealed that the SII was superior to the NLR and PLR in predicting hemodynamically severe coronary stenosis. It has been reported[44] that SII is a predictor of severe aortic stenosis and correlated with aortic valve area. Additionally, Kelesoglu et al[31,45] determined that SII is an independent predictor of contrast nephropathy in NSTEMI patients and coronary collateral circulation formation.

In a recent study[46] conducted by the authors of this study, it was determined that SII is an independent predictor of postprocedural contrast nephropathy in patients undergoing transcatheter aortic valve implantation for severe aortic stenosis. Similarly, the findings of this study indicated that SII is an independent predictor for the development of NRP in ACS patients undergoing saphenous PCI. Accordingly, an SII cut-off value of 975 predicted NRP in ACS patients with a sensitivity 74% and specificity of 80%.

Limitations

Apart from its strengths mentioned earlier, there were also some limitations in this study:

1. First, it was designed as a single-center, retrospective, and cross-sectional study. Therefore, the study findings could not be generalized to the general population.
2. Secondly, the sample size was relatively small. Therefore, further large-scale studies are needed on this patient population subject to the interventions of the saphenous vein, which make up less than 10% of all percutaneous interventions, yet valuable.
3. Thirdly, it could not be determined whether predilatation has occurred due to missing data.

Conclusions

The study findings indicated that SII, which can be easily calculated from a single complete blood count test, is an independent predictor of the development of NRP in ACS patients undergoing saphenous PCI.

Authors' Contribution

All authors made substantial contributions to (1) conception and design of the study, and acquisition, analysis and interpretation of data, (2) drafting or revising the manuscript to include important intellectual content, and (3) approval of the final version of the manuscript readily to be published.

Conflict of Interest

The authors do not have any potential conflict of interest regarding the research, authorship and/or publication of this article.

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Ethics Approval

The study protocol was approved by the Ankara City Hospital Clinical Trials and Ethics Committee.

Informed Consent

Not applicable due to the retrospective nature of the study.

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