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A New Inflammatory Marker of the No-reflow Phenomenon after Percutaneous Coronary Intervention (PCI) to Saphenous Venous in Patients with Coronary Artery Disease

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Abstract

Background: Although numerous mechanisms regarding the no-reflow phenomenon (NRP) have been mentioned, they have not yet been fully elucidated. The NRP can impact the success rate even in a technically flawless percutaneous coronary intervention (PCI), which can be annoying. Before the procedure, there is no specific parameter or index that can assess a significant factor such as NRP that has a direct impact on the success of the PCI.

Objectives: The present study aimed to evaluate the relationship between the systemic immune-inflammation index (SII) and NRP in patients who underwent PCI for saphenous vein graft (SVG).

Methods: In this retrospective cohort study, 312 coronary artery bypass grafting (CABG) patients admitted to primary or elective SVG and those who underwent PCI between January 2014 and December 2021 were selected. Routine blood samples were taken from the patients at the time of admission, and SII was calculated as the ratio of the product of the total neutrophil count and the total platelet count to the lymphocyte count. The reperfusion rates after PCI were evaluated according to the thrombolysis in myocardial infarction (TIMI) grade flow and myocardial blush grade (MBG). Following the procedure, those with an angiographic TIMI flow grade of ≤ 2 or TIMI flow grade of 3 and a final MBG of < 2 were considered NRP.

Results: The number of 85 patients (27.2%) were diagnosed with NRP. The SII and ST-elevation myocardial infarction were found to be independent predictors for NRP in multivariate logistic regression analysis (P<0.05). The SII predicted NRP with a sensitivity of 86% and a specificity of 80% (AUC: 0.866, 95% CI: 0.823 to 0.910, P<0.001) using a cut-off point of 13.45.

Conclusion: The SII is an independent predictor that can be easily calculated from the whole blood test to predict no-reflow development, which is a frustrating complication in patients following the PCI to the saphenous vein. This predictor can enable us to pre-evaluate the non-operational reasons affecting the procedure's success.

Keywords: Coronary artery bypass graft, No-reflow phenomenon, Systemic immune inflammation index

1. Background

Coronary artery bypass grafting (CABG) is a revascularization technique utilized as an alternative to percutaneous coronary intervention (PCI) in patients with high synergy between PCI with Taxus and cardiac surgery (SYNTAX) scores or certain patient groups (1). Saphenous vein grafts (SVGs) are the most often used grafts in CABG because they can be procured easily and have little to no impact on venous circulation. However, 10-15% of SVGs get blocked in the first year following CABG (2), and SVG patency rates are half in the initial decade following surgery due to degenerative and/or occlusive disease (3). Vasa vasorum injury during saphenous graft removal lowers graft survival and escalates graft occlusion (4). Furthermore, increased inflammatory mediator levels and exposure to arterial pressures improper for its physiology promote SVG occlusion (4). As a result, SVGs exhibit atheroma plaques with thinner and more fragile fibrous caps and more lesion mass than native arteries (5). The PCI remains the first revascularization method employed in SVG diseases. The PCI to SVG constitutes 5% to 10% of total PCIs (6). Percutaneous SVG procedures provide numerous problems, including slow or no-reflow, distal embolization, type 4a/5 myocardial infarction (MI), and restenosis(7). The no-reflow phenomenon (NRP) may occur during native vessel PCI or, more typically, during SVG PCI (8). While certain studies reported a 4% incidence of NRP in SVG PCIs, the most recent publications reported it to be up to 15% occurrence (8).

The systemic immune inflammation index (SII) is a new inflammatory marker index composed of neutrophils, lymphocytes, and platelets that has been investigated in the last decade. It is a more sensitive metric in evaluating the patient's

inflammatory status due to the inclusion of three inflammatory factors in a single index and the ease with which it can be assessed in whole blood with a single laboratory test. Moreover, it has been illustrated in numerous SII studies to be a strong and independent prognostic predictor of poor outcomes in most forms of cancer (9). Some studies have demonstrated that SII is superior to other inflammatory markers, such as neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR), in diagnosing coronary artery disease, which develops as a consequence of inflammation (10). The NRP can impact the success rate even in a technically flawless PCI, which can be annoying. However, no study in the literature demonstrated a link between SII levels and the development of NRP in patients who underwent primary PCI to SVG. Before the procedure, there is no specific parameter or index that can assess a significant factor, such as NRP, that has a direct impact on the success of the PCI. Therefore, the present study aimed to examine the link between SII and NRP following SVG PCI.

2. Objectives

The aim of the present investigation was to evaluate the relationship between SII and NRP in patients who underwent PCI for saphenous vein graft (SVG).

3. Methods

3.1. Study design and participants

In this retrospective cohort study, between January 2014 and December 2021, 426 consecutive patients with CABG underwent PCI/percutaneous transluminal coronary angioplasty (PTCA) on saphenous graft at Ankara City Cardiovascular Hospital and Ankara Yüksek Ihtisas Training and Research Hospital, Turkey, were selected. The number of 92 patients who met the exclusion criteria (severe kidney disease, use of anticoagulation, anemia, infection, and steroid use) were excluded from the study. Another 22 patients were excluded from the group due to missing data. Finally, a total of 312 patients were included in the study (Figure 1).

The reperfusion rates after PCI were evaluated according to the thrombolysis in myocardial infarction (TIMI) grade flow and myocardial blush grade (MBG). Following the procedure, those with an angiographic TIMI flow grade of ≤ 2 or TIMI flow grade of 3 and a final MBG of < 2 were considered NRP (5).

Comparative tables were made by categorizing the patients according to the presence and absence of NRP. Clinical data such as localization of the treated SVG vessel, type and length of stent placed, duration and nature of pain in the anamnesis, Killip score, time to discharge, and in-hospital death were collected through patient files and the in-hospital electronic

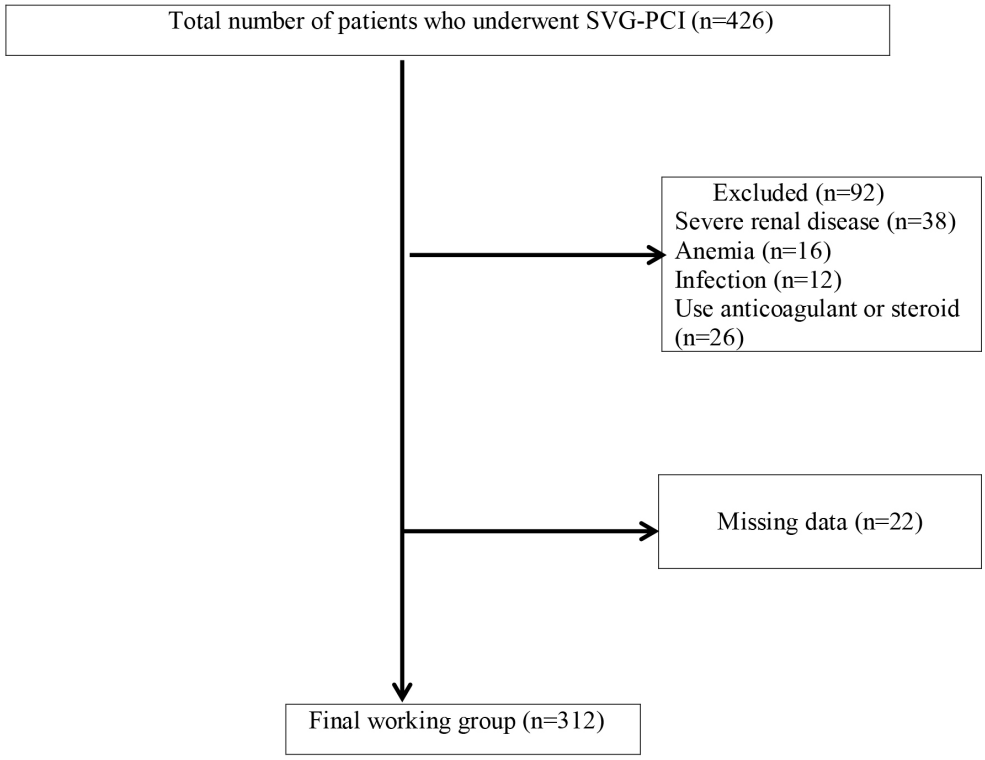

Figure 1. Flowchart of the study

system. The 1-year survival of the patients and the status of the patients who had passed at least 1 year after the operation were checked over the phone and via a different system affiliated with the Ministry of Health. The Killip classification was made by the cardiologist who first saw the patient. Specifically, Killip Class I patients had no evidence of heart failure. Killip Class II patients had mild heart failure with rales involving one-third or less of the posterior lung fields and systolic blood pressure of 90 mm Hg or higher. Moreover, Killip Class III patients had pulmonary edema with rales involving more than one-third of the posterior lung fields and systolic blood pressure of 90 mm Hg or higher. Finally, Killip Class IV patients had cardiogenic shock with any rales and systolic blood pressure lower than 90 mm Hg (11).

3.2. Systemic immune inflammation index (SII)

Routine blood samples were taken from the patients at the time of admission. Whole blood parameters included hemoglobin, platelet count, white blood cell count, and total neutrophil and lymphocyte counts. As in previous studies, NLR was calculated as the ratio of total neutrophil to lymphocyte count, and SII was calculated as the ratio of the product of the total neutrophil count and the total platelet count to the lymphocyte count (12).

3.3. Ethical consideration

The study protocol was approved by the academic and ethical committee of the Ankara City Hospital, Turkey (E2-22-2774). The local ethics board and all participating patients approved the research protocols regarding the Declaration of Helsinki.

3.4. Statistical analysis

The SPSS software (version 21.0, SPSS Inc., Chicago, Illinois, USA) was used to perform statistical analysis. Continuous variables were defined as means ± standard deviation or median (range), and categorical variables were expressed as percentages. The Kolmogorov-Smirnov test was employed to define the normality of the distribution. Categorical variables were compared with the Chi-square or Fisher's exact test, and continuous variables were compared with the Mann-Whitney-*U* test or Student t-test. The logarithm of SII was taken for the regression analysis since the SII variables were not normally distributed. Independent predictors of NRP were found using the multivariate logistic regression analysis. The multivariate model contained all significantly associated variables based on the P-value of the univariate regression analyses (P<0.05). Receiver operating characteristics (ROC) curve analysis defined the optimum cut-off point of SII to estimate NRP. A P<0.05 was considered statistically significant.

4. Results

A total of 312 patients were included in the study; 27.2% had no-reflow (n=85). In both groups, there was no difference in age and gender between the NRP group and the normal reflow group. In addition, there was a significant difference between the two groups regarding ACS type (P<0.001). Demographic, clinical, and laboratory characteristics were compared between the groups with NRP and normal reflow (Table 1). Neutrophile and platelet counts and SII were significantly higher in the NRP compared to the normal flow group. On the contrary, left ventricular ejection fraction (LVEF) (%) and lymphocyte count were lower in the NRP group. On the other hand, there was no significant difference between the two groups regarding medications, comorbidities, and other laboratory parameters (Table 1).

Table 1. Some demographic and laboratory characteristics

Variables	No-reflow (-) (n=227)	No-reflow (+) (n=85)	P-value
Demographics			
Age (year)	66.50 ± 10.34	65.45 ± 10.04	0.418 [1]
Gender (male)	178 (78.4%)	69 (81.2%)	0.591 [2]
ACS type			**< 0.001** [2]
Elective	121 (53.3%)	30 (35.3%)	
STEMI	20 (8.8%)	23 (27.1%)	
NSTEMI	86 (37.9%)	32 (37.6%)	
Comorbidity			
Diabetes mellitus	96 (42.5%)	45 (52.9%)	0.099 [2]
Hypertension	150 (66.4%)	55 (64.7%)	0.782 [2]
Heart failure	54 (23.8%)	21 (24.4%)	0.916 [2]
Smoking	72 (31.7%)	33 (39.7%)	0.214 [2]
Treatments			
Statin	212 (93.4%)	76 (89.4%)	0.240 [2]
Acetyl salicylic acid	219 (96.5%)	81 (95.3%)	0.629 [3]
Clopidogrel	189 (83.6%)	67 (79.5%)	0.408 [2]
Biochemical tests			
Glucose (mg/dl)	118.50 (62.00-400.00)	127.00 (78.00-335.00)	0.075 [4]
Urea (mg/dl)	37.00 (15.00-118.00)	34.00 (14.00-113.00)	0.122 [4]
Creatinine (mg/dl)	1.00 (0.50-2.30)	3.80 (2.70-4.70)	**0.024** [4]
Albumin (gr/dl)	3.90 (2.40-39.00)	3.7 (3.5-3.9)	0.747 [4]
Total protein (gr/dl)	6.90 (5.00-74.00)	6.80 (4.80-64.00)	0.564 [4]
Admission Troponin (ng/l)	0.04 (0.00-44.00)	0.70 (0.03-125.00)	**< 0.001** [4]

Table 1 Continue			
Peak CK MB (ng/ml)	18.00 (3.30-199.00)	35.00 (14.00-250.00)	**< 0.001** [4]
Sedimentation (mm/h)	12.00 (4.00-129.00)	12.50 (1.00-97.00)	0.834 [4]
LDL-C (mg/dl)	104.00 (32.00-622.00)	118.00 (41.00-287.00)	0.029 [4]
Triglyceride (mg/dl)	145.00 (40.00-1666.00)	141.00 (55.00-1420.00)	0.880 [4]
HDL-C (mg/dl)	41.00 (6.70-96.00)	40.00 (21.00-259.00)	0.540 [4]
Total cholesterol (mg/dl)	174.00 (5.00-700.00)	189.00 (109.00-579.00)	**0.009** [4]
CRP (mg/dl)	4.00 (0.20-123.60)	7.50 (0.30-146.00)	0.414 [4]
Blood parameters			
WBC (K/μL) × 10^3)	10.60 (4.70-25.00)	11.80 (6.90-17.00)	**< 0.001** [4]
Neutrophile (K/μL) × 10^3)	5.70 (1.90-14.20)	9.10 (3.70-19.70)	**< 0.001** [4]
Lymphocyte (K/μL) × 10^3)	2.70 (1.00-8.90)	1.62 (0.20-9.00)	**< 0.001** [4]
Platelets (K/μL) × 10^3)	200914.32 ± 69807.89	232435.29 ± 66136.12	**< 0.001** [1]
Hemoglobin (g/dL)	13.59 ± 1.84	13.54 ± 1.68	0.857 [1]
Hematocrit (%)	41.16 ± 5.72	39.19 ± 9.34	0.088 [1]
Monocytes (K/μL) × 10^3)	0.70 (0.10-8.50)	0.60 (0.30-1.10)	0.718 [4]
MPV (fl)	9.56 ± 1.30	9.42 ± 1.06	0.475 [1]
SII × 10^3	12.85 (10.86-14.94)	14.15 (11.71-16.71)	**< 0.001** [4]
LVEF (%)	46.92 ± 10.25	43.59 ± 9.70	**0.015** [1]

ACS: Acute coronary syndrome, STEMI: ST elevation myocardial infarction, NSTEMI: non-ST elevation myocardial infarction, LVEF: Left ventricular ejection fraction, HDL-C: High-density lipoprotein cholesterol, Ldl-C: Low-Density lipoprotein cholesterol, CRP: C-reactive protein, WBC: White blood cell, MPV: Mean platelet volume, SII: Systemic immune inflammation index. Statistical tests used: [1] Student's t-test, [2] Chi-square test, [3] Fisher's exact test, [4] Mann-Whitney *U* test.

Angiographic and procedural characteristics and outcomes are indicated in Table 2. Stent type differed between both groups (P=0.033). In addition, stent length, in-hospital mortality, duration of hospital stay, and one-year mortality were higher in the NRP group compared to the normal flow group. However, the duration of pain was higher in the normal reflow group. There was no difference between the two groups regarding the location of the saphenous graft and Killip score.

Presentation with ST-elevation myocardial infarction (STEMI) and SII was associated with NRP development in univariate logistic regression analysis. The authors evaluated both variables with multivariate logistic regression analysis. Presentation with a higher SII (odds ratio [OR]: 7.812, 95% confidence interval [CI]: (3.672-16,619), P<0.001) and STEMI (odds ratio [OR]: 5.419, 95% confidence interval [CI]: (1.663-17.657), P=0.005) were independent predictors of NRP development (Table 3). The area under the ROC was constructed for the SII (area under the curve [AUC]: 0.866, 95% confidence interval [CI]: (0.823-0,910, P<0.001), which was an independent predictor of NRP. Using a cut-off point of 13.45, SII predicted NRP with a sensitivity of 86% and a specificity of 80% (Figure 2).

Table 2. Angiographic and procedural characteristics and outcomes

Variables	No-reflow (-) (n=227)	No-reflow (+) (n=85)	P-value
Location of the saphenous graft			0.258 [1]
RCA	96 (42.3%)	45 (52.9%)	
Diagonal	30 (13.2%)	4 (4.7%)	
Cx	31 (13.7%)	9 (10.6%)	
LAD	10 (4.4%)	4 (4.7%)	
Obtuse marginalis	59 (26.0%)	23 (27.1%)	
Procedural data			
Stent type			**0.033** [1]
DES	113 (49.8%)	30 (35.2%)	
BMS	114 (50.2%)	55 (64.8%)	
Stent length (mm)	20.00 (8.00-89.00)	24.50 (8.00-83.00)	**0.003** [2]
Duration of pain (hour)	4.00 (0.10-180.00)	1.00 (0.10-60.00)	**0.002** [2]
Clinical outcomes			
Killip score			0.053 [3]
I	209 (92.1%)	72 (84.7%)	
II-III-IV	18 (7.9%)	13 (15.3%)	
In hospital mortality n (%)	0 (0.0%)	7 (8.2%)	**< 0.001** [3]
Duration of hospital stay (day)	2.00 (0.00-22.00)	3.00 (1.00-10.00)	**< 0.001** [2]
1-year mortality n (%)	15 (6.6%)	12 (14.1%)	**0.036** [1]

LAD: Left anterior descending artery; Cx: Circumflex artery; RCA: Right coronary artery; DES, Drug-eluting stent; BMS, bare metal stent. Statistical tests used: [1] Chi-square test, [2] Mann-Whitney *U* test, [3] Fisher's exact test.

Table 3. Univariate and multivariate regression analysis for predictors of no-reflow

Variable	Univariate Analysis			Multivariate Analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
SII	7.273	4.478-11.812	**< 0.001**	7.812	3.672-16.619	**< 0.001**
Clinic status (ref: elective)						
STEMI	4.638	2.257-9.532	**< 0.001**	5.419	1.663-17.657	**0.005**

SII: Systemic Immune–Inflammation Index, STEMI: ST-elevation myocardial infarction, CI: confidence interval; P < 0.05 demonstrates the statistical significance

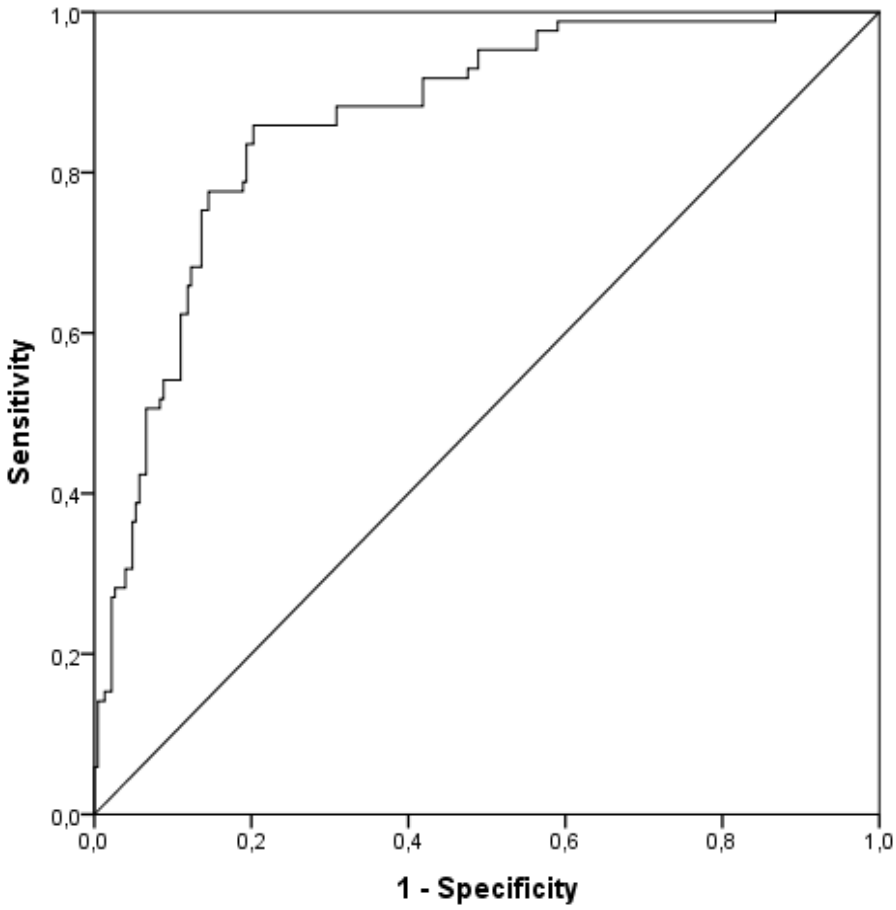

Figure 2. ROC curves for SII for the no-reflow phenomenon. AUC: Area under the curve

5. Discussion

A thorough literature review revealed no study on the relationship between NRP and SII in patients who underwent saphenous PCI. Consequently, SII was an independent predictor for NRP in patients with CABG.

The number of patients revascularized by CABG has increased in tandem with the increase in the patient population diagnosed with coronary artery disease (CAD). We have gained the ability to recognize and intervene early in more people with coronary diseases thanks to the advancement of coronary imaging methods in recent years, which resulted in a variety of issues. Saphenous interventions are more challenging and unfavorable in CABG patients due to longer intervention duration, more opaque delivery than native vein PCI, as well as graft and catheter incompatibility. Along with interventions to SVGs, many negative and undesirable complications, such as NRP, have been encountered more often (8).

The term NRP refers to inadequate myocardial tissue perfusion following a transient period of ischemia without signs of a mechanical obstruction, such as a dissection, spasm, or thrombus in the epicardial artery (8). Although NRP was reported in 2-5% of all PCI patients, the risk in acute coronary syndrome (ACS) patients approached 30% (13). The combination of ACS and saphenous vein interventions may increase the risk of NRP (13). It is a serious problem for interventional cardiologists as no specific treatment exists for this condition. Current procedural and pharmacological strategies have limited success in preventing and managing NRP when it occurs (4). Some methods to prevent NRP are direct stenting without predilation, short stent use, embolism protection devices, and excimer laser (4). Pharmacologically, there are limited studies on agents, such as adenosine to the distal bed, nicardipine, and nitroprusside (4).

In the present study, the rate of NRP was greater in ACS patients. Non-ACS patients have a lower likelihood of NRP. In a study of 127 patients, Eid-Lidt et al. (3) observed NRP in 15% of unselected saphenous PCI, while in another publication with 205 patients, this proportion was determined to be 18% (14). The NRP incidence was 27% for the patient population in the present investigation.

Previous studies demonstrated that NRP is an independent predictor of increased in-hospital mortality and is linked to heart failure and malignant arrhythmias resulting from prolonged acute ischemia (5). A prolonged no-reflow/slow flow has a poor prognosis (4). The correlation of NRP with mortality

after postprocedural cardiovascular treatments and the paucity of a therapeutic option has driven cardiologists to comprehend the pathophysiology of NRP better, resulting in new investigations. Although not thoroughly explained, the authors have indicated the potential mechanisms that could result in NRP (15, 16). It is currently unknown why some patients with similar risk factors who present with ACS may develop NRP differently. In numerous studies, NRP has been linked to various inflammatory mediators across multiple patient groups (17, 18).

The neutrophil count is an independent predictor of NRP in patients with STEMI, as reported by Wang et al. (19). According to a study conducted by Dogan et al., low lymphocyte count was revealed to be an independent predictor of NRP (20). In addition, Kocas et al. reported that neutrophil lymphocyte ratio was an independent predictor of high TIMI frame count (21). It was found in our previous study that NRP was associated with the ratio of C-reactive protein to albumin (5).

Further studies are being conducted on additional patient populations, and novel prognostic markers as inflammatory predictors of abnormal coronary flow have been identified. The immunothrombosis model, divided into hemostasis and the immune system and supposed to depict inflammation more accurately, has provided new evidence (22, 23). Nevertheless, SII, a recently identified marker for inflammation, was considered to reflect patients' inflammatory and immunothrombotic statuses simultaneously.

The SII index initially emerged as a prognostic marker for various malignancies (9, 24). The ability of predicting the prognosis of the NRP with a single blood test and a single index has aroused the attention of interventional cardiologists. In the past five years, numerous studies have been conducted on the SII index.

Erdoğan et al. reported that the SII index outperformed the NLR and PLR in predicting hemodynamically severe coronary stenosis via fractional flow reserve (FFR) in patients with chronic coronary syndrome (25). The SII index was found to be a predictor of severe aortic stenosis and had a significant correlation with the aortic valve area (26). In a study by Kelesoglu et al., the SII index was indicated to be a reliable predictor of contrast nephropathy in non-ST elevation myocardial infarction (NSTEMI) patients (12). They also demonstrated that the SII index was an independent predictor for the development of coronary collateral circulation (27).

Our recent study revealed that SII is an independent predictor of postprocedural contrast nephropathy in patients undergoing transcatheter aortic valve implantation for severe aortic stenosis (28). The present research indicated that the SII index is an independent predictor of NRP in the patient population undergoing PCI to saphenous graft. In addition, the optimum cut-off point for SII was determined to be 13.45, which predicted the risk of developing NRP with 86% sensitivity and 80% specificity.

The present study has some limitations. It is unlikely to extrapolate the results of this single-center, retrospective, and cross-sectional study to the entire population. Although interventions to the saphenous vein constitute less than 10% of all percutaneous interventions, making this patient population pertinent, further studies with more patients should be conducted. Due to missing data, it is unclear to what extent the patients had predilatation.

6. Conclusion

The SII is an independent predictor that can be easily calculated from the whole blood test to predict no-reflow development, which is a frustrating complication in patients following the saphenous vein PCI. This predictor can enable us to pre-evaluate the non-operational reasons affecting the procedure's success.

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None.

Footnotes

Conflicts of Interest: The author(s) do not have any potential conflict of interest for the research, authorship and/or publication of this article.
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