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Original Article

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The relationship between the no-reflow phenomenon and the systemic immune-inflammation index in saphenous vein graft interventions

Abstract

Aim: In our retrospective study, we examined patients who underwent percutaneous intervention (PCI) for ischemia involving saphenous vein grafts (SVG). Our objective was to analyze the impact of inflammation and thrombotic events on the no-reflow phenomenon (NRP) post-intervention. For this purpose, we aimed to determine whether the Systemic Immune-Inflammation Index (SII) is a risk factor for the NRP. Patients were divided into two groups based on the occurrence of NRP, and we investigated whether there was a statistically significant difference in SII between the groups.
Materials and Methods: This retrospective study included 30 patients who had previously undergone surgical revascularization and underwent PCI on SVG due to ischemia between May 4, 2023, and July 31, 2024. Post-procedural blood flow was evaluated, and patients were divided into two groups based on the development of NRP. The relationship between NRP and SII was examined.
Results: The study demonstrated that patients who experienced the NRP had significantly higher SII levels. Additionally, the duration of the procedure was significantly longer in patients with no-reflow. Systemic risk factors, such as age, gender, and comorbidities, were similar between the no-reflow and normal flow groups.
Conclusion: This study indicates that inflammation plays a key role in determining flow outcomes following PCI. Further clinical studies focused on reducing inflammation and improving flow are needed.

Keywords: Coronary artery bypass graft, no-reflow phenomenon, percutaneous coronary intervention, systemic immune-inflammation index, inflammation

INTRODUCTION

In cases of ischemia, particularly in conditions such as acute myocardial infarction (AMI) due to coronary artery occlusion, the primary treatment method is the restoration of blood flow (1). The preferred approach for this is percutaneous coronary intervention (PCI), while coronary artery bypass grafting (CABG) offers an alternative under certain circumstances (2). During PCI, insufficient blood flow may lead to the development of the no-reflow phenomenon (NRP), a complication associated with poor clinical outcomes. NRP is the insufficiency of blood flow despite adequate mechanical patency following PCI in the coronary arteries (3). The pathophysiology of NRP is multifactorial, with contributing factors including endothelial dysfunction and an increased thrombus burden (4).

Blood flow is a combination of the pushing force from the proximal coronary artery and the pulling force from the distal region, with endothelial functions shaping the flow (5). Disruptions in these factors can impair blood flow and result in NRP. The

multifactorial nature of NRP suggests that it cannot be attributed to a single cause (6). Literature data also support the presence of complex and multifactorial pathways in the development of NRP (7). Inflammation and platelet functions, which influence atherosclerosis, also affect NRP (8). Currently, there is no specific scoring system available to predict NRP. However, the systemic immune-inflammation index (SII), calculated using platelet count and the neutrophil-to-lymphocyte ratio (NLR), provides a means to assess both thrombotic and inflammatory burden simultaneously. Previous studies have demonstrated a relationship between elevated SII and NRP during PCI (9).

It has been shown that SII, which allows for the simultaneous evaluation of the multifactorial process, is associated with NRP during PCI in coronary arteries (10). However, its effect on saphenous vein graft (SVG) interventions has not been sufficiently studied. SVGs are more prone to the development of NRP compared to native coronary arteries and carry a higher thrombus burden. It is crucial to predict the occurrence of NRP during SVG interventions (11). In this study, we aimed to investigate the predictive value of SII for NRP in AMI patients undergoing PCI on SVGs.

MATERIALS AND METHODS

This study was designed retrospectively. Patients who had previously undergone CABG and underwent PCI on SVG due to AMI at Hatay Dörtyol State Hospital between May 4, 2023, and July 31, 2024, were analyzed. The presence of an acutely thrombosed lesion in the SVG was required for inclusion. PCI was defined as the crossing of a guidewire through the culprit lesion followed by balloon angioplasty or stent implantation.

Inclusion criteria included AMI originating from the saphenous vein graft, absence of cardiogenic shock, and no stenosis greater than 50% at or beyond the anastomosis site. The exclusion criteria for the study were determined as the indication for coronary angiography being stable angina, the presence of cardiogenic shock, EF<40%, the presence of moderate or severe valve regurgitation/stenosis, failure to advance the floppy guidewire beyond the lesion during PCI, failure to perform balloon dilation or stent implantation on the SVG, and interventions performed on native coronary arteries or the anastomosis site. Patients with diffuse disease or more than 50% atherosclerotic stenosis in the native vessel after anastomosis were not included in the study. If an anastomosis of the left internal mammary artery to the left anterior descending artery was present, and PCI was performed on the LIMA, these patients were excluded from the study. Left internal mammary artery interventions were not considered as SVG interventions. After screening 82 patients, 30 met the inclusion criteria and were selected for analysis. The 52 patients who were excluded from the study had a history of CABG but met one or more of the mentioned exclusion criteria. PCI was performed using standard techniques, and all patients received appropriate medications once the decision for PCI was made. Coronary flow was assessed using the Thrombolysis in Myocardial Infarction (TIMI) scoring system (12). NRP was defined based on TIMI flow grades in post-procedural angiograms (13). Patients with TIMI flow grades of 0–2 were classified as NRP (+), while those with TIMI grades of 3 were classified as NRP (−).

Laboratory values collected included total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG). From the complete blood count, neutrophil, platelet, and lymphocyte counts were recorded, and the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated. Additional parameters, including white blood cell (WBC) count, eosinophils, hemoglobin (Hgb), monocytes, and mean platelet volume (MPV), were also recorded. Biochemical values, including creatinine, estimated glomerular filtration rate (e-GFR), C-reactive protein (CRP), albumin, glucose, total protein, and glycosylated hemoglobin (HbA1c), were documented.

The SII was calculated as platelet count × NLR. Additional potential predictors of NRP, such as the CRP/albumin ratio (CAR), mean platelet volume/lymphocyte ratio (MPLR), and monocyte/HDL-C ratio (MHR), were also calculated.

During PCI, procedural factors were recorded, including the diameter and length of the implanted stent, the coronary artery to which the SVG was anastomosed, the diameters of the SVG and the distal native vessel, the drug group used for glycoprotein (Gp) IIb/IIIa inhibition, and balloon usage. Possible factors associated with NRP, with a particular focus on SII, were investigated.

Data Management and Analyses

Statistical analyses were conducted using a commercially available software package (SPSS version 16.0, SPSS, Chicago, IL). Continuous variables were expressed as mean±SD, and categorical variables were expressed as counts and percentages. Differences were considered statistically significant at $p < 0.05$. Normality was analyzed using the Kolmogorov-Smirnov test. Homogeneity of variance was assessed using the Levene test and the Lilliefors significance correction test. For further intra-group analyses, one-way analysis of variance (ANOVA) and its nonparametric counterpart, the Kruskal-Wallis test, were used. Categorical variables were compared using the chi-square test or Fisher's exact test.

Ethical Considerations

This study was conducted in accordance with Good Clinical Practice (GCP) guidelines and the principles outlined in the Declaration of Helsinki, ensuring the protection of patient data and confidentiality. Ethical approval was obtained from the Ethics Committee of Hatay Mustafa Kemal University (approval date: August 6, 2024; approval no: 46). Since the study is retrospective in nature, written informed consent was not required for the review of patient data.

RESULTS

The study population consisted of 30 patients, 17 of whom exhibited the NRP. The results comparing the NRP (+) and NRP (−) groups are presented in Table 1. Since SII, LMR, LDL-C, TG, WBC, HbA1c, and procedural time did not follow a normal distribution, their median and minimum-maximum values were reported. Other parameters followed a normal distribution.

Table 1. Comparison of demographic, clinical, and laboratory characteristics between the NRP (+) and NRP (−) groups

Parameter	No Reflow (-) Mean±Std Dev (n=13)	No Reflow (+) Mean±Std Dev (n=17)	p
Age (year)	63.2±4.98	66.3±5.71	0.42
Male (n, %)	10, 76.92	12, 70.59	0.13
HT (n, %)	9, 69.23	13, 76.47	0.24
DM (n, %)	12, 92.31	15, 88.24	0.18
Smoker (n, %)	3, 23.08	4, 23.53	0.95
MHR	39.6±8.18	13.8±6.66	0.12
SII	1088.10 (92.05-2572.24)	4368.22 (427.40-13680.11)	**<0.001**
NLR	1.76±0.98	5.84±4.49	**0.003**
PLR	84.21±16.31	147.18±8.53	**0.018**
LMR	2948.72 (173.98-5364,58)	2251.84 (1155.74- 24333.33)	0.06
MPLR	4.41±2.09	6.38±3.59	0.09
CRP/Alb	0.21±0.04	0.46±0.24	0.12
TC (mg/dL)	202.31±52.31	186.35±50.4	0.40
LDL-C (mg/dL)	119.46 (48.08-171.30)	125.88 (80.71-202.60)	0.80
HDL-C (mg/dL)	44.85±10.21	39.88±9.64	0.18
Triglycerides (mg/dL)	179.31 (84.13-293.24)	190.88 (91.21-348.75)	0.82
WBC (10^9/L)	7.31 (3.21-13.54)	6.22 (4.67-15.68)	0.07
Hemoglobin (g/dL)	13.08±2.29	12.85±2.33	0.78
Lymphocytes (10^9/L)	3.34±2.24	2.83±3.3	0.63
Neutrophils (10^9/L)	4.55±2.08	9.79±4.64	**<0.001**
Monocytes (10^9/L)	0.588±0.21	1.61±2.77	0.19
Platelets (10^3/µL)	213.62±66.12	253.88±68.84	0.11
MPV (fL)	11.13±0.85	10.7±0.95	0.21
RDW (%)	29.72±15.49	27.03±14.86	0.63
Creatinine (mg/dL)	1.046±0.41	1.153±0.33	0.43
e-GFR (mL/min/1.73m²)	83.04±29.06	69.44±29.56	0.21
Glucose (mg/dL)	198.85±111.97	218.24±134.64	0.67
HbA1c	7.30 (4.30-10.70)	8.40 (5.20-11.70)	0.06
Stent length [mm]	13.85±10.5	13.62±8.38	0.95
Stent diameter [mm]	1.43±1.81	2.13±1.81	0.47
Procedural time (min)	73 (2.4-51.2)	87 (3.1-61.3)	0.08

CRP/Alb: C-reactive protein to albumin ratio, DM: diabetes mellitus, e-GFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, HDL-C: high-density lipoprotein cholesterol, HT: hypertension, LDL-C: low-density lipoprotein cholesterol, LMR: lymphocyte to monocyte ratio, MHR: monocyte to hemoglobin ratio, MPLR: mean platelet volume to lymphocyte ratio, MPV: mean platelet volume, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, RDW: red cell distribution width, SII: systemic immune-inflammation index, TC: total cholesterol

In terms of gender distribution, 76.92% of the patients in the NRP (−) group were male, compared to 70.59% in the NRP (+) group (p=0.132). The average age was 63.2±4.98 years in the NRP (−) group and 66.3±5.71 years in the NRP (+) group (p=0.42). No in-hospital mortality was observed.

All patients included in the study underwent PCI within the first 24 hours following hospital admission. The mean procedural time was 26.5 minutes in the NRP (+) group and 9.5 minutes in the NRP (−) group, and this difference was statistically significant (p<0.001). The use of Gp IIb/IIIa inhibitors was 100% (17) in the NRP (+) group and 23.8% (3) in the NRP (−) group, also showing statistical significance (p<0.001). In the NRP (+) group, stents were implanted in 11 patients, while in the NRP (−) group, stents were implanted in 13 patients. Balloon dilation was performed in the 6 patients in the NRP (+) group who did not receive a stent.

A total of 23 patients underwent PCI on the SVG to the right coronary artery (RCA), and 7 patients on the SVG to the left circumflex artery (LCx), with no significant difference between the two groups (p=0.51). All patients included in the study had a LIMA-LAD anastomosis. In the NRP (+) group, 3 patients had an SVG anastomosed to the diagonal artery, while in the NRP (-) group, 2 patients had such an anastomosis. All patients had SVGs to the RCA and LCx. SVGs connected to any branch of the RCA or LCx were considered as being connected to the main artery. No patients had more than one SVG to the LCx or RCA, and sequential anastomosis was not present in any of the SVGs to the LCx or RCA. The degree of atherosclerotic disease in the native vessel before the anastomosis, to which the intervened SVG was connected, was evaluated in both groups. In both groups, 2 patients had >90% stenosis before the anastomosis, while the remaining patients had chronic total occlusions. The severity of pre-anastomotic vessel disease was similar between the two groups. There was insufficient data regarding how many years prior the patients had undergone CABG surgery.

The procedural time, demographic characteristics, and distribution of risk factors, such as hypertension (p=0.24) and diabetes mellitus (p=0.18), were similar between the two groups. The NRP (+) group had significantly higher SII (p<0.001), NLR (p=0.003), and PLR (p=0.018) ratios. Among metabolic parameters, higher MHR, LMR, and MPLR ratios were observed in the NRP (+) group, although these differences were not statistically significant. There was no significant difference between the groups in parameters such as the CAR, TC, LDL-C, HDL-C, TG, WBC, Hgb, lymphocytes, monocytes, platelets,MPV, red cell distribution width, creatinine, e-GFR, HbA1c, glucose, stent length, or stent diameter.

DISCUSSION

In our study, the significantly higher levels of SII, NLR, and PLR in the NRP (+) group indicate a more pronounced inflammatory response in these patients. This suggests that patients with NRP (+) experience higher levels of inflammation and cellular stress compared to those in the normal flow group. The significantly longer procedural time in the NRP (+) group further suggests that the NRP presents greater challenges during intervention. Upon reviewing the angiographic images, it was observed that the extension of the procedure time occurred after the development of NRP. The additional interventions required to restore blood flow contributed to the prolongation of the procedure. Our study does not provide direct information on the effect of prolonged procedure time on the development of NRP during standard PCI interventions. In a study by Shiomi et al., delays in perfusion were associated with increased mortality (14). However, in our study, procedural duration was similar between the groups. The relationship between delayed PCI and the occurrence of NRP is beyond the scope of this study. Gender distribution was found to be similar between the two groups, as were systemic risk factors such as hypertension and diabetes mellitus. Previous studies have demonstrated that systemic risk factors are associated with NRP (15). Since our study population consisted of patients who had undergone CABG surgery, systemic risk factors were prevalent in both groups. We believe that the results may differ in other populations with different characteristics.

The findings of this study are consistent with similar research in the literature, confirming that inflammation markers are elevated, and procedure times are prolonged in NRP (+) patients. It is well established that inflammation plays a significant role in the pathophysiology of NRP (6). In this study, the elevated levels of inflammatory markers such as SII, NLR, and PLR further highlight the critical role of inflammation in the development of NRP. The notably high SII levels in NRP (+) patients, in particular, indicate the severity of the systemic inflammatory response.

However, the CAR did not reach statistical significance in our study. In contrast, a study conducted by Kanal et al. found that elevated CAR was associated with NRP in SVG interventions (16). This difference may be attributable to the smaller sample size in our study.

These findings suggest that patients with NRP exhibit higher levels of inflammation and cellular stress markers and require longer procedural times. Gender distribution and systemic risk factors, such as hypertension and diabetes mellitus, were similar between the two groups. Additionally, no significant differences were observed in metabolic parameters between the NRP (+) and NRP (−) groups. Patients from approximately the last year were included in our study, and the total number of patients was small. PCI strategies, antiplatelet therapy approaches, and stent technologies have evolved over the years. Including only the last year helps to achieve a more homogeneous group in terms of factors that may influence NRP. We do not recommend evaluating a broader time range. To increase the number of patients, designing and conducting multicenter studies may be more beneficial.

CONCLUSION

Our study demonstrates that inflammation plays a significant role in the development of the NRP. It is evident that treatment strategies targeting inflammation are necessary for the prevention and management of NRP. Future large-scale, prospective studies are needed to further elucidate the pathophysiology of NRP and optimize treatment approaches. This study included patients from the past year, and given the continuous advancements in drug and material technology for coronary interventions, examining more recent patient data will likely yield valuable insights in the future. The year in which the patients included in our study underwent CABG surgery was unclear. The main limitations were the lack of evaluation of additional factors such as the degree of diffuse disease in the vessels and collateral circulation.

In our study, we investigated the effect of the SII on the development of the NRP. The results indicate that elevated SII levels are associated with an increased risk of NRP. Nonetheless, further research is required to assess the impact of anti-

inflammatory treatments on the prevention and management of NRP. Such studies would provide valuable insights into the potential advantages of targeting inflammation to improve clinical outcomes associated with NRP. Moreover, previous studies have demonstrated that the administration of colchicine before CABG surgery or PCI significantly reduces post-procedural markers of myocardial injury. Its anti-inflammatory effects on atherosclerosis are also being explored (17). Investigating the potential impact of colchicine on NRP in SVG interventions may be beneficial, as its anti-inflammatory properties could aid in the management of NRP.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethical approval for this study was obtained from the Ethics Committee of Mustafa Kemal University on August 6, 2024 (Approval No: 46).

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