

## A Newly Defined Inflammatory Predictor of the Postprocedural No-Reflow/Slow-Flow Phenomenon in Patients with Non-ST Segment Elevation Myocardial Infarction: Aggregate Index of Systemic Inflammation

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### Abstract

**Objective:** This study aimed to investigate the relationship between the Aggregate Index of Systemic Inflammation (AISI) and NRF/SF development in non-ST-elevation myocardial infarction (NSTEMI) patients undergoing percutaneous coronary intervention (PCI).

**Methods:** This retrospective observational study included 1092 NSTEMI patients who underwent PCI. Complete blood count-derived inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and AISI, were calculated before PCI. AISI was calculated using the "neutrophil count x monocyte count x platelet/lymphocyte count" formula. NRF/SF was defined as post-procedural TIMI flow <3 in the absence of mechanical obstruction. The study cohort was divided into 2 groups based on a median AISI score of 298. After determining the parameters associated with NRF/SF through univariate analysis, multivariate logistic regression analysis was performed to identify independent predictors. The De-Long test was conducted to assess the discriminatory ability and predictive performance of inflammation-based indices.

**Results:** A total of 94 (8.6%) patients suffered from NRF/SF, and it was more common in patients with high AISI values compared to those with low values ( $p < 0.001$ ). Considering the inflammatory parameters, higher NLR (OR= 1.347,  $p < 0.001$ ), higher PLR (OR= 1.003,  $p = 0.017$ ), higher AISI (OR= 1.003,  $p < 0.001$ ) and lower LMR (OR= 0.713,  $p < 0.001$ ) independently predicted the NRF/SF development. De-Long test analysis revealed that AISI has better predictive performance compared to other inflammation-based scores (AUC= 0.703,  $p < 0.001$ ).

**Conclusion:** As an independent predictor of the NRF/SF phenomenon, AISI can serve as a practical and cost-effective biomarker for the early diagnosis of high-risk patients.

**Keywords:** Aggregate index of systemic inflammation; inflammation; myocardial infarction; no-reflow.

## ST Segment Yükselmesiz Miyokard Enfarktüsü Olan Hastalarda İşlem Sonrası No-Reflow Fenomeni Gelişiminin Yeni Tanımlanmış Enflamatuvar Belirteci: Sistemik Enflamasyonun Agregasyon İndeksi

### Özet

**Amaç:** Bu çalışma, perkütan koroner girişim (PKG) uygulanan ST segment yükselmesiz miyokard enfarktüsü (STYzMI) hastalarında Sistemik Enflamasyon Agregasyon İndeksi (AISI) ile no-reflow/slow flow (NRF/SF) gelişimi arasındaki ilişkiyi araştırmayı amaçlamıştır.

**Yöntem:** Bu retrospektif gözlemsel çalışmaya, PKG uygulanan 1092 STYzMI hastası dahil edildi. PKG öncesinde, nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR), lenfosit-monosit oranı (LMR) ve AISI'yi

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içeren enflamasyon temelli indeksler hesaplandı. AISI, "nötrofil sayısı x monosit sayısı x trombosit/lenfosit sayısı" formülü kullanılarak hesaplandı. NRF/SF, mekanik obstrüksiyon olmaksızın işlem sonrası TIMI akımın <3 olması olarak tanımlandı. Çalışma kohortu, ortalama AISI skoru (298) baz alınarak 2 gruba ayrıldı. Tek değişkenli analiz yoluyla NRF/SF ile ilişkili parametreler belirlendikten sonra, bağımsız öngörücüleri belirlemek için çok değişkenli lojistik regresyon analizi yapıldı. Enflamasyon temelli indekslerin ayırt edici yeteneğini ve tahmin performansını değerlendirmek için De-Long testi uygulandı.

**Bulgular:** Toplam 94 (%8,6) hastada NRF/SF gelişmiş olup, düşük AISI grubuna kıyasla yüksek AISI grubunda istatistiksel olarak anlamlı derecede daha fazlaydı ( $p < 0,001$ ). Enflamatuvar parametreler dikkate alındığında, daha yüksek NLR (OR= 1.347,  $p<0.001$ ), daha yüksek PLR (OR= 1.003,  $p=0.017$ ), daha yüksek AISI (OR= 1.003,  $p<0.001$ ) ve daha düşük LMR (OR= 0.713,  $p<0.001$ ) bağımsız olarak NRF/SF gelişimini öngördü. De-Long testi analizi, AISI'nin diğer enflamasyon bazlı skorlara kıyasla daha iyi tahmin performansına sahip olduğunu ortaya koydu (AUC=0.703,  $p<0.001$ ).

**Sonuç:** NRF/SF fenomeninin bağımsız bir öngörücüsü olarak AISI, yüksek riskli hastaların erken teşhisi için pratik ve uygun maliyetli bir biyobelirteç görevi görebilir.

**Anahtar sözcükler:** Sistemik inflamasyonun agregasyon indeksi; enflamasyon; miyokard infarktüsü; no-reflow.

## Introduction

Non-ST-elevation myocardial infarction (NSTEMI) accounts for approximately two-thirds of all acute coronary syndrome (ACS) presentations and is characterized by myocardial necrosis without persistent ST-segment elevation.<sup>[1,2]</sup> It is most often caused by partial thrombotic occlusion or distal embolization following plaque rupture or erosion.<sup>[3]</sup> Despite early invasive strategies, NSTEMI continues to be associated with substantial morbidity and mortality.<sup>[1]</sup>

Percutaneous coronary intervention (PCI) is the cornerstone of reperfusion in NSTEMI.<sup>[4]</sup> However, even after successful epicardial recanalization, some patients exhibit inadequate tissue-level perfusion, a condition termed no-reflow (NRF) or slow-flow (SF) phenomenon.<sup>[5]</sup> NRF corresponds to complete failure of microvascular reperfusion (TIMI flow 0–1), whereas SF is defined by delayed distal opacification (TIMI 2) despite the absence of angiographic obstruction.<sup>[5,6]</sup> Both are linked to larger infarct size, left ventricular dysfunction, and higher mortality.<sup>[6–9]</sup>

Multiple mechanisms contribute to NRF/SF, including distal microembolization, endothelial injury, vasospasm, platelet activation, and ischemia-reperfusion damage.<sup>[10,11]</sup> Inflammatory processes act as a central upstream driver in the development and progression of these pathophysiological pathways. Moreover, inflammation is integral to atherosclerotic disease, and growing evidence indicates that an increased inflammatory burden is linked to a higher incidence of adverse cardiovascular events among patients with ACS.<sup>[12]</sup> In recent years, evidence has increasingly pointed to systemic inflammation as a major determinant of microvascular dysfunction.<sup>[12–16]</sup>

Several inflammation-based scoring systems have been investigated in relation to NRF/SF and are well-documented in the literature. Among these, inflammatory indices derived from routine complete blood count, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have been identified as independent predictors of poor coronary flow and adverse cardiac events.<sup>[17–20]</sup> However, these indices reflect only single aspects of the inflammatory process. The Aggregate Index of Systemic Inflammation (AISI) offers a broader evaluation of systemic inflammation and thrombotic activity. AISI has been

shown to predict mortality and major adverse cardiac events in patients with heart failure and ACS.<sup>[21,22]</sup> Nevertheless, its role in predicting post-PCI NRF/SF in NSTEMI remains unclear. This study aimed to evaluate the association between AISI and the development of NRF/SF after PCI in NSTEMI patients and to compare its predictive performance with NLR, PLR, and LMR.

## Materials and Methods

### Study Population

The patient cohort consisted of 1,092 patients presenting with NSTEMI who were retrospectively identified from a single-center PCI cohort covering January 2021 to December 2023. The diagnosis was established according to the current guidelines.<sup>[1,2]</sup>

Patients with a history of coronary artery bypass grafting or those who have undergone PCI on a saphenous vein graft, stent thrombosis or restenosis, history of MI and primary PCI within 1 year, active infection, any malignancy, hematologic or autoimmune disorders, chronic inflammatory diseases, or missing data were excluded. Demographic, clinical, laboratory, and angiographic data were obtained from the hospital electronic database.

This study was retrospective in design; therefore, written informed consent from participants was not obtained. The study was carried out in compliance with the Declaration of Helsinki and received approval from the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee. (No: 2025-04-02, date: 05.12.2025)

### Angiographic Evaluation

All coronary angiographies were performed using the Judkins technique. PCI procedures were carried out using standard protocols with drug-eluting stents. Coronary flow was classified according to the Thrombolysis in Myocardial Infarction (TIMI) grading system.

The NRF/SF phenomenon was defined as post-procedural TIMI flow <3 despite the absence of residual stenosis, spasm, or dissection. All angiograms were independently reviewed by two experienced interventional cardiologists who had no knowledge of the patients' data, and discrepancies were resolved by consensus.

## Laboratory Measurements

Peripheral venous blood was drawn from the antecubital region at the time of hospital admission, prior to the index PCI procedure. These samples were processed for routine hematological evaluation, including complete blood count measurements, and were simultaneously used for the assessment of standard biochemical parameters as part of the baseline laboratory work-up. All laboratory analyses were performed before coronary intervention to ensure that the measured values reflected the patients' preprocedural inflammatory and metabolic status. Laboratory measurements of blood samples were carried out using fully automated hematological and biochemical analyzer platforms in accordance with standard clinical procedures. Complete blood count-derived inflammatory indices; (i) neutrophil to lymphocyte ratio (NLR); (ii) platelet to lymphocyte ratio (PLR); (iii) lymphocyte to monocyte ratio (LMR); (iv) aggregate index of systemic inflammation (AISI) is calculated by multiplying the counts of neutrophils, monocytes, and platelets and then dividing the product by the lymphocyte count (neutrophil  $\times$  monocyte  $\times$  platelet) / lymphocyte).

To assess the effect of systemic inflammation, patients were categorized into two subgroups based on a median AISI score of 298: a lower AISI group ( $\leq 298$ ) and a higher AISI group ( $> 298$ ). Baseline clinical, laboratory, and angiographic characteristics were compared between these subgroups, as well as between patients with and without NRF/SF.

## Statistical Analysis

Numeric data were summarized as mean  $\pm$  standard deviation when normality assumptions were met, whereas non-Gaussian distributed data were presented as median and interquartile range. Nominal or ordinal variables were presented as proportions and compared between groups using the chi-square test. The distributional characteristics of variables measured on a continuous scale were evaluated using skewness and kurtosis statistics. Depending on the distribution characteristics, intergroup comparisons were performed using either the Student's t-test or the Mann–Whitney U test. Parameters demonstrating an association with the occurrence of the NRF/SF phenomenon in univariable analyses were subsequently entered into a multivariable logistic regression model. Effect estimates were reported as odds ratios (OR) with corresponding 95% confidence intervals (CI). To minimize the risk of overfitting, an event-per-variable ratio of at least 10 was maintained, and only variables achieving a univariate p-value  $< 0.05$  were considered for multivariable modeling. Multicollinearity among covariates was evaluated using the variance inflation factor, with values  $< 5$  considered acceptable. The discriminative performance of AISI, NLR, PLR, and LMR for predicting NRF/SF development was assessed using receiver operating characteristic (ROC) curve analysis, with diagnostic accuracy quantified by the area under the curve and corresponding 95% confidence intervals. An AUC value  $\geq 0.70$  was interpreted as acceptable discriminatory ability, whereas values below this threshold were considered insufficient.<sup>[23]</sup> Comparison of the

discrimination abilities of the above-mentioned inflammatory markers in determining the development of NRF/SF was performed by pairwise comparison of ROC curves using the method of DeLong. The optimal cut-off point was determined by maximizing the combined diagnostic performance, defined as the point at which the sum of sensitivity and specificity was highest, in accordance with the Youden index criterion. The threshold for statistical significance was accepted as  $p < 0.05$ . All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 software program (IBM Corp., Armonk, NY, USA). Comparisons of ROC curves of the inflammation-based scores and determination of cut-off value were performed using the MEDCALC software program (MedCalc Software bv, Ostend, Belgium).

## Results

This retrospective study included 1092 patients with NSTEMI, of whom 812 were male (74.4%), with a mean age of  $61.9 \pm 12.5$  years. 94 patients (8.6%) suffered from NRF/SF development. Individuals with higher AISI values appeared to have a higher history of HF ( $p = 0.017$ ), more severe CAD ( $p = 0.014$ ), and suffered from more NRF/SF development ( $p < 0.001$ ), while there were no significant differences among other demographic and clinical parameters (Table 1).

Comparative analysis of laboratory findings revealed distinct differences in hematological profiles across the AISI strata. Patients classified within the higher AISI category demonstrated significantly elevated counts of white blood cells (WBC), neutrophils, monocytes, and platelets, accompanied by a relative reduction in lymphocyte levels with markedly increased NLR and PLR values, along with lower LMR values in the high AISI group, with all comparisons reaching strong statistical significance ( $p < 0.001$ ). In contrast, assessment of routine biochemical parameters did not show meaningful variation between the groups, indicating that the observed differences were predominantly driven by inflammatory cell-related hematological indices rather than biochemical abnormalities (Table 2).

In univariate analysis, variables significantly associated with NRF/SF were age, diabetes, hypertension, smoking, LVEF, SYN-TAX and GRACE scores, WBC and all inflammatory-based scores including NLR, PLR, LMR and AISI ( $p < 0.05$ ) (Table 3). In order to determine the independent predictors for NRF/SF development, multivariate logistic regression analyses were performed. Additionally, to prevent collinearity, four separate multivariate logistic regression models were constructed. Each model contained one inflammatory-based index with clinical covariates significant in univariate analysis, enabling assessment of the independent predictive value of each index. Among the clinical parameters, smoking, LVEF, and GRACE were found to be independent predictors of NRF/SF in all models. In terms of inflammatory parameters, higher NLR (OR= 1.347,  $p < 0.001$ ), higher PLR (OR= 1.003,  $p = 0.017$ ), higher AISI (OR= 1.003,  $p < 0.001$ ) and lower LMR (OR= 0.713,  $p < 0.001$ ) independently predicted the NRF/SF development (Table 4). Furthermore De-Long test revealed that AISI had better and superior dis-

**Table 1. Demographic and clinical parameters of the study cohort grouped according to low and high AISI values**

Variables	All population (n= 1092)	Low AISI* (≤ 298; n= 546)	High AISI* (> 298; n= 546)	p
Male gender, n %	812 (74.4)	402 (73.6)	410 (75.1)	0.579
Age, years	61.9±12.5	62.6±12.6	61.2±12.4	0.068
BMI, (kg/m <sup>2</sup> )	27.7±3.3	27.6±3.3	27.7±3.2	0.583
Hypertension, n (%)	669 (61.3)	347 (63.6)	322 (59.0)	0.120
Diabetes, n (%)	380 (34.8)	193 (35.3)	187 (34.2)	0.703
Hyperlipidemia, n (%)	512 (46.9)	252 (46.2)	260 (47.6)	0.628
Smoking, n (%)	480 (44.0)	232 (42.5)	248 (45.4)	0.329
Family history, n (%)	388 (35.5)	199 (36.4)	189 (34.6)	0.527
CAD history, n (%)	457 (41.8)	230 (42.1)	227 (41.6)	0.854
Previous MI, n (%)	321 (29.4)	161 (29.5)	160 (29.3)	0.947
PCI history, n (%)	341 (31.2)	169 (31.0)	172 (31.5)	0.845
Heart Failure, n (%)	192 (17.6)	81 (14.8)	111 (20.3)	0.017
CRF history, n (%)	135 (12.4)	74 (13.6)	61 (11.2)	0.232
Killip III-IV, n (%)	92 (8.4)	49 (9.0)	43 (7.9)	0.513
Hemodynamic instability, n (%)	24 (2.2)	15 (2.8)	9 (1.6)	0.214
Grace score	98.1±22.7	99.1±23.0	97.2±22.5	0.173
LVEF, %	51.4 ±9.6	51.5 ±9.6	51.3 ± 9.7	0.695
Medications, n (%)				
Acetylsalicylic acid	390 (35.7)	192 (35.2)	198 (36.3)	0.705
ADP blockers	129 (11.8)	65 (11.9)	64 (11.7)	0.925
Beta-Blockers	322 (29.5)	159 (29.1)	163 (29.9)	0.791
RAS Blockers	496 (45.4)	260 (47.6)	236 (43.2)	0.145
CCBs	425 (38.9)	218 (39.9)	207 (37.9)	0.495
Statin	242 (22.2)	114 (20.9)	128 (23.4)	0.308
Antianginals	108 (9.9)	60 (11.0)	48 (8.8)	0.224
Syntax score	20.1±6.0	19.7±5.8	20.6±6.3	0.014
TIMI <3 flow, n (%)	94 (8.6)	26 (4.8)	68 (12.5)	<0.001
Nonfatal MI, 30 days, n (%)	21 (1.9)	8 (1.5)	13 (2.4)	0.271
CV-caused mortality, 30 days, n (%)	5 (0.5)	2 (0.4)	3 (0.5)	0.654

\*: Low and high AISI values were determined according to the median value. BMI: Body mass index; CAD: Coronary artery disease; MI: Myocardial infarction; PCI: Percutaneous coronary intervention; CRF: Chronic renal failure; LVEF: Left ventricular ejection fraction; GRACE: The Global Registry of Acute Coronary.

crimutory ability (AUC 0.703, 95% CI 0.651–0.754,  $p < 0.001$ ) than other inflammatory-based scores (Fig. 1). ROC curve analysis also identified an AISI threshold exceeding 543 as the optimal discriminative value for predicting NRF/SF occurrence, yielding 47% sensitivity and 83% specificity.

## Discussion

The main finding of the current study is that elevated AISI values independently predict NRF/SF in NSTEMI patients undergoing PCI. Compared to other inflammation-based indices, AISI was the only inflammatory parameter with adequate and best discriminatory ability and better predictive performance.

In the setting of acute myocardial infarction, the primary goal of PCI is to achieve complete epicardial reperfusion. Nevertheless, a subset of patients with NSTEMI experience persistent

impairment of myocardial microcirculation despite successful epicardial recanalization, a condition referred to as no-reflow or slow-flow.<sup>[24]</sup> This phenomenon substantially attenuates the clinical efficacy of PCI and has been consistently associated with unfavorable outcomes. The presence of NRF/SF is linked to ongoing myocardial injury, maladaptive ventricular remodeling, and an increased risk of short- and long-term mortality, underscoring its role as a significant and unresolved complication of contemporary PCI strategies.<sup>[6,8,24,25]</sup>

NRF/SF is a complex and multifactorial clinical condition that can arise as a result of numerous factors leading to distal microvascular occlusion, endothelial damage, and reperfusion-induced oxidative stress.<sup>[24,26]</sup> Although the underlying mechanisms remain incompletely understood, several mechanisms have been proposed that act independently or in combination

**Table 2. Laboratory parameters of the study cohort grouped according to low and high AISI values**

Variables	All population (n= 1092)	Low AISI* (≤ 298; n= 546)	High AISI* (> 298; n= 546)	p
Glucose (mg/dL)	112.4 ± 26.7	111.9±24.1	112.9±29.0	0.507
eGFR (mL/min/1.73 m <sup>2</sup> )	81.2±23.6	80.5±24.2	81.9±23.0	0.319
Albumin (g/dL)	3.9±0.5	3.9±0.5	3.9±0.4	0.395
CRP (mg/dL, IQR)	5.3 [3.4–8.2]	5.1 [3.3–8.4]	5.3 [3.5–8.1]	0.983
Troponin I (ng/mL, IQR)	0.06 [0.02–0.21]	0.06 [0.02–0.19]	0.06 [0.02–0.22]	0.103
TC (mg/dL)	192.1±41.5	191.4±42.5	192.7±40.5	0.618
LDL-C (mg/dL)	116.3±35.6	116.1±35.8	116.4±35.3	0.864
HDL-C (mg/dL)	39.2±10.0	39.4±10.3	39.1±9.7	0.592
Triglyceride (mg/dL, IQR)	124.0 [100.0–172.8]	123.0 [101.0–171.3]	124.5 [100.0–173.3]	0.743
Haemoglobin (g/dL)	13.5±1.8	13.6±1.8	13.3±2.2	0.188
WBC (10 <sup>9</sup> /L)	8.5±2.1	7.9±1.8	9.1±2.2	<0.001
Neutrophil (10 <sup>9</sup> /L)	5.1±1.7	4.2±1.2	5.8±1.7	<0.001
Lymphocyte (10 <sup>9</sup> /L, IQR)	2.1 [1.7–2.6]	2.2 [1.9–2.8]	1.9 [1.5–2.5]	<0.001
Monocyte (10 <sup>9</sup> /L, IQR)	0.5 [0.4–0.7]	0.5 [0.4–0.6]	0.6 [0. –0.7]	<0.001
Platelet (10 <sup>9</sup> /L)	251.9±70.5	228.5±62.0	275.3±70.8	<0.001
NLR (IQR)	2.3 [1.8–3.1]	1.9 [1.5–2.4]	2.9 [2.3–3.7]	<0.001
PLR (IQR)	117.3 [88.0–159.6]	98.4 [75.8–127.2]	141.0 [106.9–187.2]	<0.001
LMR (IQR)	3.9 [3.0–5.1]	4.9 [4.0–6.3]	3.2 [2.4–3.9]	<0.001
AISI (IQR)	298.5 [204.2–476.7]	204.3 [151.7–247.9]	476.2 [358.6–638.7]	<0.001

eGFR: Estimated glomerular filtration rate; CRP: C-reactive protein; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; WBC: White blood count.

**Table 3. Univariate logistic regression analysis of all parameters associated with NRF/SF**

Variables	OR (95% CI)	p	Variables	OR (95% CI)	p
Hypertension	1.728 (1.080–2.762)	0.022	WBC	1.163 (1.061–1.275)	<0.001
Diabetes	1.654 (1.080–2.533)	0.021	NLR	1.375 (1.189–1.591)	<0.001
Smoking	1.729 (1.128–2.648)	0.012	PLR	1.004 (1.001–1.006)	0.008
LVEF, %	0.974 (0.955–0.994)	0.011	LMR	0.693 (0.593–0.811)	<0.001
Syntax score I	1.038 (1.006–1.072)	0.020	AISI	1.003 (1.002–1.004)	<0.001
GRACE	1.011 (1.002–1.020)	0.017			

NRF/SF: no-reflow/slow flow; OR: Odds ratio; CI: Confidence interval; LVEF: Left ventricular ejection fraction; GRACE: The Global Registry of Acute Coronary Events; WBC: White blood count; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; AISI: Aggregate index of systemic inflammation.

in the development of NRF/SF, including distal embolization of thrombotic debris, prolonged myocardial ischemia and damage, leukocyte infiltration, vasoconstriction, activation of inflammatory pathways, and cellular edema.<sup>[7,9,24,26,27]</sup> Systemic inflammation is one of the key underlying mechanisms causing leukocyte adhesion, endothelial dysfunction, and platelet aggregation. Indeed, in several previous studies, endothelial injury, neutrophil accumulation, reactive oxygen species, and activation of the coagulation cascade arising from inflammation have all been linked to the development of the NRF/SF phenomenon.<sup>[25]</sup> Furthermore, literature data suggest that inflammatory biomarkers are associated with the development of NRF/SF, and that these markers may play a role in identifying individuals at risk for NRF/SF.<sup>[24–28]</sup> Also, inflammation-based markers derived from these CBC components, such as NLR, PLR and LMR, have been linked

to NRF/SF and adverse cardiac events in the setting of acute coronary syndrome.<sup>[19,24,29]</sup> In a study conducted by Wagdy et al.<sup>[29]</sup> found that higher NLR on admission are useful predictive parameter for the occurrence of NRF/SF post-primary PCI. In another one, preintervention PLR has been found to be a strong and independent predictor of the NRF/SF phenomenon after primary PCI.<sup>[19]</sup> Additionally, another study involving an NSTEMI population found that preprocedural low LMR levels were an independent predictor for occurrence of NRF/SF, and the authors suggested that LMR could be a useful inflammatory marker in identifying high-risk patients.<sup>[24]</sup> In line with the literature, this study found that pre-procedure NLR, PLR, and LMR levels were independent determinants of NRF/SF development. The newly defined inflammation-based score AISI includes neutrophils, monocytes, and platelets—key mediators of in-

**Table 4. Factors that were found to be independently associated with the NRF/SF phenomenon development in multivariate logistic regression analysis models including inflammation-based scores**

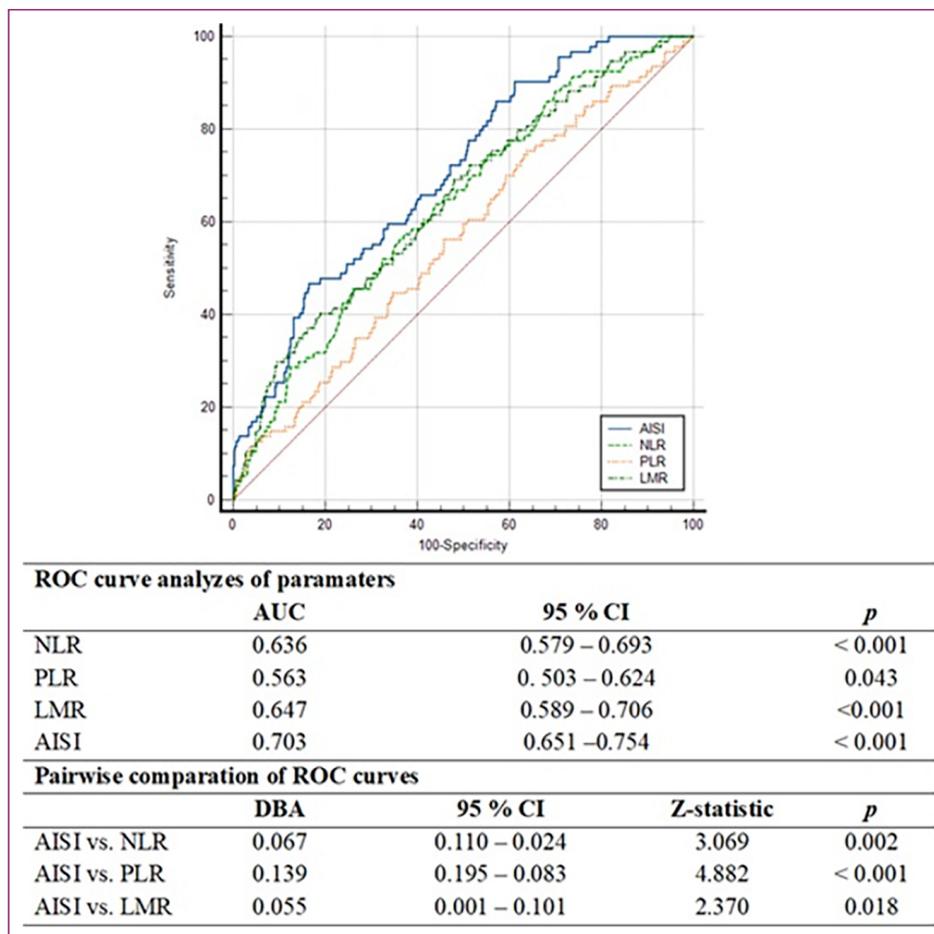
Variables	Model 1 Multivariate OR (95% CI)	p	Model 2 Multivariate OR (95% CI)	p
Hypertension	1.603 (0.968–2.654)	0.066	1.595 (0.968 – 2.630)	0.067
Diabetes	1.346 (0.845–2.143)	0.211	1.318 (0.830 – 2.092)	0.242
Smoking	2.069 (1.320–3.243)	0.002	2.098 (1.342 – 3.279)	0.001
LVEF, %	0.975 (0.955–0.995)	0.015	0.974 (0.954 – 0.994)	0.010
Syntax score I	1.023 (0.989–1.057)	0.189	1.025 (0.991 – 1.059)	0.152
GRACE	1.011 (1.001–1.021)	0.026	1.012 (1.002 – 1.022)	0.015
NLR	1.347 (1.155–1.570)	<0.001	–	–
PLR	–	–	1.003 (1.001 – 1.006)	0.017
	Model 3 Multivariate OR (95% CI)		Model 4 Multivariate OR (95% CI)	
Hypertension	1.560 (0.945 – 2.574)	0.082	1.619 (0.964 – 2.719)	0.068
Diabetes	1.276 (0.801 – 2.032)	0.305	1.381 (0.856 – 2.227)	0.186
Smoking	1.927 (1.230 – 3.021)	0.004	1.977 (1.244 – 3.141)	0.004
LVEF, %	0.974 (0.954 – 0.994)	0.012	0.975 (0.954 – 0.996)	0.019
Syntax score I	1.022 (0.988 – 1.057)	0.213	1.023 (0.988 – 1.059)	0.201
GRACE	1.013 (1.003 – 1.023)	0.010	1.010 (1.000 – 1.020)	0.049
LMR	0.713 (0.610 – 0.833)	<0.001	–	–
AISI	–	–	1.003 (1.002 – 1.004)	<0.001

NRF/SF, no-reflow/slow flow; OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; GRACE, The Global Registry of Acute Coronary Events; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; AISI, aggregate index of systemic inflammation.

flammation and thrombosis—while inversely accounting for lymphocyte-driven immune regulation. Therefore, it has been suggested that it may more comprehensively reflect the severity of inflammation and thus be a powerful tool for assessing the prognosis of diseases.<sup>[21]</sup> Indeed, previous studies have suggested that high AISI levels are associated with poor outcomes in several cardiovascular diseases, including heart failure, hypertension, and acute coronary syndrome.<sup>[21,22,30]</sup> Previous evidence from distinct clinical populations has demonstrated that elevated AISI levels are strongly linked to adverse long-term outcomes, including increased all-cause and cardiovascular mortality, even after adjustment for conventional risk factors. These associations have been consistently observed in chronic conditions such as heart failure and hypertension, where higher AISI values were shown to reflect a substantially greater risk of unfavorable cardiovascular and cardio-cerebrovascular events.<sup>[21,22]</sup> In the present study, no statistically significant difference was observed between groups with high and low AISI values in terms of 30-day cardiovascular mortality and non-fatal myocardial infarction; we believe this is related to the relatively low incidence of these events. However, the main focus of our study was not cardiovascular outcome, but rather elucidating the role of AISI, an inflammation-based score, in the development of the NRF/SF phenomenon. This study is the first of its kind on this subject. The current study revealed that the NRF/SF phenomenon was more frequent in individuals with high AISI values, and preprocedural increased AISI levels were an independent pre-

dictor of NRF/SF development in NSTEMI patients undergoing PCI. In the present study, the association of AISI and other inflammation-based markers mentioned above with the development of NRF/SF is consistent with the literature, and therefore, we believe that our findings support the role of inflammation in the development of NRF/SF in patients with ACS undergoing PCI. Moreover, we observed that AISI had better discriminatory power and superiority compared to other inflammation-based markers such as NLR, PLR, and LMR, which had previously been shown to be associated with NRF/SF development. We think one possible reason for this superior performance is that, as mentioned above, AISI reflects the severity of inflammation more comprehensively than other inflammation-based markers.

The current study had several limitations that needed to be considered. First, the retrospective, single-center nature of this study limits generalizability and may introduce selection bias. Additionally, the sample size is relatively small, and to ensure good specificity and homogeneity in the study design, only NSTEMI patients were included in the study instead of the entire non-ST-elevation ACS population. Second, inflammation indices were measured only once, which might not reflect dynamic changes in systemic inflammation. Third, NRF/SF has been defined angiographically only, based on TIMI flow grade, which indicates epicardial flow rather than actual microvascular perfusion. Fourth, unmeasured confounders such as subclinical infection or medications could not be fully excluded. Finally, the results of this analysis should be interpreted as exploratory in



**Figure 1.** Comparisons of the discriminatory abilities of the inflammation-based scores in determining NRF/SF development.

ROC: Receiver operating characteristic; AUC: Area under the curve; CI: Confidence interval; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; AISI: Aggregate index of systemic inflammation; DBA: Difference between area; NRF/SF: No-reflow/slow flow.

nature and primarily viewed as hypothesis-generating rather than definitive evidence. Accordingly, confirmation of these findings will require future investigations with more rigorous methodological designs and validation in large, multicenter cohorts.

The present study demonstrates that elevated preprocedural AISI is independently associated with the development of no-reflow/slow-flow phenomena following PCI in patients with NSTEMI. Beyond its independent predictive value, AISI showed superior discriminatory performance when compared with commonly used inflammation-based indices, including NLR, PLR, and LMR, suggesting that it may more effectively reflect the complex inflammatory and thrombotic milieu contributing to microvascular dysfunction. Given that AISI is easily calculated from standard complete blood count parameters without additional cost or testing burden, it represents a pragmatic and accessible biomarker for routine clinical practice. Incorporation of AISI into preprocedural risk assessment may facilitate earlier identification of patients at increased risk for adverse coronary microvascular outcomes and may support more individualized procedural planning, intensified pharmacological strategies, and

closer periprocedural monitoring. Future prospective and multicenter studies are warranted to further validate these findings and to clarify the incremental value of AISI when integrated with established clinical and angiographic risk models.

#### Disclosures

**Ethics Committee Approval:** The study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (no: 2025-04-02, date: 05/12/2025).

**Informed Consent:** Informed consent was obtained from all participants.

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