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Systemic Immune-Inflammatory Index Is Associated with Residual SYNTAX Score in Patients with ST-Segment Elevation Myocardial Infarction

ABSTRACT

Background: Systemic immune-inflammatory index (platelet count × neutrophil–lymphocyte ratio) is a new marker that predicts adverse clinical outcomes in coronary artery diseases. Our aim was to investigate the relationship between the systemic immune-inflammatory index and residual SYNTAX score in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.

Methods: In this retrospective study, 518 consecutive patients who underwent primary percutaneous coronary intervention (PCI) with the diagnosis of ST-segment elevation myocardial infarction were analyzed. The severity of coronary artery diseases was determined by residual SYNTAX score. In the receiver operating characteristic curve analysis, systemic immune-inflammatory index with an optimal threshold value of 1025.1 could detect the presence of a high residual SYNTAX score; the patients were divided into 2 groups as low (326) and high (192) according to the threshold value. In addition, binary multiple logistic regression analysis methods were used to evaluate independent predictors of high residual SYNTAX score.

Results: In binary multiple logistic regression analysis, systemic immune-inflammatory index [odds ratio = 6.910; 95% CI = 4.203-11.360; $P < .001$] was an independent predictor of high residual SYNTAX score. In addition, there was a positive correlation between the systemic immune-inflammatory index and residual SYNTAX score ($r = 0.350$, $P < .001$). In the receiver operating characteristic curve analysis, the systemic immune-inflammatory index with an optimal threshold value of 1025.1 could detect the presence of a high residual SYNTAX score with 73.8% sensitivity and 72.3% specificity.

Conclusion: Systemic immune-inflammatory index, an inexpensive and easily measurable laboratory variable, was an independent predictor of the increased residual SYNTAX score in patients with ST-segment elevation myocardial infarction.

Keywords: Coronary artery disease, residual SYNTAX score, systemic immune-inflammatory index

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INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is a clinical condition requiring urgent treatment of cardiovascular events that cause more than one-third of all deaths worldwide.[1] More than 40% of STEMI have multiple coronary artery lesions.[2] Insufficient revascularization may occur after PCI due to the complexity of the coronary anatomy and the clinical condition of the patient. The residual SYNTAX score (RSS) is a feasible and reliable score that measures the severity and complexity of residual stenosis after the revascularization of the culprit lesion. It has been determined that a higher RSS in patients after PCI is closely associated with more adverse outcomes, side effects, and mortality.[3] In addition to that, complete revascularization has been shown to be associated with lower adverse event rates.[4]

In clinical trials and research, inflammatory cells and immune system components, including lymphocytes, neutrophils, and platelets, have been shown to be involved in the pathophysiology of the atherosclerotic process.[5] In addition,

increased levels of inflammatory markers in patients with acute coronary syndrome (ACS) have been associated with the complexity of coronary artery disease (CAD) and poor prognosis in cardiovascular disease.[6] The systemic immune-inflammation index (SII) is a novel biomarker for inflammation and was calculated as (neutrophil count) × (platelet count)/(lymphocyte count) and was found to be associated with malignancy and CAD prognosis.[7,8] Recent studies on cardiovascular diseases have shown that increased SII is a good indicator for in-hospital and long-term clinical outcomes for patients undergoing PCI for myocardial infarction (MI) and was also found to be significantly associated with the severity of CAD and increased SYNTAX (SxS) score in patients who underwent coronary angiography with the diagnosis of stable angina pectoris.[9,10] Moreover, it has also been shown to be a predictor of the SxS score.[10]

However, no study in the literature shows the relationship between SII and RSS. This study aimed to examine the relationship between SII, which can be calculated by simple blood parameters, and RSS, a marker associated with adverse clinical outcomes in STEMI patients undergoing percutaneous coronary intervention.

METHODS

Study Population

Five hundred twelve consecutive patients were included in our retrospective study. Primary PCI was performed in the catheter laboratory for these patients diagnosed with STEMI between February 2016 and November 2019. ST-segment elevation myocardial infarction is defined if there is >1-2 mm of ST elevation in 2 adjacent chests or limb leads on the electrocardiogram (ECG) or new left bundle branch block (LBBB) with a clinical table coherent with typical chest pain. Exclusion criteria were as follows hematological, autoimmune, inflammatory disease, malignancy, history of coronary artery bypass grafting surgery, severe liver or kidney disease, and patients used to immunosuppressive medication. In our study, only culprit lesions related to STEMI were revascularized, and patients with multiple CAD who applied revascularization to nonculprit lesions were removed from the study. Data were obtained after a systematic review of the patient's hospital records. Demographic, clinical, biochemical, and echocardiographic evaluations were recorded from all subjects. Before primary percutaneous intervention in our hospital, complete blood count and broad biochemistry parameters were routinely taken for STEMI patients. Cholesterol parameters were evaluated with the Friedewald equation. The platelet count was then multiplied by the neutrophil count and divided by the lymphocyte count to measure the basal SII value. The mean SII value for the patients was determined, and the patients were divided into 2 groups as lower (group 1) and higher (group 2) than the mean SII value. Echocardiography was performed and recorded for each patient in the coronary intensive care unit after the procedure.

Angiographic Evaluation

Coronary angiography was applied to each patient as soon as possible from admission. The angiographic procedures were performed either via femoral or radial artery. Two cardiologists experienced in interventional cardiology separately evaluated coronary angiographic images. The severity of CAD is calculated for every patient.[11] The score calculation is performed as previously described, and first, SxS was calculated for all patients.[12] After that, RSS was calculated as SxS however according to the postprocedural residual coronary artery occlusion after PCI to the responsible lesion associated with STEMI. The values of SxS and RSS of all patients were calculated using the SxS calculator website (www.syntax Score.com). Residual SYNTAX score >8 was accepted as high RSS.[4] Additionally, clinical variables such as age, left ventricular ejection fraction (LVEF), renal function, gender, presence of chronic obstructive pulmonary disease, and peripheral vascular disease were registered for the calculation of SxS II. In the coronary angiographic evaluation, the variability between the 2 observers was less than 5%.

Statistical Analysis

Statistical analysis of the study was performed with the Statistical Package for Social Sciences Version 24.0 program (SPSS Inc., Chicago, Ill, USA). Primarily, whether the variables were normally distributed or not was evaluated by visual (histograms and probability curves) and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk). Normally distributed continuous variables were expressed as mean ± standard deviation, nonnormally distributed continuous variables were expressed as median (interquartile range), and categorical variables were expressed as percent (%). Receiver operating characteristic (ROC) curve and Youden index [max (sensitivity + selectivity – 1)] were used to identify the predictive value of the SII index that best detects high RSS value. Statistical analysis of numerical variables between independent groups was performed with Student's *t*-test or Mann–Whitney *U* test. Categorical variables such as high and low SII values were analyzed using chi-square or Fisher's exact test. Pearson and Spearman's analysis evaluated the correlation between the SII index and other numerical variables. Binary multiple logistic regression analysis was performed to identify independent predictors of high RSS. If the area under the ROC curve was above 0.5 and the *P*-value was <.05, it was considered statistically significant.

HIGHLIGHTS

- Systemic immune-inflammatory index is a new marker that predicts adverse clinical outcomes in coronary artery diseases.
- Residual SYNTAX score (RSS) in patients after PCI is closely associated with more adverse outcomes, side effects, and mortality.
- Systemic immune-inflammatory index, an inexpensive and easily measurable laboratory variable, was an independent predictor of increased RSS in patients with ST-segment elevation myocardial infarction.

Table 1. Clinical Characteristics and Laboratory Findings of the Study Population

	All Patients (n=518)	SII < 1036 (n=326)	SII > 1036 (n=192)	*P*
Age, years	55.5 ± 1.2	54.5 ± 10.6	57.3 ± 11.9	**.006**
Gender (female), n (%)	100 (19.3)	56 (17.2)	44 (22.9)	.110
Smoking status, n (%)	237 (45.8)	153 (46.9)	84 (43.8)	.483
Hypertension, n (%)	176 (34.0)	104 (31.9)	72 (37.5)	.194
Diabetes mellitus, n (%)	103 (19.9)	63 (19.3)	40 (20.8)	.678
Peripheral artery disease, n (%)	15 (2.9)	10 (3.1)	5 (2.6)	.761
Total cholesterol, mg/dL	199.5 ± 42.5	201 ± 43.1	197.2 ± 41.7	.330
LDL cholesterol, mg/dL	120.9 ± 38.01	119 ± 37	124 ± 39	.231
HDL cholesterol, mg/dL	40 (34-46)	39 (33-45)	41 (35-49)	**.002**
Triglyceride, mg/dL	177 (118.2-258)	200.5 (134-283)	137 (105-206)	**<.001**
Creatinine, mg/dL	0.83 (0.73-1.0)	0.87 (0.74-1.02)	0.81 (0.72-0.97)	**.049**
Glucose, mg/dL	135 (110-187)	130 (108-166)	147.5 (112-231)	**.001**
ALT, U/L	20 (15-30)	20 (15-29)	22.5 (16-32)	**.034**
AST, U/L	25 (19-40)	23 (18-34)	31 (20-56)	**<.001**
C-reactive protein, mg/dL	4.06 (2-9.27)	3.96 (1.85-8.54)	5.20 (2.23-12.98)	.054
Hemoglobin, g/dL	14.6 (13.2-15.6)	14.8 (13.6-15.7)	14.3 (13-15.3)	**.033**
Leukocyte, 10^3/μL	11.9 (9.6-14.0)	11 (9-13.1)	13 (11.2-15.4)	**<.001**
Lymphocyte, 10^3/μL	2.47 (1.7-3.6)	3 (2.2-4.3)	1.8 (1.3-2.3)	**<.001**
Neutrophil, 10^3/μL	7.6 (5.7-10.0)	6.3 (5.03-8.2)	10.3 (8.4-12.5)	**<.001**
Eosinophil, 10^3/μL	0.11 (0.04-0.23)	0.17 (0.09-0.29)	0.05 (0.02-0.13)	**<.001**
Platelet, 10^3/μL	259 (222-316.2)	253 (218-307)	270.5 (233.5-327.5)	**.001**
SII score	1036.8 ± 880.3	578.7 ± 242.7	1814.7 ± 1015.4	**<.001**

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SII, systemic immune-inflammatory index.

RESULTS

After determining inclusion and exclusion criteria, a total of 518 patients who underwent PCI with the diagnosis of STEMI were included in our study. In the whole population, the mean age was 55.5 years, and 19.3% of the patients were female. In the ROC curve analysis, SII with an optimal threshold value of 1025.1 could detect the presence of high RSS. Patients were separated into 2 groups by the threshold value of low SII (<1025 as group 1) and high SII (>1025 as group 2). The rate of high SII was 37.1%, and 192 patients were in the high SII group. Table 1 shows the demographic, cardiovascular risk factors, and clinical characteristics of the patients. There was no substantial difference in terms of medication, smoking, gender, co-morbid diseases including peripheral arterial disease, diabetes mellitus (DM), hypertension, and laboratory tests including C-reactive protein, total cholesterol, and low-density lipoprotein-C between the groups.

Mean age (*P* = .006), HDL cholesterol (mg/dL) (*P* = .002), glucose (mg/dL) (*P* = .001), alanine aminotransferase (μ/L) (*P*= .034), aspartate aminotransferase (μ/L) (*P* < .001), leukocyte (10^3/μL) (*P* < .001), platelet (10^3/μL) (*P* = .001), neutrophil (10^3/μL) (*P* < .001), and SII score (*P* < .001) values were higher in group 2, while creatinine (mg/dL) (*P* = .049), TG (mg/dL) (*P* < .001), hemoglobin (g/dL) (*P*=.033), lymphocyte (10^3/μL) (*P* < .001), and eosinophil (10^3/μL) (*P* < .001) values were lower in group 2.

Angiographic evaluations and cardiac systolic functions of the study group are shown in Table 2. There was no difference between the 2 groups regarding the culprit's vessels. LVEF was lower in group 2 (*P* = .001); however, SxS (*P* < .001), SYNTAX score II PCI (*P* < .001), and RSS (*P* < .001) were higher in group

Table 2. Angiographic Evaluation and Cardiac Systolic Functions of the Study Population

	All Patients (n=518)	SII < 1036 (n=326)	SII > 1036 (n=192)	*P*
Ejection fraction (%)	50 (40-55)	50 (42-55)	45 (40-50)	**.001**
Culprit vessel, n (%)				
• LAD	260 (50.2)	155 (47.5)	105 (54.7)	.287
• CXA	91 (17.6)	61 (18.7)	30 (15.6)	
• RCA	167 (32.2)	110 (33.7)	57 (29.7)	
SYNTAX score	15 (9.8-21.0)	13 (9-18)	19 (13-25)	**<.001**
SYNTAX score group, n (%)				
• Low (≤22)	414 (79.9)	294 (90.2)	120 (62.5)	**<.001**
• Moderate to high (>22)	104 (20.1)	32 (9.8)	72 (37.5)	
SYNTAX score II PCI	24.8 (18.6-33.1)	23.6 (17.8-31.5)	26.9 (21-36)	**<.001**
Residual SYNTAX score	3 (0-7)	1.5 (0-6)	5.3 (0-12.3)	**<.001**
Residual SYNTAX group, n (%)				
• Low (8≤)	411 (79.3)	297 (91.1)	114 (59.4)	**<.001**
• High (>8)	107 (20.7)	29 (8.9)	78 (40.6)	

CXA, circumflex artery; LAD, left anterior descending; RCA, right coronary artery; SII, systemic immune-inflammatory index.

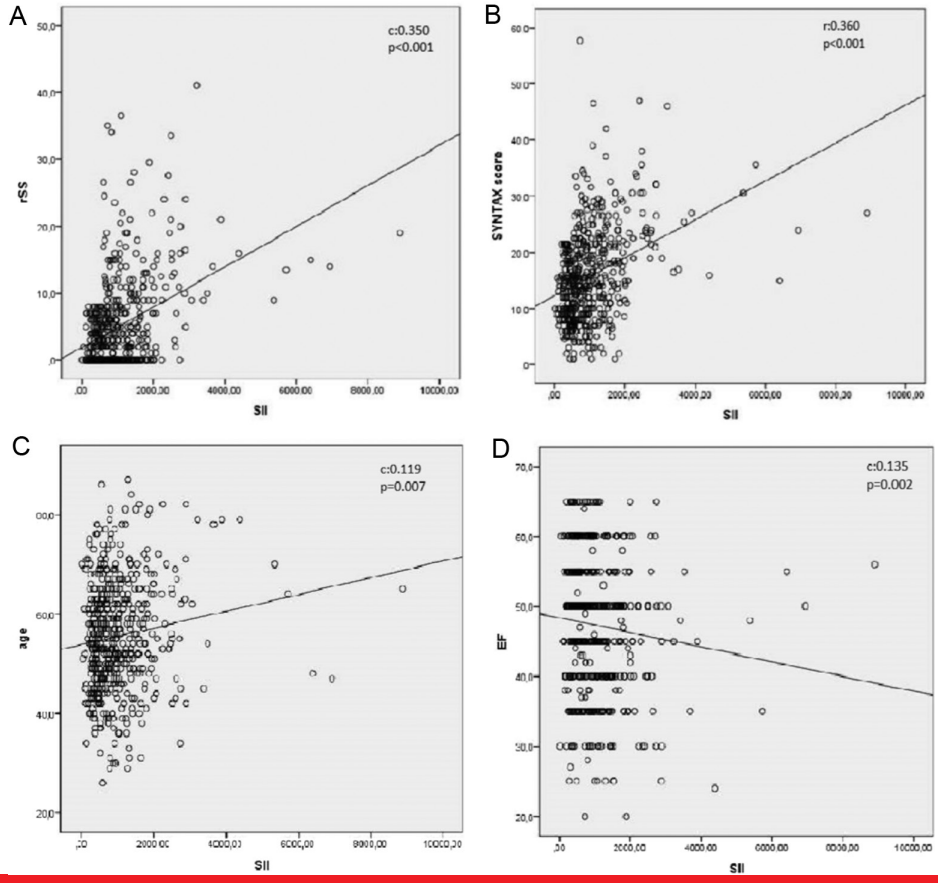

Figure 1. Correlation of SII with RSS (A) SYNTAX score (B), Age (C) and EF (D). EF, indicates ejection fraction; SII, systemic immune-inflammation index; RSS, remaining SYNTAX score.

2. In addition to that, percentage of number of patients with moderate to high SxS ($P < .001$) and high RSS ($P < .001$) were higher in patients with high SII. The relationship between SII and changes such as RSS ($P < .001$), SYNTAX score ($P < .001$), age ($P = .007$), and EF ($P = .002$) is shown in Figure 1.

Independent predictors of high RSS were determined by multiple logistic regression analysis (Table 3). In multiple logistic regression analysis, high SII score (odds ratio (OR) = 6.910; $P < .001$; 95% CI = 4.203-11.360), forward age (OR = 1.032; $P = .005$; 95% CI = 1.010-1.055), and DM (OR = 1.935; $P = .021$; 95% CI = 1.104-3.393) were determined to be independent predictors of a higher RSS.

Correlation between SII and clinical variables was demonstrated using correlation analysis (Table 4). A positive correlation was determined between SII and RSS ($r = 0.350$, $P < .001$). Moreover, SII was positively correlated with age ($r = 0.119$, $P = .007$), SxS ($r = 0.360$, $P < .001$), and SxS II ($r = 0.212$, $P < .001$). However, a negative correlation was found between SII and LVEF ($r = -0.135$, $P = .002$).

To identify the cut-off value for the SII that best defines the existence of high RSS, the (ROC) curve was drawn (Figure 2). The cut-off value was determined as 1025.1 by the Youden index (AUC 0.821, 95% CI = 0.781-0.861, $P < .001$). With this cut-off value, a sensitivity of 73.8%, and a specificity of 72.3%, the presence of high RSS can be detected.

DISCUSSION

Our study discussed that SII could predict RSS, since neutrophilia, thrombocytopenia, and lymphopenia were found to be more common in patients with elevated RSS. This study shows that SII, a new marker that includes neutrophil, platelet, and lymphocyte counts, is an independent predictor of increased RSS. Additionally, not only SII but also age and DM are independent predictors of increased RSS. This is the

Table 3. Independent Predictors for RSS with Multiple Logistic Regression Analysis

	Multiple Analysis		
	Odds Ratio	95% CI (Lower-Upper)	*P*
Age	1.033	1.010-1.057	**.004**
Creatinine	1.036	0.595-1.805	.899
Hypertension	1.584	0.949-2.644	.078
Diabetes mellitus	1.971	1.114-3.486	**.020**
Ejection fraction	0.993	0.968-1.019	.592
AST	1.003	0.999-1.007	.155
Triglyceride	1.000	0.998-1.002	.741
SII group	6.267	3.726-10.543	**<.001**

AST, aspartate transaminase; RSS, residual SYNTAX score; SII, systemic immune-inflammatory index.

Table 4. Correlation of SII with Other Parameters

	Correlation Coefficient	*P*
Age	0.119	.007
Ejection fraction	−0.135	.002
SYNTAX score	0.360	<.001
SYNTAX II score	0.212	<.001
RSS	0.350	<.001

RSS, residual SYNTAX score.

first study in the literature to show the association of SII with higher RSS.

Acute coronary syndrome is an inflammatory cardiovascular disease that results from vascular inflammation, disruption of lipid metabolism, and the complex interactions of immune systems and rupture of fragile plaques.[13,14] Previous studies have shown that inflammatory cells (e.g., white blood cells and subtypes) can be used in predicting the prognosis of patients with acute myocardial infarction (AMI).[15] In addition to that, reduction of inflammatory response slowed the formation of atherosclerosis in patients and reduced possible cardiovascular events.[16] Complete blood cell count is commonly used to reflect the inflammatory state of the patient. Systemic immune-inflammatory index is a new inflammatory index that includes 3 different types of inflammatory cells that can be easily obtained from a complete blood count and can more comprehensively represent the immune and inflammatory status in patients.[17] In patients with stable angina pectoris undergoing PCI, SII was shown to be significantly associated with CAD severity, increased SxS, and major cardiovascular and cerebrovascular events (MACCE).[9,10] In this study, similar to previous studies, we found that SII has the ability to predict severity of high SxS, RSS, and CAD.

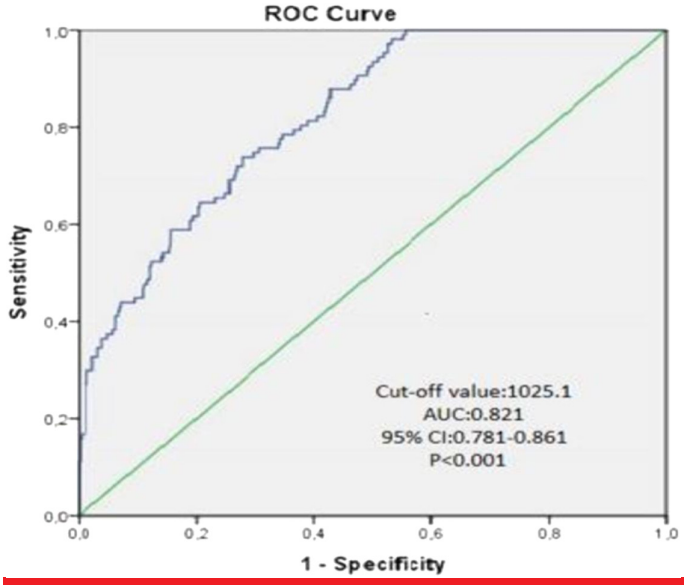

Figure 2. Receiver operating characteristic curves indicate the discriminative ability of the SII. SII indicates systemic immune-inflammation index.

It has been shown that increased WBC count is a predictor of mortality in AMI patients.[18] Neutrophils are the amplest WBC subparameters in blood; it is observed in damaged myocardial cells and is significant cofactors for atherosclerotic plaque destabilization.[19] Vascular damage due to increased neutrophil activity triggers actuation of the coagulation cascade, occlusion of microvessels by coagulation with platelets, and myocyte necrosis, plaque rupture, and increased thrombosis by secretion of proinflammatory cytokines.[20] In addition, neutrophils are related to increased viscosity of blood and activating coagulation, as well as inducing microvascular or reperfusion injury.[21,22] Consequently, raised neutrophil activation is associated with the existence and severity of atherosclerosis. It is also an independent predictor of adverse cardiovascular events.[23,24] Lymphocytes, another subtype of WBC, are important white blood cells in the immune system response and are involved in all stages of atherosclerosis development. Progression of inflammation in atherosclerotic lesions triggers lymphocyte apoptosis. With apoptosis of lymphocytes, the atherosclerotic plaque enlarges, and the lipid core grows, which triggers plaque cracking and subsequent thrombus formation.[20] Low lymphocyte count has been shown to be an independent indicator of MI, heart failure, and death in patients with CAD.[23,25] Parallel to these previous studies, our study had correlated findings that patients with increased SII scores had increased neutrophil count and decreased lymphocyte count in laboratory studies.

On the other hand, platelets have both an aggregate and procoagulant role in the formation of arterial thrombosis. In addition, platelets play an important role in the process of atherosclerosis and inflammation.[26] Inflammation causes a prothrombotic state due to thrombocytosis.[27] Activated platelets interact with endothelium, leukocytes, and inactivated platelets, contributing to the atherosclerotic and inflammatory processes. In addition, activated platelets cause the release of various inflammatory mediators that can further activate platelets and cause a vicious circle.[28] Previous studies have determined that platelets play an important role in the improvement and prevalence of CAD and may also be a precursor of CAD.[29] Our study had similar findings in terms of platelet count that patients with higher SII scores had increased count of platelets in their complete blood count.

Moreover, our study showed that in addition to SII, age and DM are independent predictors of RSS and the complexity of CAD. It is well known that increased age and presence of DM are closely related to the complexity of CAD and associated with prognosis in patients with CAD. Previous randomized controlled trials showed this association between aging and DM with CAD.[30,31] Our study results are compatible with these findings that aging and the presence of DM are associated with RSS and independent predictors of increased RSS.

The SII value is an easy-to-use and cost-effective index calculated using the numbers of WBC subtypes from the routine complete blood count test at hospital admission. The score

is calculated based on the subtypes of WBC, and due to high neutrophil and platelet levels and low lymphocyte concentration, a high SII might be associated with increased inflammatory activity and therefore lead to poor clinical outcomes.

In recent studies, SII has been shown to determine the severity of CAD and to be a risk factor for atherosclerosis development, and a high SII value is significantly correlated with SxS.[21] It has been shown to predict long-term clinical outcomes, and a high SII value is independently related to adverse clinical prognosis.[20] However, in previous studies, the relationship between RSS and SII has not yet been explored. More than 40% of STEMI patients undergoing primary PCI have multivessel CAD, and this is an independent indicator of mortality.[32,33]

Residual SYNTAX score indicates the degree of angiographic completeness and complexity of revascularization after PCI. It has been shown in the ACUITY study that RSS is associated with prognosis.[34] In subsequent studies, a high RSS (>8) was a powerful predictor of unplanned revascularization, cardiovascular mortality, first-year mortality, and major adverse cardiovascular event (MACE), whereas STEMI patients with low RSS showed significant reductions in first-year MACE.[16] In addition, another study showed that the extent and seriousness of obstructive CAD could predict ACS, MI, and death independently severity of ischemia.[35]

Study Limitations

Our study has limitations that should be considered. This study was a single-center and retrospective cross-sectional study. As the patients were not followed up due to the nature of the study, no comment could be made on the prognosis. The study had a relatively small sample size. Other cardiovascular risk factors such as atherosclerosis in peripheral vessels, ankle-arm index, and carotid intima-media thickness could not be evaluated in all patients included in the study. The drugs used by the patients were not taken into account. In addition, no comparison was made between other indexes and SII in RSS prediction. Therefore, prospective studies in larger populations are needed to confirm our results.

CONCLUSION

As a result, our study resulted in similar findings to previous studies. Furthermore, and in addition to those findings, in the results of our study, higher SII was associated with higher RSS in STEMI patients. In addition, SII was correlated with RSS as SII could determine the existence of high RSS with 73.8% sensitivity and 72.3% specificity. In conclusion, SII, a cheap and easily accessible laboratory parameter, was an independent predictor of incremented RSS in STEMI patients.

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Local Ethics Committee. Ethics Committee Decision Date: 01.06.2022 and Decision Number: 2022.05.34.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.A., S.K.; Design – M.A., S.K.; Supervision – S.K.; Fundings – M.K., Y.A.; Materials – G.D.; Data Collection &/or Processing – M.A., S.S.; Analysis and/orInterpretation – M.A., S.K., S.Y.; Literature Search – M.A., A.A.Ş., M.E.; Writing – M.A.; Critical Review – A.A.Ş., S.K., M.E.

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