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Relation Between Systemic Immune-Inflammation Index and Post PCI Bleeding Risk in STEMI Patients

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Abstract

Objectives: To investigate the relationship between the systemic immune-inflammation index (SII) and bleeding complications in ST-elevated myocardial infarction (STEMI) after percutaneous coronary intervention (pPCI).

Materials and Methods: This retrospective study included 1778 patients who presented with STEMI and underwent pPCI. Patients were divided into two groups: those who developed bleeding and those who did not. The SII values and CRUSADE bleeding score were calculated.

Results: In the group with bleeding complications, the ages were 62 (50-73), and 69.6% were male. Multivariate analysis identified age 1.031(1.015-1.048) - p<0.001, basal creatinine 1.789 (1.366-2.342) - p<0.001, SII 1.163 (1.028-1.315)- p=0.013 as significant predictors of bleeding complications.

Conclusion: The easily calculated SII may help predict bleeding complications in STEMI patients undergoing pPCI.

Keywords: ST elevation myocardial infarction, bleeding, systemic immune-inflammation index

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Introduction

Coronary artery disease (CAD) continues to be a common cause of morbidity and mortality[1]. During and after percutaneous coronary intervention (pPCI), anticoagulant and antiaggregant treatments are necessary[2-4]. This situation presents a risk of bleeding[5]. Various bleeding events, from simple skin ecchymosis to more serious intracranial or gastrointestinal bleeding, can be observed in hospitalized patients with ST-elevated myocardial infarction (STEMI). In particular, as comorbidities and age increase, bleeding complications occur more frequently. Both morbidity and mortality increase due to bleeding, as well as the hospital stay lengthens. In this context, minimizing, preventing, or identifying the risk of bleeding is extremely important[6,7].

To lessen the risk of bleeding, the patient should be evaluated as a whole, considering age and comorbidities, and patient-based, dose-adjusted treatment should be applied. Current guidelines include adjustments in time and dose considering both bleeding-ischemia risk and the patient's clinical condition in dual antiplatelet therapy recommendations[8,9].

The systemic immune-inflammation index (SII) was calculated using neutrophil, lymphocyte, and platelet counts. Many studies have shown its relationship with acute coronary syndromes, CAD, and certain heart rhythm disorders. Additionally, the relationship between the SII and STEMI thrombus load, recurrent myocardial infarction, and short- and long-term mortality has been determined[10-13]. In our study, we aimed to reconnoiter the effect of the SII in predicting bleeding complications in patients hospitalized with a diagnosis of STEMI.

Materials and Methods

Study Population

The study was conducted retrospectively at a single center on 1778 patients who were diagnosed with a diagnosis of STEMI and underwent PCI. The symptoms of the patients were detected within the first 12 hours. At the time of diagnosis, each patient was administered clopidogrel (600 mg) or ticagrelor (180 mg) with aspirin (300 mg) and dose- adjusted heparin in the emergency service before being sent to the laboratory. The diagnosis of STEMI was made according to the latest guidelines of the European Society of Cardiology[14]. Demographic and clinical features, previous medical history, physical examination, laboratory examination, and intervention-related data were obtained from the patient's file and the hospital and national database. Coronary angiography was performed via femoral Access in 90% of the patients and via 10% radial access. Primary PCI was performed in all patients.

Patients with advanced kidney and liver disease, a history of malignancy, and coagulopathy, as well as those who were breastfeeding or pregnant, were not included in the study. The study was conducted according Ankara Etlik City Hospital No. 1 Clinical Research Ethics Committee (approval no.: AEŞH-EK-1-2023-610, date:11.10.2023). The Declaration of Helsinki and was approved by the ethics committee. The study design was retrospective; thus, patient consent was not obtained.

Bleeding complications in patients were noted. Major bleeding was defined as ISTH, a fall in hemoglobin level of 2 g/dL or more, or documented transfusion of at least 2 units of packed red blood cells, (b) involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, intramuscular with compartment syndrome, retroperitoneal[15]. The CRUSADE bleeding score was calculated using an online calculator[16]. Minor bleeds occurs in many patients, we did not report clinically meaningless bleeding events such as minor nose, gum bleeding, and ecchymoses.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as percentages. The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. The statistical analysis of clinical data between

the two groups consisted of unpaired t-tests for parametric data and Mann-Whitney U test analysis for non-parametric data. Continuous and categorical variables were analyzed using the chi-square test and Student's t-test as appropriate. Two-tailed p<0.05 was accepted as statistically significant. Statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 1778 patients were included in the study. In the group with observed bleeding complications (n=112. 6%), the average age was 62 (50-73), and 69.6% were male. In the group without bleeding complications, the mean age was 55 (47-64), and 81.2% were male. In the bleeding group, diabetes and hypertension were significantly higher (p<0.05). Left ventricular ejection fraction values were lower in the bleeding group (p <0.001). Other basal characteristics of the groups are presented in Table 1.

In the bleeding group, peak troponin I, glucose, white blood cell, neutrophil, C-reactive protein, creatinine, neutrophil-to-lymphocyte ratio (NLR), SII, and crusade scores were higher than in the non-bleeding group (p<0.05). The laboratory findings for the patient groups are presented in Table 2.

The most common bleeding complication observed was an access site problem, accounting for 43 (38.4%). The rate of major bleeding was 23 (21.6). Sources of bleeding complications are presented in Table 3. The SII was higher in the bleeding group (Figure 1).

In the multivariate analysis, age 1.031(1.015-1.048, p<0.001), basal creatinine 1.789 (1.366-2.342, p<0.001), SII 1.163 (1.028-1.315, p=0.013) were identified as significant predictors of bleeding complications (Table 4).

Scatter dot plot of the correlation between SII, CRUSADE score showed in Figure 2.

Table 1. Baseline characteristics of patients with STEMI

Variables	Non-bleeding group n=1666	Bleeding group n=112	p-value
Age, years	55 (47-64)	62 (50-73)	<0.001
Male gender, n (%)	1362 (81.2)	78 (69.6)	0.003
Diabetes mellitus, n (%)	369 (22.0)	42 (37.5)	<0.001
Hypertension, n (%)	659 (39.3)	57 (50.9)	0.015
Current smoker, n (%)	932 (55.6)	44 (39.3)	0.001
Dislipidemi, n (%)	672 (40.1)	36 (32.1)	0.097
Previous ASA usage, n (%)	35 (2.1)	2 (1.8)	0.828
Systolic BP, mm Hg	131.17±30.45	129.78±38.26	0.706
Diastolic BP, mm Hg	77.79±18.45	76.39±23.21	0.534
Heart rate, bpm	76.96±15.63	76.69±21.15	0.892
LVEF, %	48.0 (42.0-55.0)	43.0 (35.0-50.0)	<0.001
Contrast volume, mL	270 (210-300)	280 (220-320)	0.136
Anterior MI, n (%)	810 (48.6)	65 (58.0)	0.063
Non-anterior MI, n (%)	856 (51.4)	47 (42.0)	
TIMI thrombus grade, n (%) 1-2 (low) 3 (middle) 4-5 (high)	 101 (6.1%) 466 (28.0%) 1099 (66.0%)	 7 (6.3%) 24 (21.4%) 81 (72.3%)	 0.321 0.330 0.166
ASA loading dose 300 mg, %	1082 (64.9)	106 (94.6)	0.032
Klopidogrel giving loading dose, n (%)	696 (41.8)	49 (43.7)	0.148
Tikagrelor giving loading dose, n (%)	970 (58.2)	63 (56.3)	0.225

ASA: Acetylsalicylic acid, BP: Blood pressure, LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, TIMI: Thrombolysis in myocardial infarction

Table 2. Baseline laboratory findings of patients with STEMI

Variables	Non-bleeding group n=1666	Bleeding group n=112	p-value
Basal troponin I, ng/L	1.98 (0.72-4.56)	2.34 (0.90-6.46)	0.102
Peak troponin I, ng/L	78.0 (36.7-166.0)	120.0 (47.0-244.0)	<0.001
Glucose, mg/dL	125.0 (103.0-163.0)	144.0 (117.5-220.5)	<0.001
Hemoglobin, g/dL	14.0 (13.0-15.0)	13.4 (11.5-14.9)	0.001
eGFR, mL/min/1.73m^2	89.0 (73.0-104.0)	70.5 (51.0-90.0)	<0.001
White blood cell, ×103/µL	12.17±3.62	13.86±4.60	<0.001
Neutrophil, ×103/µL	9.35±3.47	11.01±4.21	<0.001
Lymphocyte, ×103/µL	1.97±1.03	1.89±0.85	0.427
Platelet, ×103/µL	256.4±65.5	261.37±67.90	0.433
Total cholesterol, mg/dL	178.91±43.80	165.08±40.97	0.007
HDL, mg/dL	38.52±12.08	40.39±14.05	0.130
LDL, mg/dL	114.62±38.69	103.12±33.37	0.003
Triglyceride, mg/dL	138.57±92.69	135.21±61.11	0.614
Lipoprotein (a)	24.96±19,33	23.55±32.25	0,834
C-reactive protein, mg/L	13.27±11.84	20.33±17.50	<0.001
Albumin, g/dL	3.7 (3.5-4.0)	3.5 (3.2-4.0)	0.004
Creatinine, mg/dL	0.87 (0.75-1.00)	0.96 (0.80-1.32)	<0.001
NLR	5.00 (3.21-7.85)	6.04 (02-8.74)	0.005
PLR	138. (101.3-199.2)	149.7 (107.6-204.8)	0.489
SII x10^3	1243.9 (777.3-2008.3)	1539.4 (995.7-2381.8)	0.003
CRUSADE score	24.0 (17.0-33.0)	36.0 (23.5-50.0)	<0.001

eGFR: Estimated glomerular filtration rate, HDL: High-density lipoprotein, LDL: Low-density lipoprotein; NLR: Neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, SII: Systemic immune-inflammation index, *STEMI: ST-Elevation myocardial infarction*

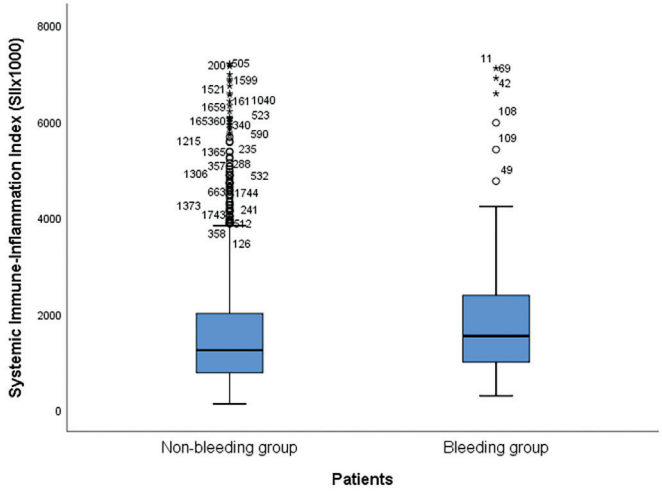

Figure 1. Box plot of the SII according to bleeding and nonbleeding groups

SII: Systemic immune-inflammation index

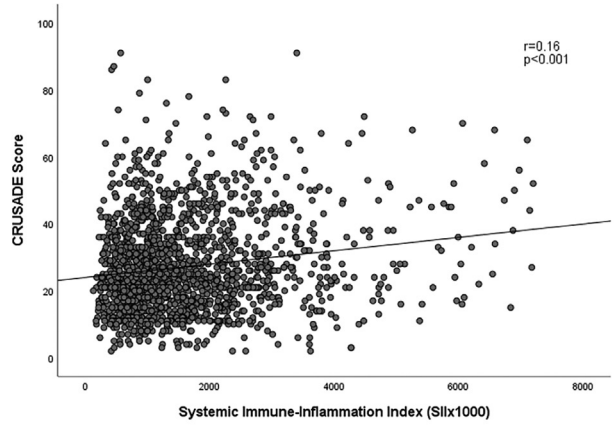

Figure 2. Scatter dot plot of the correlation between SII and CRUSADE scores

SII: Systemic immune-inflammation index

Discussion

In this study, we found that the SII, age, and creatinine levels predicted in-hospital bleeding complications in STEMI patients undergoing PCI. To our knowledge, this study is the first to investigate the relationship between SII and bleeding complications in patients with STEMI.

As is well known, STEMI commonly develops after plaque rupture, requiring emergency treatment. Despite advancements in stent, balloon, and PCI technologies, anti-ischemic and anticoagulant agents are administered to patients before and after the procedure. As a natural consequence of these hemostatic agents, undesired bleeding events are sometimes observed[17]. The most common bleeding complication is access site bleeding, in addition to gastrointestinal, urinary system, cardiac, retroperitoneal, and intracranial bleeding[18-20]. In clinical practice, bleeding is classified as major and minor bleeding. A situation is called major bleeding if it is related to hemodynamic instability, occurs anatomically in a critical area, requires transfusion of 2 units or more erythrocyte suspension, or causes a fall in hemoglobin levels of 2 g/dL or more (if the basal value is known)[21]. It is understandable from this point that bleeding events can lead to life-threatening situations. Additionally, hospitalization time and costs increase because of bleeding, and occurrences of re-infarction and acute thrombosis events are observed because of the interruption or discontinuation of anti-ischemic drugs[22,23]. In this context, it is extremely important to predict and prevent undesired bleeding events.

As patients' creatinine levels increase, bleeding complications also increase. In our study, the creatinine level was significantly higher in the bleeding group. Despite dose adjustments for several drugs with renal excretion in clinical practice, bleeding events can still occur[24]. During PCI in STEMI patients, contrast-induced nephropathy can develop due to the contrast substance given[25]. In addition to dose adjustments, appropriate hydration is extremely important, especially in patients who will take contrast substances for any reason, to prevent contrast-induced nephropathy and carefully use nephropathy-causing drugs carefully[26].

Table 3. Post MI bleeding events (n=112)

Access site, n (%)	43 (38.4)
Urinary system, n (%)	12 (10.7)
Gastro intestinal system, n (%)	36 (31.1)
Intracranial, n (%)	2 (1.8)
Retroperitoneum, n (%)	4 (3.6)
Tamponade, n (%)	1 (0.9)
Other, n (%)	14 (12.5)
Minor, n (%)	89 (79.4
Major, n (%)	23 (21.6)

MI: Myocardial infarction

Table 4. Univariate and multivariate analyses for predictors of post MI bleeding

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.040 (1.024-1.056)	<0.001	1.031 (1.015-1.048)	<0.001
COPD	1.322 (0.595-2.934)	0.493		
Creatinine	1.994 (1.491-2.666)	<0.001	1.789 (1.366-2.342)	<0.001
Basal troponin	1.010 (0.991-1.028)	0.302		
Lipoprotein (a)	0.997 (0.966-1.028)	0.832		
TIMI thrombus grade	1.199 (0.854-1.683)	0.294		
Contrast volume	1.002 (0.999-1.004)	0.140		
SII	1.221 (1.063-1.402)	0.005	1.163 (1.028-1.315)	0.013

COPD: Chronic obstructive pulmonary disease, MI: Myocardial infarction, SII: Systemic immune-inflammation index, TIMI: Thrombolysis in myocardial infarction, OR: odds ratio, CI: Confidence interval

With increasing age, fragility also increases, and dose adjustments are made when administering anti-ischemic and anticoagulant drugs. It is no coincidence that age is a component of HAS-BLED scoring. In a study conducted by Franken et al.[27], it was observed that as age increases, bleeding complications increase.

Although the relationship between age and creatinine levels with bleeding has been demonstrated, no study has shown the relationship between SII, which is calculated using neutrophil, lymphocyte, and platelet counts, and bleeding, which can indicate the status of inflammatory, immune, and coagulation cascades. The SII has been found to be related to the development, monitoring, and prognosis of many diseases, particularly those in which inflammation plays a role in pathogenesis. The study by Guzel and Kis[28] investigated the relationship between the SII and the Atherogenic plasma index (AIP) in assessing the severity of coronary lesions through fractional flow reserve measurements. They found that although the SII possessed higher sensitivity, the AIP also significantly predicted the severity of coronary lesions. In a study conducted by Dolu et al.[29], it was shown that the SII is related to a high thrombus load in STEMI patients[30]. Moreover, there are studies that have investigated the SII in estimating short- and long-term mortality in STEMI patients.

In our study, we found that SII can predict bleeding in STEMI patients. The first stage of the hemostatic process involves platelet plug formation after endothelial damage. Subsequently, the coagulation cascade is activated. Platelets are activated in the area of vascular injury to provide the initial hemostatic response by forming a platelet plug to stop bleeding. Injury to the endothelium exposes subendothelial elements that are normally protected from circulating blood, and endothelial cell activation can promote the collection of platelets, other cell types, and procoagulant factors. The activated platelets initiate the initial hemostatic process by developing adhesion, aggregation, secretion, and procoagulant activities. Proinflammatory cytokines can affect platelet formation, activation, and function, leading to bleeding or thrombosis[31].

Many previous studies have shown that the NLR predicts many bleeding events[32]. In this context, the SII contains both platelet count and NLR and may be more guiding in terms of bleeding prediction.

The CRUSADE bleeding score is a tool that predicts bleeding in post-myocardial infarction patients by evaluating the patient's heart rate, systolic blood pressure, hematocrit, creatinine clearance, gender, presence of heart failure symptoms on admission, history of vascular disease, and presence of diabetes mellitus[33]. In our study, we found a positive correlation between SII and the CRUSADE bleeding score. This relationship contributes to the SII's ability to predict bleeding.

Study Limitations

The main limitation of this study is its retrospective nature. The relatively lower number of patients included in the study can also be considered a limitation. A comparison of patients who underwent radial and femoral intervention for bleeding and SII could not be performed due to the lack of sufficient number of patients and data. STEMI is a morbid and fatal disease. Bleeding complications can occur after pPCI in STEMI patients. The SII was higher in the bleeding group. Finally, the easily calculated SII may help predict bleeding complications in patients undergoing pPCI.

Conclusion

The easily calculated SII may help predict bleeding complications in patients undergoing pPCI. This approach may provide additional benefits to clinicians in managing medications and conditions that cause bleeding in this patient group.

Ethics

Ethics Committee Approval: The study was conducted according Ankara Etlik City Hospital No. 1 Clinical Research Ethics Committee (approval no.: AEŞH-EK-1-2023-610, date:11.10.2023). The Declaration of Helsinki and was approved by the ethics committee.

Informed Consent: Retrospective study.

Footnote

Authorship Contributions

Surgical and Medical Practices: Kalkan K, Akdi A, Tunca Ç, Kürklü HA, Akgün O, Concept: Kalkan K, Akdi A, Tunca Ç, Özbebek YE, Kıvrak A, Akdoğan M, Akgün O, Tanık VO, Design: Kalkan K, Tunca Ç, Özbebek YE, Özkaya İbiş A, Kürklü HA, Tanık VO, Data Collection and/or Processing: Kalkan K, Tunca Ç, Özkaya İbiş A, Akdoğan M, Analysis and/or Interpretation: Kalkan K, Tunca Ç, Kıvrak A, Literature Search: Kalkan K, Tunca Ç, Akdoğan M, Writing: Kalkan K, Tunca Ç, Kürklü HA.

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