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Door to Balloon Time of Non-ST Elevation Myocardial Infarction May be Reconsidered According to Systemic Immune-Inflammation Index

Aim	Early diagnosis and treatment is very important in acute coronary syndromes (ACS). Previous studies showed that not all non-ST elevation myocardial infarction (NSTEMI) patients should be considered and treated in the same way. The systemic immune-inflammation index (SII), which is an easily accessible, rapidly computed, and cost-effective parameter, was evaluated in this study to determine the optimal intervention time for NSTEMI.
Material and methods	469 patients diagnosed with ACS were included to the study. STEMI and NSTEMI patients were compared according to their SII. Univariate and binary logistic regression analysis were performed to determine which parameters have a significant effect on the discrimination of types of myocardial infarction.
Results	The mean age of the patients was 61.43±11.52 yrs, and 348 (74.2%) were male. NSTEMI patients with an SII value higher than 768×10^9/l may be assumed to be STEMI ($p<0.001$). Univariate analysis and binary logistic regression showed that only SII and hypertension had statistically impact on differentiation of STEMI and NSTEMI. In addition, SII value of 1105×10^9/l was the cut-off point for discrimination of cardiovascular survival ($p<0.001$, AUC =0.741). This study was performed to find out which NSTEMI patients should be treated percutaneously immediately after first medical contact according to SII. It was found that, SII value of higher than 768×10^9/l is related with STEMI.
Conclusion	In conclusion, NSTEMI patients with a SII value higher than 768×10^9/l may be considered as STEMI and treated with in 120 min after first contact. In addition, SII was found to be a cardiovascular mortality predictor after myocardial infarction, and this may be used for identifying high-risk patients after percutaneous coronary intervention.

Keywords	Acute coronary syndrome; ST elevation myocardial infarction; systemic immune-inflammation index
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Introduction

Coronary artery disease (CAD) is one the leading cause of world-wide morbidity and mortality [1]. Acute coronary syndromes (ACS) consist of ST elevation myocardial infarction (STEMI), non-STEMI myocardial infarction (NSTEMI), and unstable angina pectoris [2]. According to the latest European Society of Cardiology Guideline of Acute Coronary Syndromes (ACS) in Patients Presenting without Persistent ST-Segment Elevation, NSTEMI is recommended to be treated percutaneously during the first 24 hr [3]. Unlike NSTEMI, percutaneous revascularization in STEMI cases should be treated in the first 120 min after the first medical contact [4]. STEMI usually occurs due to acute total occlusion of coronary arteries (ATOCA); however, the range of occlusion, either total or partial, varies in NSTEMI. Therefore, all degrees of coronary stenosis in NSTEMI should not be treated in the same manner.

Differentiation of STEMI and NSTEMI relies mainly on electrocardiography (ECG) [5]. However, an ECG recorded soon after new onset total coronary occlusion may not show ST elevation. In this case, the patient is held for the results of blood tests, and, if a new ECG is not performed, the patient is assumed to have NSTEMI. Some studies have been performed to clarify this situation [6, 7]. However, there has been no study on this issue and its relationship with the systemic immune-inflammation index (SII), which is easily available at the time of the first examination and which has a relationship with cardiovascular events.

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The SII is a well-known parameter that is used to consider the inflammatory and immune status simultaneously [8]. This parameter consists of blood platelet (Plt), neutrophil (Neu), and lymphocyte (Lym) counts (SII = Plt × (Neu/Lym). The SII has been studied previously in a very wide range of disease groups [9, 10]. Importantly, previous studies found that higher SII values were associated with greater CAD severity and mortality [8, 11]. However, the relationship between SII and ATOCA has not been studied in STEMI and NSTEMI patients with regard to the time for optimal intervention.

Therefore, we aimed to determine whether the optimal intervention time for NSTEMI should be reconsidered according to the SII value. In addition, the relationship between the SII and long-term outcome after ATOCA was also studied.

Material and methods

Patient Selection

This retrospective study included 469 consecutive patients diagnosed with NSTEMI without ATOCA or with NSTEMI or STEMI and having at least one totally occluded coronary artery. These patients were seen between October 2018 and March 2020 at a single center. All patients were older than 18 yrs. All ECG and blood parameters were evaluated by two cardiology specialists. Culprit lesions responsible for ACS were in the proximal region of the index arteries, according to the BARI protocol (BARI 1, 12, and 18) [12]. Informed consent for angiography and data collection was given by all patients. The study was carried out in accordance with the October 2008 Declaration of Helsinki, and the study was approved by the local ethics committee (Ethic Decision Number: 2022–47).

NSTEMI has been defined as an increase in myocardial injury markers in combination with typical symptoms of myocardial ischemia but without ST-segment elevation [3]. STEMI has been defined as a typical symptom of myocardial injury with ST-segment elevation >1 mm in ≥2 contiguous leads and/or a new onset of left bundle branch block [4].

The exclusion criteria were 1) patients younger than 18 yrs, 2) patients with coincident trauma and sepsis, 3) patients that died from causes unrelated to ACS, 4) patients with malignancies, hematological disease, oncological disease, or usage of drugs impacting white blood cells (antibiotics, chemotherapeutics, etc.), 5) patients lacking clinical data.

All patients were followed-up after the angiographic procedure for a specific time. The patient's status (alive or dead) was obtained from hospital records or from phone conversations with patients and/or their relatives. Cardiovascular mortality was assumed as death related with ACS, including cardiac mechanical complications and arrhythmias; these data were obtained from the national medical care system.

Clinical Parameters

Demographic data (age, gender, smoking status, hypertension (HT), diabetes mellitus (DM), and CAD, congestive heart failure were collected from hospital records. Blood parameters (hemoglobin (Hgb), hematocrit (Hct), white blood cell (WBC), Neu, Lym, monocyte (Mono), Plt, plateletcrit (Pct), high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (Trig), and cholesterol) were also measured. All blood parameters were obtained in the first 6 hr of ACS.

Two cardiology specialists evaluated the coronary angiographies. In case of a conflict, a 3rd cardiology specialist examined the angiographies. 70% or more stenosis of the coronary arteries was defined as diseased vessel. All patients were treated percutaneous transluminal coronary angioplasty (PTCA), according to the coronary artery that had the ACS-related culprit lesion. Blood parameters were collected at the first medical contact.

Statistical Analyses

IBM SPSS Statistics for Windows v. 23 was used for statistical analyses and p values <0.05 were considered statistically significant. The Kolmogorov-Smirnov test was performed to determine if the continuous variables were normally distributed. The Mann–Whitney U test was used for non-normally distributed variables. Categorical and continuous data are expressed as ratios (%) and mean±SD, respectively. Categorical parameters were compared with chi-square tests. Normally distributed, continuous data were compared with independent-samplet-tests and one-way ANOVAs. A receiver operating characteristic (ROC) curve was used along with the Youden index to determine the optimal cut-off values of SII [13]. Pearson correlation analyses were used to examine relationships between SII and continuous parameters.

Univariate analyses were performed to determine which parameters had major effects for discrimination of the myocardial infarction types. In addition, binary logistic regression was performed to investigate which variables have statistical significance in discriminating between STEMI and NSTEMI.

Survival analyses were computed by the Kaplan–Meier method. Patients who had not died during the follow-up period were assumed to be survivors. Overall survival time (OS) was calculated from the date of the procedure to the date of mortality resulting from cardiovascular causes. A Kaplan–Meier curve for survival analysis was plotted to assess the prognosis between subgroups, divided according to the ROC curve cut-off points, as determined with log-rank, Breslow, and Tarone-Ware tests.

Table 1. Comparison of baseline demographic data and blood parameters according to myocardial infarction types

Variable	STEMI	NSTEMI	p
Age, yr	61.92±11.95	60.22±10.35	0.12
Male	249 (53.1%)	230 (21.1%)	0.56
Smoking	171 (36.5%)	74 (15.8%)	0.68
HT	232 (49.5%)	81 (17.3%)	0.03
DM	159 (33.9%)	62 (13.2%)	0.61
CAD	55 (11.7%)	22 (4.7%)	0.89
SII ×10⁹/l	1691±1529	743±530	<0.01
Exitus	26 (5.5%)	4 (0.9%)	0.06
Number of diseased vessels			
1	168 (35.8%)	82 (17.5%)	0.17
2	108 (23%)	38 (8.1%)	0.17
3	56 (11.9%)	17 (3.6%)	0.17
Hgb (g/dl)	14.29±1.92	14.29±1.85	0.98
Platelet (10⁹/l)	259.22±72.13	233.18±63.67	<0.01
WBC (10⁹/l)	13.47±8.47	10.46±3.48	<0.01
HDL (mg/dl)	41.07±12.85	40.65±9.30	0.73
LDL (mg/dl)	119.76±37.92	124.20±38.69	0.26
Trig (mg/dl)	145.90±115.74	157.88±89.96	0.29

Data are number (%) or mean±SD. CAD, coronary artery disease; DM, diabetes mellitus; Hgb, hemoglobin; HDL, high density lipoprotein; HT, hypertension; LDL, low density lipoprotein; NSTEMI, non-ST segment elevation myocardial infarction; SII, systemic immune-inflammation index; STEMI, ST segment elevation myocardial infarction; Trig, triglycerides; WBC, white blood cell.

Table 2. SII values of all STEMI and NSTENI patients and of those with ATOCA, grouped according to the location of the culprit coronary artery lesion(s)

Variable	STEMI	NSTEMI	p
For all patients (n=469)	n=332	n=137	
SII×10⁹/l	1691±1529	743±530	<0.01
LAD culprit lesion (n=207)	1779±1642	778±674	<0.01
CX culprit lesion (n=104)	1752±1303	746±429	<0.01
RCA culprit lesion (n=158)	1549±1469	692±436	<0.01
Patients with ATOCA (n=400)	n=332	n=68	-
SII ×10⁹/l	1691±1529	791±465	<0.01
LAD culprit lesion (n=177)	1779±1642	700±579	<0.01
CX culprit lesion (n=86)	1752±1303	849±436	<0.01
RCA culprit lesion (n=137)	1549±1469	790±359	<0.01

Data are mean±SD.
ATOCA, acute total occlusion of coronary arteries; CX, circumflex artery; LAD, left anterior descending artery; RCA, right coronary artery; SII, systemic immune inflammation index.

Results

Baseline Demographic Characteristics

Baseline demographic characteristics of the 469 studied ACS patients are compared according to myocardial infarction types (STEMI or NSTEMI) in Table 1. The mean patient age was 61.4±11.5 yrs, and 348 (74.2%) patients were male. 332 (70.8%) patients were diagnosed as STEMI.

Comparison of the Two Types of Myocardial Infarction

The SII of STEMI patients significantly exceeded that of NSTEMI patients (p<0.01; Table 2), and this was true for all locations of the culprit lesion, (p<0.01 for LAD, CX, and RCA; Table 2). For patients with ATOCA, the SII of STEMI patients also significantly exceeded that of NSTEMI patients (p<0.01; Table 2), and this was true for all locations of the culprit lesion, (p<0.01 for LAD, CX, and RCA; Table 2).

NSTEMI patients with and without ATOCA were also compared according to SII. These values did not differ significantly. SII for NSTEMI with ATOCA=797±466×10⁹/l; SII for NSTEMI without ATOCA=685±590×10⁹/l (p=0.97).

ROC curve analysis revealed a significant difference between the STEMI and NSTEMI groups (p<0.001). The area under curve was 0.802, with the cut-off point of 768×10⁹/l (sensitivity = 79.5% and specificity = 65.7%; Figure 1). Interestingly, in the ATOCA patients, when STEMI and NSTEMI were compared according to ROC curve, the cut-off point was similar at 768×10⁹/l (sensitivity=79.5%, specificity=61.8% and AUC=0.775). According to the both analyses in this study population, patients with SII values bigger than 768×10⁹/l may be assumed as STEMI. ROC curve analyses were also performed

Table 3. Univariate analysis of myocardial infarction subtypes according to clinical parameters

Dependent Variable (n=435) Source	Type III Sum of Squares	F	p
SII	8.577	45.257	<0.01
Age	0.001	0.003	0.95
Gender	6.162	0.000	0.99
Smoking	0.051	0.272	0.60
HT	1.394	7.358	0.007
DM	0.003	0.017	0.89
CAD	0.209	1.100	0.29
Number of Diseased Vessel	0.600	3.164	0.07
Hgb	0.179	0.943	0.33
HDL	0.063	0.331	0.56
LDL	0.018	0.093	0.76
Trig	0.263	1.390	0.24
HDL / LDL	0.263	1.389	0.24
Trig / HDL	0.147	0.777	0.38

CAD, coronary artery disease; DM, diabetes mellites; HDL, high density lipoprotein; Hgb, hemoglobin; HT, hypertension; LDL, low density lipoprotein; SII, systemic immune inflammation index; Trig, triglycerides.

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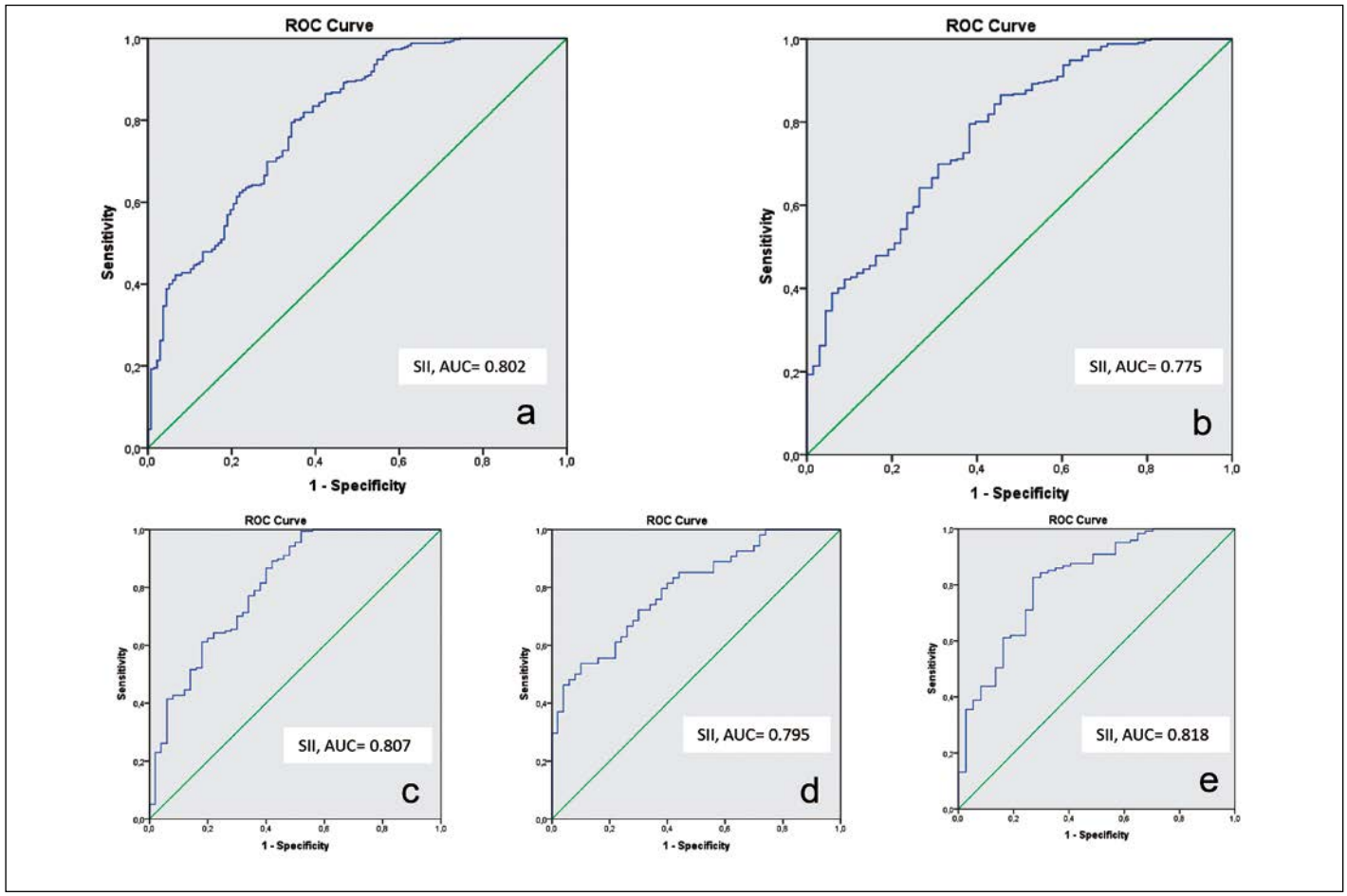
Table 4. Binary logistic regression of myocardial infarction subtypes according to clinical parameters

Variable	B	S.E.	Wald	df	p	Exp(B)	95% CIfor Exp(B)	
							Lower	Upper
SII	-0.002	0.000	51.500	1	<0.01	0.998	0.997	0.998
Age	0.001	0.012	0.005	1	0.94	1.001	0.977	1.025
Gender	-0.006	0.330	0.000	1	0.98	0.994	0.521	1.896
Smoking	0.210	0.265	0.627	1	0.42	1.234	0.734	2.076
HT	0.739	0.266	7.699	1	0.006	2.094	1.242	3.530
DM	0.209	0.253	0.680	1	0.41	1.232	0.750	2.025
CAD	-0.212	0.327	0.418	1	0.52	0.809	0.426	1.537
Hgb	-0.091	0.083	1.202	1	0.27	0.913	0.775	1.074
HDL	-0.014	0.019	0.500	1	0.48	0.986	0.950	1.024
LDL	-0.007	0.014	0.268	1	0.60	0.993	0.965	1.021
Cholesterol	0.012	0.014	0.669	1	0.41	1.012	0.984	1.040
Trig	-0.001	0.003	0.238	1	0.62	0.999	0.993	1.004

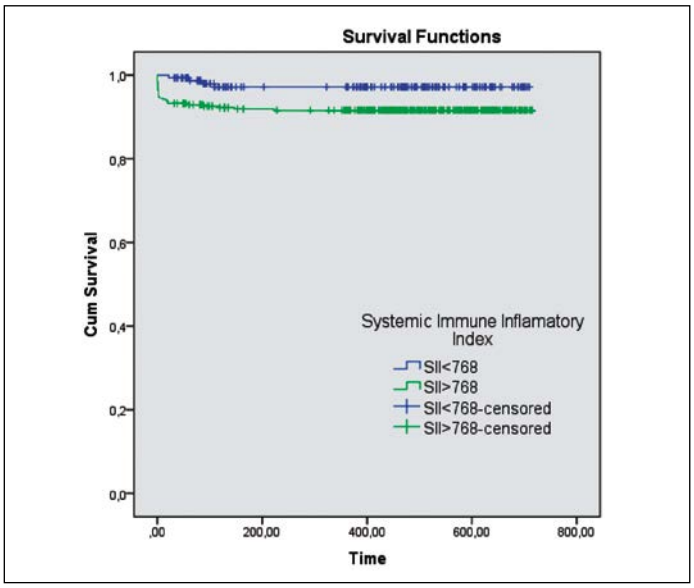
CAD, coronary artery disease; DM, diabetes mellites; HDL, high density lipoprotein; Hgb, hemoglobin; HT, hypertension; LDL, low density lipoprotein; SII, systemic immune inflammation index; Trig, triglycerides.

Figure 1. ROC curve analyses of the subgroups according to STEMI and NSTEMI



a) ROC curve analysis of SII parameter according to STEMI and Non-STEMI patients. b) ROC curve analysis of SII parameter according to STEMI and Non-STEMI with acute total occluded coronary artery. c) ROC curve analysis of SII parameter according to STEMI and Non-STEMI in only LAD culprit lesion d) ROC curve analysis of SII parameter according to STEMI and Non-STEMI in only CX culprit lesion e) ROC curve analysis of SII parameter according to STEMI and Non-STEMI in only RCA culprit lesion.

Figure 2. Kaplan-Meier survival curves of long-term mortality according to the SII cut-off value



Kaplan–Meier survival curves of long-term mortality according to SII cut-off value (Log Rank: p=0.018, Breslow: p=0.015 and Tarone–Ware:p=0.016

individually to compare STEMI and NSTEMI for the artery containing the culprit lesion. All findings were significantly different between the groups (Figure 1). STEMI and NSTEMI were compared according to number of diseased vessels. The difference between these groups was not significant (p=0.55).

STEMI and NSTEMI groups were analyzed with the univariate method to determine which parameters had major effects. SII, age, smoking status, HT, DM, CAD, number of diseased vessels, hemoglobin, WBC, HDL, LDL, triglyceride (Trig), LDL/HDL, and Trig/HDL ratio were compared. Only SII and HT showed significant differences between the groups (p<0.01 and p=0.007, respectively; Table 3).

SII was analyzed with the aforementioned parameters to determine which significantly affects the SII. HT was not associated with increased SII (p=0.27); however, SII was positively correlated with age (p=0.006). In light of these data, binary logistic regression was performed to investigate whether inclusion of other variables such as age, HT, DM, CAD changed the aforementioned results. Only SII and HT had a statistically difference between STEMI and NSTEMI groups (p<0.01 and p=0.006, respectively; Table 4).

Long-term follow-up

The SII values of cardiovascular disease survivors and those who died from cardiovascular causes differed significantly (p=0.006). ROC curve analysis showed that an SII value of 1105×10^9/l was the cut-off point (sensitivity= 83.3% and specificity=57.9%) for discrimination of cardiovascular survivors from those who died from cardiovascular causes (p<0.01, AUC=0.741). Patients with values greater than 1105×10^9/l are more likely to die from cardiovascular causes. The Kaplan–Meier Curve was plotted with the event-free survival data from the follow-up time. Mean follow-up time was 436.9±208.7 days, and 30 (6.4%) patients dieddue to any cardiovascular reason during the follow-up period. Long-term mortality was significantly different according to the SII cut-off value (p=0.018, p=0.015, and p=0.016 for Log Rank, Breslow, and Tarone–Waretests, respectively; Figure 2). In addition, mortality was compared according to the two types of myocardial infarction, and there was no significance between the groups (p=0.071, p=0.055, and p=0.062 for Log Rank, Breslow, and Tarone-Ware tests, respectively).

Discussion

STEMI is usually seen afterrupture of an atherosclerotic plaque. On the other hand, NSTEMI may occur due to acute plaque rupture or to an imbalance in oxygen supply and demand due to vascular narrowing, i.e., type 1 or type 2 myocardial infarction. Ino et al. found that the incidence of culprit plaque rupture (CPR), thin-cap fibroatheroma (TCFA), and red thrombus was significantly higher in STEMI compared with NSTEMI (70% vs. 47%, 78% vs. 49%, and 78% vs. 27%, respectively) [14]. In addition, another study showed that the prevalence of CPR and TCFA were higher in STEMI (70.4 and 76.6%) than in NSTEMI (55.6 and 56.3%) [15]. As noted above, STEMI patients require more CPR than NSTEMI patients. However, it was also observed that NSTEMI have frequent plaque ruptures. In the light of these data, we studied patients with both STEMI and NSTEMI, and we also compared STEMI and NSTEMI with ATOCA.

STEMI generally emerges with abrupt total occlusion of coronary arteries (Thrombolysis in Myocardial Infarction (TIMI) 0 flow). However, in NSTEMI, coronary artery stenosis has a wide spectrum (TIMI 0, 1, or 2). Karwowski et al. found that total occlusion in STEMI and NSTEMI was 64.4% and 26.6%, respectively [16]. Similar results were found by Aslanger et al., who found that ATOCA in NSTEMI was 28.2% [6]. 40777 NSTEMI patients were included in a meta-analysis that reached the same result (ATOCA was 25.5%) [17]. Nearly 25% of the non-STEMI patients had ATOCA. As a result, all NSTEMI patients should not be evaluated in the same manner, and patients with ATOCA classified initially as NSTEMI should be considered as STEMI. However, there is no exact diagnostic algorithm for this group of patients, and the treatment of this group is usually delayed.

Early intervention for STEMI and NSTEMI with ATOCA seems especially important. Khan et al. claimed that NSTEMI with ATOCA on coronary angiography has higher risk of mortality and that major adverse cardiac events and better risk stratification tools are needed to identify such high-risk, acute coronary syndrome patients to facilitate earlier revascularization and to potentially improve outcomes [17]. In another study, researchers also suggested that improved,

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early risk stratification techniques should be applied [18]. In addition, other researchers claimed that only ECG changes, such as ST segment elevation, have no reliable diagnostic certainty for myocardial infarction patients with ATOCA [7, 18, 19]. Regarding these data, Aslanger et al. claimed that it is time for a paradigm shift from the STEMI/NSTEMI model to anacute coronary occlusion myocardial infarction (ACOMI) model, i.e., an ACOMI/non-ACOMI model, for the acute management of myocardial infarction patients [6]. However, these recommendations depend on the ECG evaluation, and subjective assessment of ECG parameters may lead to misdiagnosis. As a result, the SII, which is an easily and rapidly determined objective parameter, was studied in the current investigation to determine whether it might be used to indicate early intervention for NSTEMI patients with ATOCA.

Hematological parameters, Neu/Lym, Neu/HDL, CRP/albumin, etc., have been proven to be useful and reliable markers for cardiovascular risk and for predicting mortality [20, 21]. Some of these parameters were also studied on acute total occluded vessels [22, 23]. These parameters are easily accessible, fast resultant, and cost-effective. SII is a well-known parameter and components of this parameter are very important for provoking acute thrombosis. Neutrophils play an important role in plaque rupture in the acute phase, and lymphocytes have chronic effects on plaque formation [24]. Hypercholesterolemia activates degranulation of neutrophils, and this situation leads to macrophage migration into atherogenic plaquethen to plaque rupture [25]. In addition, some of cytotoxic and destructive factors (myeloperoxidase, NADPH oxidase, etc.) that are released from activated neutrophils have roles in endothelial damage [26, 27]. In contrast, lymphocytes were found in a small amount of atherogenic plaques, and some lymphocytes, i.e. regulatory T cells, have atheroprotective roles due to CTLA-4 and LAG-3 proteins [28, 29]. Platelets, another component of SII, are activated in the acute thrombus state, and their number increases with the extent of the thrombus burden [30, 31]. In addition, Ozkan et al. found that SII was independently associated with large coronary thrombus in NSTEMI [32].Considering these data, increased SII leads to plaque formation and indicates the frequency of acute plaque rupture. However, comparison of the STEMI and NSTEMI patients with ATOCA according to SII has not been previously reported.

In conclusion, we aimed to show that SII may be used for the detection of ATOCA in NSTEMI patients, and thus to shorten the door to balloon time. We found that SII was higher in the STEMI patients with ATOCA than in the subgroup of NSTEMI ATOCA or in all NSTEMI patients. All NSTEMI patients and NSTEMI patients with ATOCA were compared with STEMI patients according to ROC curve analysis. A SII value of 768×10^9/l was the cut-off point for both groups. In addition, we found that a higher SII was associated with increased cardiovascular mortality. Thus, in an emergency department, NSTEMI patients with a SII value higher than 768×10^9/l may be assumed as STEMI and treated like STEMI patients. This could shorten the time to percutaneous coronary intervention to <120 min.

Limitations

This study has some limitations. Firstly, this was a retrospective study, so the persuasion level is a bit lower than that of a prospective study. Secondly, the patients' demographic data were obtained from the hospital records, and patients with lack of data were excluded from the study. This could have caused bias. Thirdly, all patients were selected from a single center. Subsequent studies should enrollmore patients to achieve more reliable results. Finally, SII is affected by many conditions (cancer, systemic disease, acute inflammatory state, etc.), and in the beginning state of these conditions, the SII might have been affected.

No conflict of interest is reported.

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