ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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ASSOCIATION BETWEEN SYSTEMIC IMMUNE-INFLAMMATION INDEX AND MORTALITY IN PATIENTS WITH NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

ST SEGMENT YÜKSELMESİZ MİYOKART ENFARKTÜS HASTALARINDA SİSTEMİK İMMÜN ENFLAMASYON İNDEKSİ VE MORTALİTE İLİŞKİSİ

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Öz

Amaç
Akut koroner sendrom mortalitesi ve morbiditesi yüksek bir sendromdur. Yüksek riskli hastaların hastane yatışı esnasında belirlenmesi ve gerekli durumlarda erken revaskülarizasyon stratejilerinin uygulanması hastalarda hayati önem arz etmektedir. Klinik pratikte bu hastaların hızlıca belirlenmesine yönelik basit, etkili, maliyeti ucuz bir indeks ihtiyacı olduğu aşikardır. Tüm bu nedenlerden dolayı bu çalışmada tarafımızca SII'nın, AKS alt grubu olan NSTEMI geçiren hastalarda mortaliteyi ön görmedeki yerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem
01.01.2022-31.12.2022 tarihleri arasından Aydın Adnan Menderes Üniversitesi Tıp Fakültesi Uygulama ve Araştırma Hastanesi koroner anjiyografi ünitesinde koroner anjiyografi işlemi uygulanan hastalar geçmişe dönük olarak tarandı. St segment yükselmesiz miyokart enfarktüsü geçiren hastalarda ve normal koroner arterler saptanan hastalarda SII [(nötrofil x platelet) / lenfosit] hesaplandı. Bu indeks ile tüm nedenlere bağlı mortalite gelişimi arasında ilişki olup olmadığı araştırıldı.

Bulgular
Grup 1 olarak değerlendirilen NSTEMI grubu SII indeks ortancası Grup II'ye göre anlamlı düzeyde yüksek bulundu (p<0.001). Mortalite gözlenen gruba ait nötrofil ve SII indeksi değerleri ortalaması, sağkalım grubuna göre istatistiksel olarak anlamlı derecede yüksek bulundu (sırasıyla p=0.002 ve p=0.019). Çok yönlü lojistik regresyon sonucunda, NSTEMI varlığı yaş (odds ratio [OR]: 9.891; 95% CI: 2.096-46.671, p<0.001) ve SII indeksinin (odds ratio [OR]: 1.001; 95% CI: 1.000-1001, p=0.039) tüm nedenlere bağlı mortaliteyi bağımsız olarak öngördüğü saptandı. NSTEMI grubunda SII indeksi 609.98 değerinden yüksek olguların sağkalım beklentisi 18 ay için %68.1, SII indeksi 609.98 değerinden düşük olgular için ise %79.3 olarak hesaplandı ancak fark istatistiksel olarak anlamlı bulunmadı (p=0.426).

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Sonuç
SII, NSTEMI hasta grubunda mortaliteyi ön görmede faydalı bir indeks olmasına rağmen sağ kalımı öngörmede yeterli değildir.

Anahtar Kelimeler: Miyokart enfarktüsü, Mortalite, SII

Abstract

Objective
Acute coronary syndrome (ACS) is a disease associated with high mortality and morbidity. It is essential to identify high-risk patients during hospitalization and to implement early revascularization strategies if necessary. There is a clear need for a simple, effective and cost-effective index for rapid identification of these patients in clinical practice. The aim of this study was to investigate the clinical significance of the systemic immune inflammation index (SII) in non-ST-segment elevation myocardial infarction (NSTEMI), a subgroup of ACS, and to evaluate its association with mortality.

Material and Method
Patients who underwent coronary angiography at the Coronary Angiography Unit of Aydın Adnan Menderes University Faculty of Medicine Research and Training Hospital between January and December 2022 were retrospectively reviewed. Individuals with a diagnosis of NSTEMI were included as group I, and individuals with normal coronary arteries during coronary angiography were included as group II (control group). Clinical variables and calculated SII values of the groups were recorded. The role of SII in predicting all-cause mortality and its effect on expected survival were evaluated.

Results
The median value of the SII index was significantly higher in the NSTEMI group (group I) than in the control group (group II) ($p<0.001$). The mean neutrophil and SII index values of the mortality group were significantly higher than those of the survival group ($p=0.002$ and $p=0.019$, respectively). Multivariate logistic regression showed that the presence of NSTEMI (odds ratio [OR]: 9.891; 95% CI: 2.096-46.671, $p<0.001$) and SII index (odds ratio [OR]: 1.001; 95% CI: 1.000-1001, $p=0.039$) independently predicted all-cause mortality. The cut-off point for the SII index was 609.98 using ROC curve analysis. Survival expectancy at 18 months was 68.1% for group I patients with SII >609.98 and 79.3% for group I patients with SII <609.98, but the difference was not statistically significant ($p=0.426$).

Conclusion
The SII score can help predict all-cause mortality in NSTEMI patients, but it is unsuitable for predicting survival.

Keywords: Myocardial infarction, Mortality, SII

Introduction

Atherosclerosis and cardiovascular diseases are common conditions that cause the death of approximately one out of every three people worldwide. This condition, which ranges from stable coronary artery disease to acute coronary syndrome (ACS), leads to the death of many people at any time without warning. Approximately 5.5-18.2% of patients treated for ACS, which includes unstable angina, non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction, die during hospitalization (1, 2).

Currently, coronary angiography and percutaneous coronary intervention are widely used to treat haemodynamically significant coronary lesions in patients with acute coronary syndromes. In addition, improvements in stent technology and implantation techniques have contributed to a reduction in the incidence of major adverse cardiovascular events in patients after the procedure. However, 10.7% of patients are readmitted to hospital within one month due to persistent ischaemia and anginal symptoms (3,4). There is a need to develop pre-procedural risk scoring to predict post-procedural complications and identify high-risk patients.

Cardiovascular disease, the leading cause of death worldwide, has a major impact on national economies due to the high cost of patient treatment and follow-up. Therefore, researchers have recently focused on the underlying pathophysiology through preventive medicine before the onset of disease. A common and popular hypothesis is that the inflammatory response is involved in the development of the disease and its progression to acute coronary syndrome. Neutrophils, lymphocytes, platelets and monocytes, the main components of the inflammatory system, are known to be primarily responsible for this response. Lymphocytes have an anti-atherosclerotic effect by regulating the immune response (5). Conversely, inflammatory mediators released by neutrophils lead to endothelial dysfunction and damage to the vessel wall. In addition,

chemokines and pro-inflammatory cytokines released by platelets also contribute to endothelial cell damage (6, 7). Neutrophils lead to the release of prothrombotic molecules via platelets, triggering the development of thrombosis within the vessel and causing the migration of monocytes into the region. The net result of all these events is cardiovascular disease. Because of these characteristics of the immune system, researchers have conducted many studies in clinical trials on the role of ratios such as neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in predicting cardiovascular disease (9). However, as each of these ratios did not take into account the effect of another inflammatory cell, they could not provide an objective, independent result. As a result, studies in this area contradict each other. Consequently, an index called the systemic immunoinflammatory index (SII) [(neutrophil X platelet)/lymphocyte], which includes the effect of all three inflammatory responses, has been developed. It was initially introduced into the literature with studies suggesting that it was effective in predicting survival in patients with oncological malignancies and many other diseases (8). More recently, however, its association with cardiovascular disease has been studied and it has been reported to be a more useful index alone in predicting these diseases compared with NLR and PLR (9, 10).

Acute coronary syndrome (ACS) is a disease associated with high mortality and morbidity. Identification of high-risk patients during hospitalization and implementation of early revascularization strategies when necessary are of vital importance in patients. In clinical practice, there is a clear need for a simple, effective, and cost-effective index for rapid identification of these patients. The aim of this study was to investigate the clinical significance of the systemic immune inflammation index (SII) in non-ST segment elevation myocardial infarction (NSTEMI), a subgroup of ACS, and to evaluate its association with mortality.

Material and Method

Selection of Patients

Patients who underwent coronary angiography at the Coronary Angiography Unit of of Aydın Adnan Menderes University Faculty of Medicine between January and December 2022 were retrospectively reviewed. Patients who presented to the emergency department with acute chest pain and whose electrocardiogram showed elevated cardiac troponin levels without persistent ST segment elevation were classified as NSTEMI patients according to the recommendations of the "2020 European Society of Cardiology NSTEMI diagnosis and treatment guidelines". Individuals with a diagnosis of NSTEMI were defined as group I, and individuals with normal coronary arteries on coronary angiography were defined as group II (control group). Demographics, comorbidities and other clinical variables were recorded. SII [(neutrophil x platelet)/lymphocyte] was calculated from the neutrophil, platelet, and lymphocyte values in the complete blood count in the blood tests routinely obtained during hospitalisation. In addition, patients who died in hospital were recorded in the hospital information operating system. Patients and their relatives were contacted via telephone numbers registered in the system and asked whether an out-of-hospital death had occurred and was recorded. Patients with active infection, malignancy, autoimmune disease, age below 18 years, and pregnancy were excluded from the study.

Statistical Analysis

SPSS 23.0 software (SPSS Inc. Chicago, IL) was used for statistical analysis. The Kolmogorov-Smirnov test was used to assess the conformity of the data to normal distribution. Parametric tests were used for data conforming to normal distribution, while nonparametric tests were used for other data. Data were analyzed using descriptive statistics (number, percentage, mean, standard deviation, median, and interquartile range), T-test, Man-Whitney U and chi-squared tests, logistic regression, and Receiving Operator Characteristic (ROC) curve. The Kaplan-Meier method was used for survival analysis. The significance level was accepted as $p<0.05$.

The ethical compliance of our study was approved by the decision of the Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine on 11.08.2022 with the number 218461. Our study was conducted according to the Declaration of Helsinki.

Results

Of the 157 patients included in the study, 76 (48.4%) were diagnosed with NSTEMI and included in group I, while 81 (52.6%) patients with normal coronary arteries were included in group II. The mean age in group I (65.5 ± 10.82) was significantly higher than in group II (56.58 ± 11.23) ($p<0.001$). The median SII Index score was 796.09 in group I and 523.04 in group II. The median SII Index score of group I was significantly higher than that of group II ($p<0.001$). Other patient characteristics and distribution of variables in the groups are shown in Table I.

In our study, which evaluated all-cause mortality, 24

Table 1 Distribution of patient characteristics and variables according to groups

	Group I (n=76)	Group II (n=81)	p value
Age (mean ± ss)	65.5 ± 10.82	56.58 ± 11.23	***<0.001**
Gender (n), (%)			**#0.02**
Male	56 (73.7)	46 (56.8)	
Female	20 (26.3)	35 (43.2)	
CAD (n), (%)	26 (34.2)	19 (23.5)	#0.09
HT (n), (%)	43 (56.6)	39 (48.1)	#0.33
DM (n), (%)	24 (31.6)	31 (38.3)	#0.4
Death (n), (%)	22 (28.9)	2 (2.5)	**#<0.001**
Neutrophil (m), (IQR)	6.51 (3.26)	4.67 (2.57)	+<0.001
Lymphocyte (mean ± ss)	2.14 ± 1.07	2.31 ± 0.79	*0.19
Platelets (mean ± ss)	260.57 ± 77.06	253.23 ± 73.87	*0.49
SII (m), (IQR)	796.09 (1032.11)	523.04) (358.34)	+<0.001

*: T-test, #: Chi-square test, +: Mann Whitney U
CAD: Coronary Artery Disease, HT: Hypertension, DM: Diabetes mellitus

Table 2 Patient characteristics in the mortality and survival groups

	Non-Survivors (n=24)	Survivors (n=133)	p value
Age (m), (IQR)	73 (10)	58 (17)	**<0.001+**
Gender (n), (%) Male Female	 15 (62.5) 9 (37.5)	 87 (65.4) 46 (34.6)	 0.81#
CAD (n), (%)	8 (33.3)	37 (27.8)	0.62#
HT (n), (%)	18 (75)	64 (48.1)	**0.025#**
DM (n), (%)	12 (50)	43 (32.3)	0.077#
NSTEMI (n), (%)	22 (91.7)	54 (40.6)	**<0.001#**

#: Chi-square test, +: Mann Whitney U
CAD: Coronary Artery Disease, HT: Hypertension, DM: Diabetes mellitus

of 157 patients (15.28%) died during follow-up. The rate of NSTEMI was 91.7% in the mortality group and 40.6% in the survival group. The association between NSTEMI and mortality was statistically significant (p<0.002). The mean age was statistically significantly higher in the mortality group (<0.001). The rate of hypertension was 48.1% in the survival group and 75% in the mortality group, and this difference was statistically significant (p=0.025). Other variables of the mortality and survival groups are shown in Table II.

Laboratory parameters of the mortality and survival groups are shown in Table III. The mean neutrophil and SII index values of the mortality group were significantly higher than those of the survival group (p=0.002 and p=0.019, respectively).

One-way logistic regression and multivariate logistic regression analysis to determine the relationship between variables and all-cause mortality are shown in Table IV. Multivariate logistic regression showed

Table 3 Laboratory parameters of the mortality and survival groups

	Non-Survivors (n=24)	Survivors (n=133)	p value
Neutrophil (m), (IQR)	7.6 (4.4)	4.96 (2.27)	**0.002+**
Lymphocyte (mean ± ss)	1.36 ± 1.85	2.27 ± 0.77	0.074*
Platelets (mean ± ss)	256.52 ± 92.01	256.13 ± 72.11	0.984*
SII (m), (IQR)	1389.34 (2518.92)	534.65 (400.17)	**0.019+**

*: T-test, +: Mann Whitney U

Table 4 Evaluation of the role of variables in predicting mortality by one-way and multi-way logistic regression

	Univariate	p-value	Multivariate	p-value
	Odds ratio (95% CI)		Odds ratio (95% CI)	
Age	1.088 (1.039 -1.137)	**<0.001**	1.043 (0.991-1.098)	0.108
Hypertension	3.23 (1.208-8.657)	**0.019**	1.886 (0.604-5.884)	0.275
NSTEMI	16.093 (3,630-71,285)	**<0.001**	9.891 (2.096-46.671)	**0.004**
SII	1.001 (1.000-1.0001	**0.001**	1.001 (1.000-1.001)	**0.039**

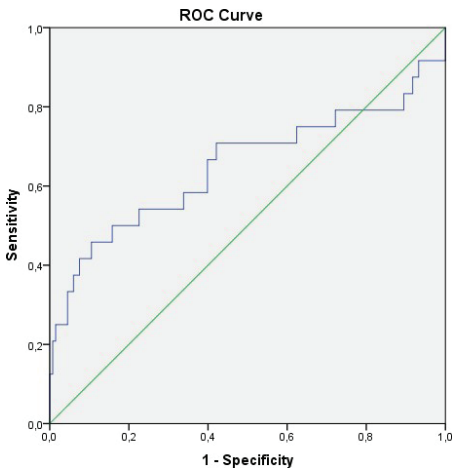

Figure 1
Evaluating the Effectiveness of the SII Index in Predicting All-Cause Mortality with ROC Curve Analysis

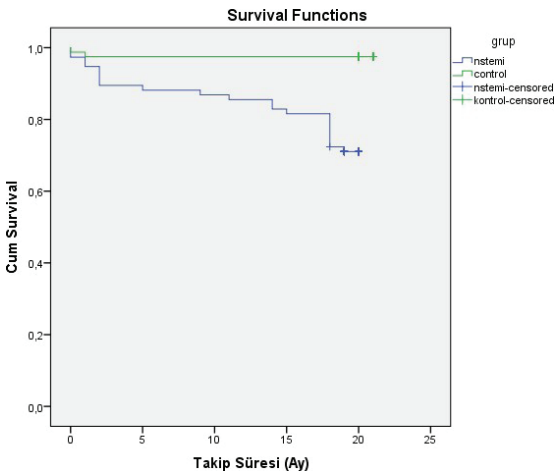

Figure 2
Assessing Survival Expectations in Groups via Kaplan-Meier Analysis

that the presence of NSTEMI (odds ratio [OR]: 9.891; 95% CI: 2.096-46.671, p<0.001) and SII index (odds ratio [OR]: 1.001; 95% CI: 1.000-1001, p=0.039) independently predicted all-cause mortality.

The cut-off point for the SII index to predict all-cause mortality was determined by ROC curve analysis (Figure 1). The SII index value predicting mortality was 609.98 with 70.8% sensitivity and 57.9% specificity (AUC: 0.650, 95% CI: 0.501 - 0.800, p: 0.019).

In the survival analysis using the Kaplan-Meier method, the 18-month survival expectancy was 72.4% in Group I and 97.5% in Group II in our study with a

median follow-up of 20 months (p<0.001) (Figure-2). Survival analysis was performed in the NSTEMI subgroup according to the cut-off point determined for the SII index. The survival expectancy at 18 months was 68.1% in patients with SII index higher than 609.98 and 79.3% in patients with SII index lower than 609.98, but the difference was not statistically significant (p=0.426) (Figure-3).

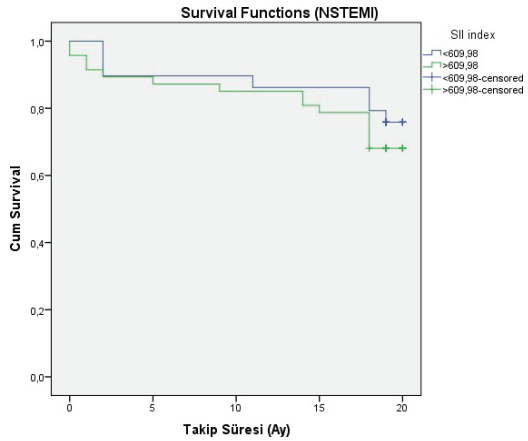

Figure 3
Assessment of the Survival Impact of the SII Index in the NSTEMI Subgroup

Discussion

In this retrospective study ın the NSTEMI group, the 18-month survival rate was 68.1% for patients with SII values above the cut off of 609.98, whereas it was 79.3% for patients with SII values <609.98. Although a better survival rate was seen in patients with a lower SII index, it was not statistically significant.

Cardiovascular disease is the leading cause of death worldwide. Since the important role of inflammation in the pathophysiology of cardiovascular disease has been recognized, the search for a marker that can be used in clinical practice to detect cardiovascular disease before it occurs has become the focus of studies. Neutrophils, platelets, and lymphocytes, which are the cornerstone of the inflammatory response, can be determined by a complete blood count, which is an inexpensive, accessible, and easily performed test in daily practice. Inflammatory cell-oriented markers developed for this purpose, such as NLR and PLR, have been retrospectively analyzed in various clinical studies and their association with cardiovascular disease has been investigated. Li et al. reported that all inflammatory markers (SII, PLR, NLR) were effective in predicting major adverse cardiac events (MACE) in their study of 1701 ACS patients. In another clinical study, the SII index was found to be a better option than PLR, CRP, and NLR in predicting cardiovascular disease (11). Because they do not include three inflammatory cells (neutrophils, platelets and lymphocytes) at the same time, the results obtained from studies using these markers are contradictory. Therefore, the SII index, which includes all three components of neutrophils, platelets, and lymphocytes, was developed. Ye et al. reported that the SII index was an effective marker for predicting cardiovascular disease in the general population in their meta-analysis in which they analyzed data from 13 studies and 152,996 participants (12). Another meta-analysis also found that the SII index was associated with an increased risk of cardiovascular disease (13). In a retrospective study conducted by Xia et al. in which 42,875 adult patients were retrospectively analyzed between 1999 and 2018, it was shown that all-cause mortality and mortality due to cardiovascular disease increased in patients with an SII index higher than 655.56 (14). In our study, the mean SII index values of the mortality group were statistically significantly higher than those of the survival group. In this regard, the results of this study are consistent with the literature.

Acute coronary syndrome (ACS) is a disease associated with high mortality and morbidity. Identification of high-risk patients during hospitalization and implementation of early revascularization strategies, if necessary, are of vital importance to patients. The need for a simple, effective, and cost-effective index for rapid identification of these patients is evident in clinical practice. The SII index is therefore a current marker that is frequently investigated in ACS patients. In a retrospective study of 389 NSTEMI patients, Özkan et al. demonstrated an association between the SII index and increased coronary thrombus burden (15). Dziedzic et al. investigated the relationship between SII index and chest pain severity in ACS patients and found that higher SII index values were linearly related to more severe chest pain (16). In another study, they retrospectively evaluated 244 postmenopausal women with ACS and found that the SII index was higher in this patient group compared with stable coronary artery disease. As a result of the subgroup analysis they performed in ACS patients, they found that the highest values were in NSTEMI patients (17). Yang et al. found that the SII index was associated with worse survival in coronary artery disease (18). Huang et al. studied 711 patients with acute myocardial infarction and found that the SII index was potentially useful in predicting all-cause mortality (19). In our study, the SII index was found to be higher in the NSTEMI group, which is a subgroup of ACS, than in the group of patients

with normal coronary arteries. Survival analysis was performed in the NSTEMI subgroup according to the cut-off point determined for the SII index, and the 18-month survival expectancy of patients with an SII index greater than 609.98 was 68.1%. Although this survival rate was lower than that of patients with an SII <609.98, the difference was not statistically significant.

Neutrophils are responsible for inflammation in the arterial wall and their increased numbers contribute to atherosclerotic plaque formation and major adverse cardiovascular events. They stimulate monocyte migration to the site of inflammation by inducing the secretion of chemotactic proteins and by increasing the levels of IL-1 beta, a proinflammatory cytokine released by macrophages. They also affect platelet and endothelial function, leading to thrombotic activity within the vessel and causing ACS (20,21,22). Sezer et al. found that elevated neutrophil levels after percutaneous coronary intervention in patients with acute myocardial infarction were associated with more microvascular perfusion damage (23). Systemic changes occur throughout the body with aging. Increased mortality may occur as a result of increased inflammation with age. A subgroup analysis of a study by Xia et al. showed that increased SII index over the age of 60 years had a higher positive correlation with mortality. They explained this finding with an age-related inability to clear the inflammatory cells present in the circulation from the body and emphasized that this may lead to an increased risk of mortality (14,24). In our study, the mean neutrophil levels of the mortality group were found to be significantly higher than those of the survival group. On the other hand, the mean age in the survival group was significantly lower than that in the mortality group, and the data obtained were evaluated according to the literature.

The SII index is inexpensive, easily calculable, and accessible for predicting mortality in patients with non-ST elevation. However, more extensive studies with larger patient populations and subgroup analysis are needed for the clinical use of the SII index in cardiovascular diseases.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The ethical compliance of our study was approved by the decision of the Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine on 11.08.2022 with the number 218461. Our study was conducted according to the Declaration of Helsinki.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data available on request from the authors.

Authors Contributions
SÇ: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing original draft.

ÖFR: Conceptualization; statistical analysis. Writing-review & editing.

BM: Formal analysis; Validation; Writing-review & editing.

SG: Formal analysis; Validation; Writing-review & editing.

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