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Evaluation of the Systemic Immune-Inflammatory Index (SII) and NAPLES Score (NS) in Patients with Non-ST-Elevation Myocardial Infarction (NSTEMI)

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Abstract

Objective: Non-ST elevation myocardial infarction (NSTEMI) is the most common type of acute coronary syndrome and has a poor prognosis. The SII and NS are derived from blood cell counts and reflects the balance between inherited and acquired immunity and the association between the immune system and endothelial dysfunction. This study aimed to compare the prognostic value of two novel inflammatory biomarkers, the systemic immune-inflammatory index (SII) and the Naples score (NS), with that of other inflammatory markers and risk scores in patients with NSTEMI.

Methods: This was a retrospective cohort analysis of 50 NSTEMI patients and 50 controls matched by age and sex who were admitted to our hospital. We calculated the SII and NS scores and other ratios, indices, and risk scores for each patient. We used Pearson's correlation coefficient and receiver operating characteristic (ROC) analysis to examine the correlations and predictive values of the SII index, NS score, and other biometric markers and risk scores.

Results: The SII and NS were significantly greater in the NSTEMI group than in the control group. They had strong positive correlations with the NLR, MHR, PLR, and TC/HDL ratio, and moderate positive correlations with TIMI and HEART scores ($r>0.3$, $p<0.01$ for both). The SII and NS also had higher AUC values than other biometric markers and risk scores ($p<0.05$ for both).

Conclusions: The SII and NS are inexpensive, widely available and easy to measure markers that may have utility for cardiac risk stratification in NSTEMI patients.

Keywords: Non ST-elevation myocardial infarction, NAPLES Score, Systemic immune-inflammatory index, Novel inflammatory biomarkers

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ST Yükselmesi Olmayan Miyokard İnfarktüsü (NSTEMI) Hastalarında Sistemik İmmün İnflamatuar İndeks (SII) ve NAPLES Skorunun (NS) Değerlendirilmesi

Öz

Amaç: Akut koroner sendromun (AKS) en sık görülen tipi olan ve kötü prognoza sahip non-ST elevasyonlu miyokard infarktüsü (NSTEMI) hastalarında, iki yeni inflamatuar biyo belirteç olan sistemik immün-inflamatuar indeks (SII) ve Naples skoru (NS) ile diğer inflamatuar belirteçler ve risk skorları arasındaki ilişki ve prognostik değer karşılaştırılmıştır. SII ve NS, kan hücre sayımlarından türetilen ve doğal ve uyarlanmış bağışıklık sistemi arasındaki dengeyi ve bağışıklık sistemi ile endoteldis fonksiyonu arasındaki ilişkiyi yansıtan indekslerdir.

Yöntemler: Bu çalışmada, hastanemize yatırılan 50 NSTEMI hastası ile cinsiyet ve yaşa göre eşleştirilmiş 50 kontrol grubu retrospektif olarak incelenmiştir. Her hastaya SII ve NS skorları ile diğer oranlar, indeksler ve risk skorları hesaplanmıştır. SII indeksi, NS skoru ve diğer biyo belirteçler ve risk skorlarının korelasyonlarını ve prediktif değerlerini incelemek için Pearson korelasyon katsayısı ve Receiver operating characteristic (ROC) curve analizi kullanılmıştır.

Bulgular: Sonuç olarak, SII indeksi ve NS skoru NSTEMI grubunda kontrol grubuna göre anlamlı derecede yüksek bulunmuştur. NLR, MHR, PLR ve TC/HDL oranı ile güçlü pozitif, TIMI ve HEART skorları ile orta derecede pozitif korelasyon göstermişlerdir ($r>0.3$, $p<0.01$ her ikisi için de). Ayrıca SII indeksi ve NS skoru, diğer biyometrik belirteçler ve risk skorlarından daha yüksek AUC değerlerine sahip olmuştur ($p<0.05$ her ikisi için de).

Sonuç: SII ve NS, ucuz, yaygın olarak kullanılabilir ve kolayca ölçülebilen belirteçler olup, NSTEMI hastalarında kardiyak risk stratifikasyonu için yararlı olabilirler.

Anahtar kelimeler: Non ST-elevasyonlu miyokard infarktüsü, NAPLES Skoru, Sistemik İmmün-İnflamatuar İndeks, yeni inflamatuar biyo belirteçler.

INTRODUCTION

Cardiovascular diseases are among the most important causes of morbidity and mortality worldwide. Among these diseases, acute coronary syndrome (ACS) has various clinical manifestations, such as myocardial infarction (MI) or unstable angina. Non ST elevation myocardial infarction (NSTEMI) is the most prevalent type of ACS and accounts for 61% of MI cases[1,2].

NSTEMI patients have a complex prognosis that depends on multiple factors, such as age, comorbidities, cardiac function and treatment strategies. These patients have lower in-hospital mortality than patients with ST-elevation myocardial infarction (STEMI) but have twice the long-term mortality risk. Thus, it is vital to conduct thorough risk assessments and clinical follow-up of these patients from the time of NSTEMI diagnosis to avoid adverse outcomes. Inflammation is an important factor in the pathogenesis and progression of NSTEMI. It begins with the rupture of atherosclerotic plaques in the coronary arteries, which causes the arterial lumen to be blocked by a thrombogenic environment. This triggers the activation and secretion of various cytokines, chemokines and adhesion molecules by different types of white blood cells, especially lymphocytes, neutrophils, monocytes and platelets. The levels of some of these inflammatory markers, such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α), are increased in NSTEMI patients and are linked to poor prognosis. However, these markers are not specific to NSTEMI and may be influenced by other factors, such as infection, trauma or malignancy[3-8].

Therefore, it is very important to evaluate inflammation with simple and inexpensive biometric markers in NSTEMI patients. These biometric markers include

neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/HDL ratio (MHR), NS score and total cholesterol/HDL cholesterol ratio (TC/HDL). These biometric markers are calculated as ratios or combinations of parameters obtained from simple blood tests, such as neutrophil, lymphocyte, monocyte, platelet and cholesterol levels. These biometric markers can reflect the relationship between the immune system and endothelial dysfunction and show the impact of inflammation on atherosclerosis. The NLR, MHR, PLR and TC/HDL ratios are biometric markers obtained from simple and inexpensive blood tests that are associated with inflammation and atherosclerosis. These ratios are used to assess the risk of ACS. These ratios are associated with adverse outcomes such as heart failure, myocardial infarction, arrhythmias and mortality in CVD patients. Studies in the literature also support that these ratios have prognostic value in NSTEMI patients. However, some studies also suggest that these ratios are not sufficient or consistent with other risk scores or inflammatory markers[9-13].

The systemic immune-inflammatory index (SII) is calculated as the product of the neutrophil count and platelet count divided by the lymphocyte count and reflects the balance between inherited and acquired immunity. SII is an important indicator of inflammatory processes associated with disease progression, especially in patients with infectious diseases or other conditions. The SII can reflect the relationship between the immune system and endothelial dysfunction associated with chronic inflammatory conditions such as cardiovascular disease (CVD). Studies in the literature support that the SII has prognostic value in NSTEMI patients[14-17]. In particular, it has been shown that the SII is associated with adverse outcomes such as mortality, myocardial infarction, stent thrombosis and heart failure in NSTEMI patients.

The Naples score (NS) score is a score that includes inflammatory markers such as the lymphocyte-monocyte ratio (LMR), NLR, total cholesterol and albumin. The NS score is used to assess the risk of acute coronary syndrome (ACS). It has been shown that the NS score is associated with adverse outcomes such as mortality, myocardial infarction and stent thrombosis in patients with high NS score. Studies in the literature also support that the NS score has prognostic value in ACS patients[18,19]. However, some studies also suggest that the NS score is not sufficient or shows lower performance compared to other risk scores.

Other scores used to assess the cardiovascular risk of NSTEMI patients include HEART (History, ECG, Age, Risk factors, Troponin) and TIMI (Thrombolysis in myocardial infarction) scores. These scores are based on clinical features such as age, ECG findings, angina frequency, cardiac biomarkers, coronary artery disease history, blood pressure and troponin level. Patients with high scores have a greater risk of mortality, myocardial infarction and ischemic complications. In this study, it was also found that these scores are sensitive and specific tests for NSTEMI diagnosis[20,21]. Studies in the literature also support that these scores have prognostic value in NSTEMI patients. However, some studies also suggest that these scores are not sufficient or consistent with each other. Therefore, it is recommended to use these scores together rather than alone.

In this study, aims to compare the SII and NS with the NLR, MHR, PLR and TC/HDL ratios and with other conventional risk scores such as the TIMI and HEART in NSTEMI patients. We hypothesized that the SII and NS would be more suitable independent predictors of in-hospital and long-term mortality than the NLR, MHR, PLR and TC/HDL ratios in this population.

METHODS

The local ethics committee approved this study (Decision Date/No: 20.09.2022/362). This study was a retrospective analysis of 50 patients with non-ST elevation myocardial infarction (NSTEMI) and 50 age and sex-matched controls who were admitted to our hospital from January 2020 to December 2020. We obtained the data from the hospital records. The NSTEMI group included patients who met the fourth universal definition of MI and had complete blood count, lipid profile, troponin level, and electrocardiogram (ECG) data at admission. We excluded patients who had previous MI, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), malignancy, chronic kidney disease, or inflammatory or infectious disease. The control group had normal coronary angiography results and no history of cardiovascular disease.

The SII was calculated as follows: SII = neutrophil count x platelet count/lymphocyte count (14). The NS score was calculated as follows: The NS score was based on the levels of NLR, LMR, serum albumin and total cholesterol. According to Galizia et al.'s method (the cutoff values of NLR and LMR were defined by MaxStat analysis), serum total cholesterol level ≤ 180 mg/dL, albumin level < 40 g/L, LMR level ≤ 4 or 44NLR level > 2.96 each was assigned 1 point and otherwise 0 point. The NS score was calculated by adding the scores of the aforementioned parameters[22,23]. The other ratios, indices, and risk scores that were calculated for each patient were: The TC/HDL, PLR, MLR, NLR, the total TIMI risk score, and the HEART score. The TIMI risk score was based on clinical features such as age, ECG findings, angina frequency, cardiac biomarkers, coronary artery disease history, and blood pressure[20]. The HEART score was based on clinical features such as history, ECG findings, age, risk factors, and troponin level[21].

Statistical Analysis

The analysis of the data was conducted utilizing the software SPSS, version 21.0 software (IBM Corp., NY, USA). Continuous variables were expressed as mean±standart deviations. Comparisons between groups were conducted with the independent samples t-test, while the chi-square test was utilized for the analysis of categorical data.

The correlations between the SII, NS and other ratios, indices, and risk scores were analyzed using Pearson's correlation coefficient. A correlation coefficient of more than 0.5 or less than -0.5 was considered strong, while a coefficient of between 0.3 and 0.5 or between -0.3 and -0.5 was considered moderate.

The predictive values of the SII, NS and other ratios, indices, and risk scores were assessed using receiver operating characteristic (ROC) analysis. The optimal cut-off values were determined by maximizing the Youden index. A higher AUC indicated a better predictive performance.

RESULTS

The study population consisted of 50 patients with NSTEMI and 50 age- and sex-matched control subjects. The baseline characteristics of the two groups are shown in Table 1. There were no significant differences between the two groups in terms of hypertension, diabetes mellitus, and left ventricular ejection fraction (LVEF). The NSTEMI group had higher TIMI and HEART scores than the control group ($p<0.001$ for both). The NSTEMI group also had significantly higher values of the SII, NS score, NLR, MHR, PLR, and TC/HDL than the control group ($p<0.05$ for all except LMR and PLR).

Table I: Baseline charesteristics of the study population

	NSTEMI		Control		P
	Mean	SD	Mean	SD	
Age, years	61.74	9.60	60.28	9.50	0.456
Gender, Male (%)	29 (60.4)		19(39.6)		0.036
Hypertansion (%)	33 (48.5)		35(51.5)		0.415
DiabetesMellitus (%)	25 (59.5)		17(40.5)		0.078
LVEF, %	50.18	8.20	58.40	8.21	<0.001
TIMI score	3.24	1.13	1.46	0.76	<0.001
HEART score	7.52	1.16	2.50	1.01	<0.001
SII	827.81	720.91	549.52	347.32	0.016
MHR	0.015	0.009	0.011	0.004	0.007
NLR	3.60	3.43	1.99	0.99	0.002
LMR	4.96	2.50	6.77	2.71	0.117
PLR	124.35	78.17	111.75	42.93	0.321
TC/HDL	4.79	1.37	4.31	1.01	0.053
NS	1.76	1.20	1.24	1.13	0.035

P <0.05 was considered statistical significant. Values are presented as n (%) or mean ± standard deviation depending on the variable distribution. Left ventricular ejection fraction (LVEF), the Systemic immune-inflammatory index (SII) and the NAPLES Score (NS), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), total cholesterol/HDL cholesterol ratio (TC/HDL), lymphocyte-monocyte ratio (LMR), monocyte-HDL ratio (MHR).

Table 2 shows the correlations between the SII, NS with other ratios, indices, and risk scores. The SII and NS had strongly positive correlations with MHR, NLR, PLR, and TC/HDL ratio ($r>0.5$, $p<0.001$ for all). The NS and SII also had moderately positive correlations with TIMI and HEART scores ($r>0.3$, $p<0.01$ for both). These results suggest that the SII and NS reflect the balance between inherited and acquired immunity and the connection between the immune system and endothelial dysfunction better than other biometric markers.

Table II: cross-correlation table between risk scores and indices

		TİMİ	HEART	SII	MHR	NLR	LMR	PLR	TC/HDL	NS
TİMİ	PearsonCorrelation		.853**	.230*	.116	.298**	-.146	.194	.060	.277**
	Sig. (2-tailed)		.000	.021	.251	.003	.147	.053	.552	.005
	N	100	100	100	100	100	100	100	100	100
HEART	PearsonCorrelation	.853**		.287**	.202*	.346**	-.170	.169	.112	.281**
	Sig. (2-tailed)	.000		.004	.043	.000	.091	.092	.265	.005
	N	100	100	100	100	100	100	100	100	100
SII	PearsonCorrelation	.230*	.287**		-.068	.931**	-.164	.863**	-.157	.557**
	Sig. (2-tailed)	.021	.004		.500	.000	.103	.000	.120	.000
	N	100	100	100	100	100	100	100	100	100
MHR	PearsonCorrelation	.116	.202*	-.068		-.061	-.330**	-.301**	.468**	.184
	Sig. (2-tailed)	.251	.043	.500		.550	.001	.002	.000	.067
	N	100	100	100	100	100	100	100	100	100
NLR	PearsonCorrelation	.298**	.346**	.931**	-.061		-.186	.798**	-.155	.572**
	Sig. (2-tailed)	.003	.000	.000	.550		.064	.000	.123	.000
	N	100	100	100	100	100	100	100	100	100
LMR	PearsonCorrelation	-.146	-.170	-.164	-.330**	-.186		-.123	.072	-.321**
	Sig. (2-tailed)	.147	.091	.103	.001	.064		.222	.477	.001
	N	100	100	100	100	100	100	100	100	100
PLR	PearsonCorrelation	.194	.169	.863**	-.301**	.798**	-.123		-.265**	.508**
	Sig. (2-tailed)	.053	.092	.000	.002	.000	.222		.008	.000
	N	100	100	100	100	100	100	100	100	100
TC/HDL	PearsonCorrelation	.060	.112	-.157	.468**	-.155	.072	-.265**		-.336**
	Sig. (2-tailed)	.552	.265	.120	.000	.123	.477	.008		.001
	N	100	100	100	100	100	100	100	100	100
NS	PearsonCorrelation	.277**	.281**	.557**	.184	.572**	-.321**	.508**	-.336**	
	Sig. (2-tailed)	.005	.005	.000	.067	.000	.001	.000	.001	
	N	100	100	100	100	100	100	100	100	100

P <0.05 was considered statistical significant. The Systemic Immune-Inflammatory Index (SII) and the NAPLES Score (NS), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), total cholesterol/HDL cholesterol ratio (TC/HDL), lymphocyte-monocyte ratio (LMR), monocyte-HDL ratio (MHR).

Figure 1 and Table 3 show the receiver operating characteristic (ROC) analysis for the predictive values of NS, SII score, and other ratios, indices, and risk scores for in-hospital and long-term mortality. The area under the curve (AUC) values for NS and SII score were significantly higher than those for other risk scores and biometric markers ($p<0.05$ for both). The optimal cut-off values for the SII, NS score, and NLR were 518.52, 1.5, and 1.94, respectively.

Table III: Receiver-operator characteristic (ROC) curve analysis

	AUC (95% CI)	P	Cutt-off	Sensitivity (%)	Spesifity (%)
SII	0.656 (0.549;0.763)	0.007	518.52	62	62
NS	0.614 (0.504;0.724)	0.050	1.50	64	60
TIMI	0.895 (0.831;0.959)	<0.001	2.50	72	88
HEART	0.990 (0.986;0.995)	<0.001	4.50	94	90
NLR	0.716 (0.616;0.816)	<0.001	1.94	64	64
MHR	0.647 (0.539;0.755)	0.011	0.0127	66	64
PLR	0.502 (0.389;0.616)	0.967	102.79	50	48
TC/HDL	0.606 (0.495;0.716)	0.069	4.46	64	62
LMR	0.374 (0.265;0.484)	0.030	5.04	42	40

Results are presented as area under curve (AUC) with 95% confidence interval (CI). P <0.05 was considered statistical significant. The Systemic immune-inflammatory index (SII) and the NAPLES Score (NS), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), total cholesterol/HDL cholesterol ratio (TC/HDL), lymphocyte-monocyte ratio (LMR), monocyte-HDL ratio (MHR).

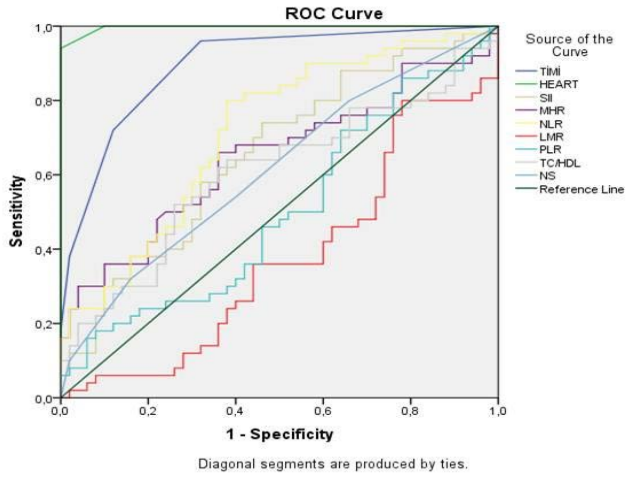

Figure 1. Receiver-operator characteristic (ROC) curve analysis

These results suggest that the SII and NS have better predictive performance than other risk scores and biometric markers in NSTEMI patients.

DISCUSSION

This retrospective cohort analysis found that the SII and NS scores are novel inflammatory biomarkers and independent predictors of mortality in NSTEMI patients. In this study, the association of increased the NS and SII with other inflammatory markers and risk scores in NSTEMI patients was demonstrated for the first time. We also showed that an increased SII and NS score together with the MLR, NLR, PLR, were independent predictors of NSTEMI; and that the SII was significantly correlated with the TIMI and HEART risk scores. In addition to the SII and NS, we studied the PLR, NLR, MLR, TC/HDL ratios which are other indicators of inflammatory status in patients with acute myocardial infarction. Patients with NSTEMI have varying prognoses depending on their characteristics, so it is crucial to stratify them by risk early on to choose the optimal treatment during hospitalization and after discharge. Several risk scores have been proposed to assess the mortality risk in ACS patients, such as the TIMI risk score and the HEART risk score.

The NS is a prognostic scoring model that combines the values of NLR, LMR, albumin and total cholesterol. It has been shown to be useful for predicting mortality in cancer patients and STEMI patients. Therefore, patients with a high NS may benefit from more intensive monitoring and treatment to prevent ischemic events, heart failure, and myocardial infarction. In our study, we found that the NS score was significantly higher in the NSTEMI patient group than in the control group, and that it correlated positively with the TIMI and HEART risk scores. These findings suggest that the NS may be a better predictor of mortality than its individual components in NSTEMI patients[24-27].

In a study conducted with 4,606 patients with heart failure, researchers showed that increased SII predicted short-term mortality[28]. In addition,

in patients with NSTEMI, increased SII level was shown to be an independent predictor of contrast-induced nephropathy[29]. A study by Güzel et al. suggests that the systemic immune inflammation index may be a potential indicator for predicting fractional flow reserve-measured coronary lesion severity[30]. All these studies indicate that increased SII levels are related to poor cardiovascular events in different cardiac pathologies. In our study, similar to these studies, the SII was statistically significantly higher in the NSTEMI patient group compared to the control group. There was also a significant positive correlation with the TIMI and HEART risk scores.

Our study showed that among the various laboratory markers used to prognosticate ACS patients, the SII and NS were more powerful predictors of NSTEMI than ratios such as the MLR, NLR and PLR. Moreover, the SII had a significant correlation between the TIMI and HEART risk scores.

CONCLUSIONS

In conclusion, the SII and NS are inexpensive, widely available and easy to measure markers that may have utility for cardiac risk stratification. Our results may stimulate further research. They may also be incorporated into routine clinical practice for patients with ACS and other cardiovascular conditions. Multicentre and large sample size studies are needed to test the applicability of these findings to a larger population.

Limitations

This study had several limitations, such as the retrospective and single-center design, single geographical location which limits the generalizability of the findings, and the exclusive focus on NSTEMI patients which restricts the applicability to other ACS populations. There may also be uncontrolled confounders that may influence the multivariate regression results. Another limitation was the absence of follow-up values of the variables that constitute the NS, which would have been useful for evaluating the NS of patients over time.

Ethics Committee Approval: The local ethics committee approved this study (Decision Date/No: 20.09.2022/362).

Conflict of Interest: The authors declared no conflicts of interest.

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