Systemic inflammation response index is associated MACE in patients with NSTEMI

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Abstract. – OBJECTIVE: Non-ST segment elevation myocardial infarction (NSTEMI) poses a significant health concern. The systemic inflammation response index (SIRI), an emerging inflammatory marker linked to conditions like stroke and cancer, has shown potential relevance. Inflammation’s pivotal role in acute coronary syndromes is well-established, yet its specific association with NSTEMI and SIRI remains unexplored. This study aims to elucidate the correlation between SIRI and major adverse cardiovascular events (MACE) in patients with NSTEMI.

PATIENTS AND METHODS: A cohort of 935 consecutive NSTEMI patients who underwent percutaneous intervention was recruited. MACE was defined to encompass all-cause death, malignant arrhythmia, and unplanned percutaneous coronary intervention. The systemic inflammation response index, a composite metric involving three distinct inflammatory cell counts, was computed as the product of neutrophil count and monocyte count divided by lymphocyte count. A receiver operator characteristic (ROC) curve analysis was used to define a cut-off level of SIRI to predict MACE. Then, the study population was divided into two groups according to the cut-off SIRI level in ROC curve analysis. The 12-month follow-up results of the patients were recorded retrospectively.

RESULTS: The participants exhibited a mean age of 64.12. Notably, the mean SIRI level registered at 1.98 among patients experiencing MACE and 4.97 among others. Through rigorous multivariate logistic regression analysis, SIRI emerged as an independent predictor of MACE. A receiver operator characteristic (ROC) curve analysis was used to define a cut-off level of SIRI to predict MACE. Then, the study population was divided into two groups according to the cut-off SIRI level in ROC curve analysis. The 12-month follow-up results of the patients were recorded retrospectively.

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CONCLUSIONS: The context of NSTEMI, SIRI emerges as a robust independent predictor of MACE. These findings underscore the potential utility of SIRI as a prognostic indicator for adverse cardiovascular events, enhancing our understanding of the disease’s pathophysiological mechanisms and potential avenues for improved clinical management.

Key Words: MACE, Non-ST elevation myocardial infarction, Systemic inflammation response index.

Introduction

Acute coronary syndrome (ACS) is a major cause of morbidity and mortality worldwide. Non-ST segment elevation myocardial infarction (NSTEMI) is the most common subtype of ACS, and it is a major health concern with increasing frequency as a result of prolonged life expectancy. Although NSTEMI has a better short-term prognosis than ST-segment elevation myocardial infarction (STEMI), its long-term prognosis is worse. Thus, risk stratification of NSTEMI patients is essential to improve morbidity and mortality.

It is well known that atherosclerosis is a chronic inflammatory process. Inflammation also plays a role in the etiology of ACS by destabilizing atherosclerotic plaque. In addition to local inflammation, the presence of a systemic inflammatory response, including activation of circulating cytokines, chemokines, adhesion molecules and various immune cells, has been demonstrated in ACS. Previous studies suggest that markers of systemic inflammatory response may be predictors of adverse clinical outcomes such as death, arrhythmia, and recurrent myocardial infarction in NSTEMI patients. In recent years, the role of various inflammatory markers such as neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR) and systemic immune-inflammatory index (neutrophil x platelet/lymphocyte), which can be easily examined in complete blood count in various patient groups in predicting cardiovascular events such as stroke and death, has been examined. Recently, a new parameter called systemic inflammation response index (SIRI) has emerged.
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This index, which has three components, including neutrophils, monocytes and lymphocytes has been associated with stroke and cancer\textsuperscript{16,17}. However, there is no information on SIRI as an independent risk factor for unfavorable prognosis in NSTEMI patients. The aim of this study was to investigate the relationship between SIRI and major adverse cardiovascular events (MACE) in NSTEMI patients.

Patients and Methods

Study Population

This study was planned as a single-center and retrospective study. The study population consisted of 935 consecutive patients with NSTEMI who underwent percutaneous intervention between January 2020 and February 2021. Patients with acute infection, chronic liver disease, chronic kidney disease, hematological diseases, systemic inflammatory and autoimmune diseases, malignancy, severe valvular heart disease and/or prosthetic heart valve, patients with elevated cardiac enzymes who did not undergo coronary angiography, patients who received blood and blood product replacement in the last three months, and patients with antibiotic use were excluded. Patients who underwent coronary artery bypass graft (CABG) surgery as a result of coronary angiography were also excluded. The 12-month follow-up results of the patients were recorded retrospectively. All-cause death, malignant arrhythmia, and unplanned percutaneous coronary intervention (PCI) were defined as MACE. Follow-up of patients with MACE was terminated. The study protocol was approved by the Institutional Ethics Committee.

Analysis of Patient’s Data and Laboratory Analysis

Demographic characteristics, cardiovascular risk factors and laboratory parameters were obtained from the hospital information system. Venous blood samples were collected on admission to the hospital. Complete blood count was measured by autoanalyzer (Atellica Hema, Siemens Healthineers, Erlagen, Germany). Biochemical measurement was performed by a molecular analyzer (Advia 2400 Chemistry System, Siemens Healthineers, Erlagen, Germany) in the hospital biochemistry laboratory.

Information on adverse events was obtained through the medical record system. Transthoracic echocardiography was performed (Philips EPIQ7, Philips Healthcare, Eindhoven, Netherlands) within 24 hours after PCI and left ventricular ejection fraction was calculated by Modified Simpson method\textsuperscript{18}.

SIRI was calculated as follows: neutrophil count x monocyte count/lymphocyte count.

Definition

SIRI is a combined index based on the count of three different inflammatory cells: neutrophils, monocytes, and lymphocytes. NSTEMI was defined as a cardiac troponin level higher than the upper limit of the normal range accompanied by ischemic symptoms or electrocardiographic changes suggestive of ischemia without persistent ST elevation\textsuperscript{19}. Patients with fasting blood glucose > 126 mg/dL, patients with a documented diabetes mellitus (DM) diagnosis, or patients who use insulin or oral antidiabetics at admission were accepted as diabetic. Hypertension was defined as current antihypertensive use or a systolic blood pressure 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Congestive heart failure (CHF) was identified as a known heart failure symptoms affirmed with reduced left ventricular ejection fraction (LVEF). Patients with previous ischemic strokes or transient ischemic attacks were defined as having a cerebrovascular accident (CVA). Hyperlipidemia was identified as total cholesterol higher than 200 mg/dL and/or low-density lipoprotein cholesterol higher than 130 mg/dL.

Major adverse cardiovascular events were defined as all-cause death, arrhythmia, and unplanned PCI. Arrhythmia included documented non-sustained and sustained ventricular tachycardia (VT) and ventricular fibrillation (VF) within the first year after PCI. Unplanned PCI was defined as those admitted to the hospital with suspected ACS and undergoing revascularization within one year of the index PCI.

Coronary Angiography and PCI

300 mg acetylsalicylic acid, loading dose P2Y12 receptor blockers, and 5,000 units of intravenous heparin were given before percutaneous coronary intervention. The treatment of PCI was implemented in all NSTEMI patients according to current guidelines\textsuperscript{5}.

Statistical Analysis

All data were analyzed using the IBM SPSS Statistics program v.24 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was utilized to evaluate the normality of distribution. The continuous variables were presented
as mean±standard deviation or median±interquartile ranges as appropriate, and the categorical variables were presented as numbers and percentages. Univariate and multivariate logistic regression analyses were performed to assess the independent predictors of MACE. Variables displaying \( p < 0.05 \) in the univariable analysis were performed in a multivariable logistic regression analysis. Subsequently, the study cohort was divided into two distinct subgroups based on the determined cutoff value, as established using the Youden index via receiver operator characteristic (ROC) analysis. A ROC curve analysis was used to define a cut-off level of SIRI to predict MACE. In conclusion, the study population was divided into two groups according to the cut-off SIRI level in ROC curve analysis. A two-tailed \( p \)-value <0.05 was defined as significant.

**Results**

A total of 935 patients was included in the study (Figure 1). Patients were divided into two groups: patients without (group 1) and with MACE (group 2). The mean age of the patients was 64.12, and 657 (70.3%) of them were males. Eighty (8.5%) of the patients had MACE during the follow-up period. Baseline demographics, clinical and laboratory parameters are shown in Table I. There is no significant difference in terms of gender between both groups. Hypertension, DM, known coronary artery disease (CAD), previous CVA and CHF were more common in group 2. Glucose, urea, creatinine, and total protein were higher in group 2. Albumin and total protein were significantly higher in group 1. Low-density lipoprotein cholesterol (LDL-C) level was higher in group 1. While the mean SIRI level was 2.3 in all patients, this ratio was 1.98 in group 1 and 4.97 in group 2 (\( p < 0.001 \)).

Patients were divided into two groups according to the cut-off SIRI level in ROC curve analysis (Table II). There was no significant difference in terms of DM, hypertension, hyperlipidemia, and previous CVA between both groups. Glucose, urea, creatinine, and LDL-C levels were significantly higher in patients with SIRI>2.3. Prasugrel was not preferred as a P2Y12 inhibitor in any of the patients in the SIRI>2.3 group. In the SIRI>2.3 group, diuretic drug use was significantly higher, and the beta-blocker use was lower. No significant difference was found between ACE (angiotensin-converting-enzyme) inhibitors or ARB (angiotensin receptor blocker) and statin use.

Univariate and multivariate logistic regression analyses were performed to assess the independent predictors of MACE. Then, variables displaying \( p < 0.05 \) in the univariable analysis were performed in a multivariable logistic regression analysis (Table III). Independent predictors for MACE after the multivariate analysis included hypertension, DM, LVEF, creatinine, SIRI, and C-reactive protein (CRP) (Table III).

Table IV shows MACE according to SIRI. A total of 80 patients (8.6%) developed MACE. It was observed in 26 patients (4.0%) in the SIRI ≤ 2.3 group and 54 patients (19.1%) in the SIRI > 2.3 group (\( p < 0.001 \)). There was a significant difference in mortality rate in both groups (\( p < 0.001 \)). No significant difference was found in arrhythmia and unplanned PCI.

A receiver operating characteristic (ROC) analysis was used to evaluate the predictive level of the SIRI for MACE. The SIRI cut-off value calculated by ROC analysis in predicting MACE was 2.3 (specificity 76%, sensitivity 68%). The area under the curve (AUC) of SIRI in predicting MACE was 0.76 (95% CI = 0.70-0.81; \( p < 0.001 \)) (Figure 2).

**Discussion**

This study examined the relationship between SIRI and MACE in patients with NSTEMI. The results of the present study suggested that SIRI is independently associated with the development of MACE in NSTEMI patients. To the best of our knowledge, it is the first study in the literature that suggests such an association in NSTEMI patients. The available evidence substantiates the involvement of immune and inflammatory dysfunction in the pathogenesis of ACS. Perturbation in the balance between proatherogenic and antiatherogenic immune networks contributes to the progression of plaques from a stable condition to an unstable state, consequently precipitating acute coronary events. Atherosclerosis is a chronic inflammatory disease of the vascular wall. The inflammatory process in atherosclerosis begins under the influence of the innate immune response. Monocytes transform into macrophages to form foam cells and phagocytize LDL-C to form the lipid core of the plaque. Studies have shown that inflammatory parameters are elevated in atherosclerotic heart disease. Inflammatory mediators such as tumor necrosis factor-alpha, interleukin 1β and 6, plasminogen activator inhibitor
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Type 1, CRP and adiponectin are involved in the chronic inflammatory response and, as a result, favor lipid accumulation with the development of atherosclerosis and cardiovascular diseases. Inflammatory parameters such as neutrophils, monocytes, lymphocytes, and platelets in the complete blood count also play an important role in the development of cardiovascular disease.

Furthermore, a reduced inflammatory response slowed the development of atherosclerosis and reduced the incidence of cardiovascular events. Various inflammatory markers such as CRP, interleukins, MLR, and NLR have been shown to predict short and long-term prognosis in ACS patients. Therefore, identifying reliable inflammatory markers that reflect the inflammatory burden and predict clinical outcomes is of great clinical significance.

NSTEMI is the most common type of ACS, and its prevalence is increasing as human life expectancy increases. Long-term mortality rates of NSTEMI have reduced significantly in association with an increase in the frequency of care that includes early interventions. However, it is useful to design several studies to predict poor clinical outcomes. It has been shown that inflammatory cells may be useful in predicting the prognosis of ACS patients. Since various

Figure 1. Research diagram.
inflammatory parameters have been shown to predict poor prognosis in acute coronary syndrome, combinations of inflammatory parameters such as NLR and MLR were examined. In some studies\(^3\), platelet/lymphocyte ratio (PLR) is regarded as an independent prognostic factor for CAD, as well as a predictor of acute and long-term death after PCI. However, the inflammatory predictor based on one or two components is rather poor and may be insufficient to predict prognosis in ACS\(^3\). The SIRI components (neutrophils, monocytes, and lymphocytes) play a significant role in atherosclerotic plaques formation and destabilization\(^3\). SIRI is a combination of three inflammatory biomarkers using only hemograms. It is a comprehensive, inexpensive, and easily accessible marker of chronic low-grade inflammation. It can show the inflammatory status in the body in detail\(^3\). SIRI also includes the NLR and MLR, which may be a useful and more sensitive inflammatory biomarker than a single parameter.

Neutrophils have been shown\(^3\) to have an important role in mediating the inflammatory response. However, high neutrophil count leads to plaque destabilization\(^4\). It is also an independent predictor of adverse cardiovascular events\(^4\). Secretion of reactive oxygen species and proteases by neutrophils leads to activation and dysregulation of the endothelial layer\(^5\). During the process of atherosclerosis, neutrophils can also increase monocyte adhesion and transmigration. Monocytes participate in plaque rupture by secreting lytic enzymes such as matrix metalloproteinases, promoting destabilization of the fibrous cap\(^5\). Monocytes are also involved in thrombus propagation, leading to a coagulation cascade\(^6\).

Lymphocytes have an important role in the regulation of the inflammatory response and in all stages of the atherosclerotic process\(^7\). Low lymphocyte counts have been associated\(^8\) with poor cardiovascular outcomes in ACS. Also, lower lymphocyte counts in patients with heart failure have a higher mortality rate\(^9\). In this study, the

<table>
<thead>
<tr>
<th>Table I. Comparison of groups according to the baseline demographics, clinical and laboratory characteristic.</th>
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<tbody>
<tr>
<td><strong>Total (n=935)</strong></td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>Male/Female (%)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
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<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Known CAD, n (%)</td>
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<tr>
<td>History of CHF</td>
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<tr>
<td>Hyperlipidaemia, n (%)</td>
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<tr>
<td>Previous CVA, n (%)</td>
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<tr>
<td>LVEF, %</td>
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<tr>
<td>SBP</td>
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<tr>
<td>Glucose (mg/dL)</td>
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<tr>
<td>Urea (mg/dl)</td>
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<td>Creatinine (mg/dL)</td>
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<td>Total protein (g/dl)</td>
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<td>Monocyte (x10^3/mL)</td>
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<td>CRP (mg/L)</td>
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<td>SIRI</td>
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Continuous data are presented as mean ± standard deviation, or median ± interquartile range. CAD: Coronary artery disease, CHF: Congestive heart failure, CVA: Cerebrovascular accident, LVEF: Left ventricular ejection fraction, MACE: Major adverse cardiovascular events, SBP: Systolic blood pressure, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, WBC: White blood cell, CRP: C-reactive protein, SIRI: Systemic inflammation response index.
parameters constituting SIRI were analyzed one by one. The number of neutrophils and monocytes was higher, and the number of lymphocytes was significantly lower in the group with high SIRI.
A study by Zhang et al. showed that higher SIRI was associated with stroke. In another study, SIRI was related to a poor prognosis in atrial fibrillation patients with ischemic stroke. SIRI has also been found to be associated with recurrence and poor prognosis in cancer patients. In another study by Yildiz et al., SIRI was analyzed according to plaque types in coronary computed tomography angiography and SIRI was predicting one-year primary endpoint poor outcomes. Furthermore, in another study conducted in a group of patients undergoing heart valve replacement, it was found that high SIRI value was associated with long-term mortality.

The mechanisms underlying the association between SIRI and adverse outcomes in NSTEMI are multifactorial. Elevated SIRI levels likely reflect a dysregulated immune response characterized by an imbalance between proatherogenic and antiatherogenic immune networks. This dysregulation may promote plaque vulnerability, endothelial dysfunction, and thrombotic events, thereby contributing to the occurrence of acute coronary events.

In this study, we found that SIRI is independently associated with the development of MACE in NSTEMI patients. Hypertension, DM, LVEF, creatinine and CRP were other independent predictors for MACE. Moreover, our study demonstrated a significant correlation between elevated SIRI and all-cause mortality in NSTEMI patients. This suggests that systemic inflammation, as reflected by SIRI, not only impacts cardiovascular outcomes but also has broader implications for overall survival. These results highlight the potential utility of SIRI as a prognostic tool for risk stratification and treatment decision-making in NSTEMI patients.

Currently, the relationship between inflammatory parameters and poor prognosis in cardiovascular diseases is examined. In our study, the inflammatory activation presented by SIRI may indicate patients at higher risk for poor clinical outcomes in NSTEMI patients. Our findings suggest that SIRI holds promise as a prognostic marker for risk stratification and outcome prediction in NSTEMI patients.

The easily available SIRI may reflect the mortality risk in the follow-up of NSTEMI patients and may provide caution in terms of closely monitoring in this regard.

**Study Limitations**

This study has several limitations. Firstly, it has a single-center and retrospective design which may limit the generalizability of its findings. Secondly, the SIRI was obtained only from the hemogram at admission to hospital. Changes in SIRI level during hospitalization were not measured. In addition, the study had a relatively small sample size.

**Conclusions**

SIRI level was associated with MACE in NSTEMI patients. It is a cheap, universal, and easily available marker, and may be useful for

![Figure 1. Receiver operating characteristics curve analysis of SIRI in predicting MACE. The area under the curve (AUC) is 0.76 (95% confidence interval 0.70-0.81, p < 0.001).](image-url)
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NSTEMI patients’ prognosis. Further studies are required to elucidate the exact role of SIRI in risk stratification of NSTEMI patients.

Authors’ Contributions
All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

Informed Consent
All patients signed an informed consent.

Ethics Approval
This study was approved by the Ethics Committee of Ankara City Hospital, Turkey (ID: E1-23-3884) and conducted according to the Helsinki Declaration of Human Rights.

Conflicts of Interest
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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