INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2023.71473
Int J Med Biochem 2023;6(2):75-83

Research Article

Evaluation of systemic inflammation markers in predicting cardiac risk in patients with acute chest pain

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Abstract

Objectives: This study aimed to evaluate systemic inflammation markers in predicting cardiac risk in patients with acute chest pain (ACP), in this way identifying cases with acute coronary syndrome (ACS) in admission to the hospital. In addition, the relationship between these markers and the HEART score was investigated.

Methods: By evaluating the laboratory/clinical data, patients with ACP (n=308) aged 18–70 were included in the study. As a result of clinical follow-up, patients were categorized into two groups: those diagnosed with ACS and those with non-ACS. Low-risk, moderate-risk, and high-risk patient groups were formed using the HEART score. From the routinely studied hemogram data, systemic immune inflammation index, systemic inflammation response index (SIRI), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio (PLR) were calculated.

Results: In determining the high-risk group, the highest area under the curve (AUC) was observed as 0.862 (95% confidence interval [CI]=0.818-0.898) at a cutoff value of 2.9 (69.3% sensitivity and 90.3% specificity) for NLR. For SIRI at a cutoff value of 2.0, the AUC value was found as 0.855 (95% CI=0.811 to 0.893), having 72.6% sensitivity and 85.2% specificity. The strongest association was between the HEART score and SIRI (r=0.612; p<0.001). Comparing patients without ACS and patients with ACS, there was no difference in lymphocyte counts, platelet counts, and PLR. In the ROC analysis for ACS, the SIRI performed that the highest AUC value was 0.858 (95% CI= 0.814 to 0.895), presenting 77.3% sensitivity and 79.5% specificity at a cutoff value of 1.19.

Conclusion: When pre-pandemic data were evaluated, higher NLR or SIRI might help risk stratification for individuals with ACP, and it could be recommended for clinical benefit in the emergency department. SIRI, which includes the number of monocytes, may be helpful as a novel index in identifying individuals with ACS.

Keywords: Acute chest pain, inflammation, neutrophil-to-lymphocyte ratio, systemic inflammation response index, the HEART score, troponin

How to cite this article: Deniz L, Yuksel Y, Arslan HF, Aral H, Bulut U. Evaluation of systemic inflammation markers in predicting cardiac risk in patients with acute chest pain. Int J Med Biochem 2023; 6(2):75-83.

Acute chest pain (ACP) is among the causes of admission to the emergency department (ED) and hospitalization. Acute coronary syndrome (ACS) is the most common reason of life-threatening ACP. Therefore, accurate identification and risk stratification of ACP is critical in the ED. The HEART score is designed to assess the short-term risk of major adverse car-

This study was presented as an oral presentation at the XXII. National Congress of Clinical Biochemistry, in Antalya (Türkiye), on 12-15 May 2022.

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Submitted: January 25, 2023 **Revised:** March 07, 2023 **Accepted:** March 21, 2023 **Available Online:** April 08, 2023

diac events (MACEs) in people who report ACP. It is helpful as a quick risk assessment method that identifies patients requiring early invasive intervention in ACP [1].

While neutrophils, monocytes, and platelets enhance atherosclerosis, lymphocytes prevent atherosclerosis [2]. Therefore, the systemic immune inflammation index (SII) is one of the indicators useful in a variety of conditions, including cancer and cardiovascular disease. The SII represents three key immune response pathways: inflammation (represented by neutrophilia), thrombosis (represented by thrombocytosis), and the body's response to stress (represented by lymphopenia) [3]. Meanwhile, as shown in previous epidemiological data, monocytes are also activated. Furthermore, monocyte counts * neutrophil-to-lymphocyte ratio (NLR) is used in the systemic inflammation response index (SIRI) as a prognostic indicator [4].

Although high-sensitive cardiac troponins (hsTn) are generally used for earlier prediction of acute myocardial infarction (AMI), there is still no standardization [5]. There may be analytical variations or other misinterpretations due to the preanalytical variables, such as sample types, age, sex, ED populations, or patients with an acute phase response [6]. Without increasing or decreasing troponin in serial sampling, values passing the assay-specific upper reference limit (URL) indicate myocardial damage but not in favor of AMI. On the other hand, observing upward deviations in troponin levels in shorter periods indicates reduced ED burden and better control of health-care resources, thanks to the ability to select those who need urgent intervention. It has been observed that there is a need for guidelines to be prepared jointly by the group consisting of laboratory specialists, clinicians, manufacturer representatives, medical statisticians, and legal regulators [7, 8].

This study aimed to evaluate systemic inflammation markers in predicting cardiac risk in patients with ACP, in this way identifying cases with ACS, in admission to the hospital. Furthermore, the relationship between these markers and the HEART score was investigated.

Materials and Methods

We retrospectively reviewed 308 patients' findings or diagnoses at admission to Istanbul Training and Research Hospital from April 2018 to September 2018.

The study included patients with ACP whose blood hsTnI level was requested because of ACS suspicion among those simultaneously blood creatinine levels and complete blood counts measured and recorded in the hospital/laboratory information system. We excluded patients aged below 18 years and above 70 years, with known active infection, malignancy, hematological disorders, severe liver failure, autoimmune disease, taking steroid therapy, intoxication, kidney failure, estimated glomerular filtration rate (eGFR) <45 mL/min, or hemoglobin <8 g/dL.

The HEART score is based on five separate variables: History (H), electrocardiogram (E), age (A), cardiovascular risk factors (R), and cardiac troponin (T). The score criteria for "H" are as follows: A score of 0 indicates a non-specific history for ACS, a score of 1 indicates a history that comprises both traditional and non-traditional ACS features, and a score of 2 indicates a specific history for ACS. The score criteria for "E" are as follows: A score of 0 indicates that the ECG is normal, a score of 1 indicates that the ECG is abnormal with non-specific repolarization anomalies, and a score of 2 indicates that there is a significant ST depression/elevation. The score criteria for "A" are as follows: A score of 0: ≤45 years, a score of 1: 45–64 years, and a score of 2: ≥65 years. The score criteria for "R" are as follows: A score of 0 indicates that there are no traditional risk variables, a score of 1: 1–2 risk variables, and a score of 2: ≥3 risk variables. Risk variables: Diabetes, obesity, smoking, hypercholesterolemia (total cholesterol ≥200 mg/dL, low-density lipoprotein-cholesterol ≥130 mg/dL), hypertension (systolic/diastolic ≥140/90 mmHg), ± a coronary artery disease (CAD) family history. This is an automatic score of 2 if you have a documented diagnosis of any of the following conditions: AMI, peripheral arterial disease, previous coronary revascularization, or stroke. The score criteria for "T" are as follows: A score of 0: troponin less than sex-specific URL, a score of 1: 1–3 times the URL, and a score of 2: ≥3 times the URL [1].

Each of the five categories have a scoring range of 0 to 2. The total HEART score ranges from 0 to 10. The low score (0–3) predicts patients who are candidates for early discharge. The moderate risk score (4–6) predicts patients who are candidates for additional observation and evaluation. And high risk score (7–10) predicts patients who are candidates for emergency intervention [9]. Using the HEART score, we achieved three groups: patients with low risk (Group 1, n=47), patients with moderate risk (Group 2, n=108), and patients with high risk (Group 3, n=153). In addition, we compared patients with non-ACS (n=39) and patients with ACS (n=269).

On February 25, 2022, the Health Sciences University Istanbul Training and Research Hospital Clinical Research Ethics Committee authorized this project, registered as 87. The Helsinki Declaration, patient rights regulations, and ethical guidelines guided the study's design.

Biochemical analysis

Complete blood count parameters were analyzed in samples anticoagulated with ethylenediaminetetraacetic acid via XN1000 (Sysmex Co., Kobe, Japan). Routine biochemistry and immunochemistry were performed via AU680 and Access 2 (Beckman Coulter Inc., Brea, California, US.). URL of hsTnI was used as 11.6 pg/mL for females and 19.8 pg/mL for males, specified by the manufacturer (Access hsTnI, reference number: B52699, document number: C11140.M, July 28, 2021, Beckman Coulter Inc., US). Plasma hsTnI levels were determined in heparinized blood samples.

The equation calculates SII: [10] (platelet count * neutrophil count)/lymphocyte count. Likewise, the equation calculates SIRI: (monocyte count * neutrophil count)/lymphocyte count [11].

Table 1. Comparing demographic and comorbidities data between the three groups, considering the HEART score level

Parameter	Low-score (n=47)		Moderate-score (n=108)		High-score (n=153)		p*
	n	%	n	%	n	%	
Age (years)	58 (51–62)		56 (49–60)		57 (52–63)		0.056
Gender							
Male	21	44.7	107	99.1	134	87.6	**<0.001**
Female	26	55.3	1	0.9	19	12.4	
Diabetes mellitus	14	30	17	16	80	52	**<0.001**
Hypertension	11	23	73	68	128	84	**<0.001**
Hyperlipidemia	14	30	82	76	133	87	**<0.001**
ARB/ACE inhibitors	14	30	67	62	116	76	**<0.001**
Beta-blockers	8	17	91	84	119	78	**<0.001**
CCB	0	0	14	13	34	22	**0.001**
Diuretics	2	4	19	18	39	26	**0.005**
ASA	6	13	78	72	111	73	**<0.001**
Anti-diabetic agent	16	34	14	13	71	46	**<0.001**
Statins	17	36	75	69	132	86	**<0.001**

*: p<0.05 statistical significance. The data is given as a number (%) or as the median (25^{th}-75^{th} percentile). Kruskal Wallis test was applied for continuous variables, and the Chi-square test was applied for discrete variables. The total HEART score ranges from 0 to 10; low-risk score: 0–3; moderate-risk score: 4–6; high-risk score: 7–10 [9]. ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blockers; CCB: Calcium channel blockers; ASA: Acetylsalicylic acid.

Statistical analysis

To evaluate if the data fit a normal distribution, the Kolmogorov–Smirnov test was used. Categorical data were exhibited as the ratio (percent) and continuous data as median (25^{th}–75^{th} percentile). Analysis for the categorical test was performed with the Chi-square test. Kruskal–Wallis or Mann–Whitney U tests were utilized to compare independent groups. The relationship between systemic inflammation parameters and HEART score in all groups was examined by Spearman correlation analysis. The diagnostic performance of the tests was evaluated using receiver operating characteristic (ROC) analysis. The appropriate cutoff value was determined using the Youden index. In order to compare the performances of the tests, ROC pairwise comparison was made, and area under the curve (AUC) values were compared. Separate logistic regression analysis was undertaken to account for covariance between the systemic inflammation indexes. All statistical evaluations were made in SPSS version 26.0 (IBM Corp, Armonk, New York, United States). p significance level was accepted as <0.05.

Results

Our study comprised 262 (85%) males and 46 (15%) females; 111 (36%) patients were diabetic, 229 (74%) were hyperlipidemic, and 212 (69%) were hypertensive. Among the patients who were hospitalized and underwent interventional procedures due to ACS, 161 (52.3%) were diagnosed with non-ST-elevation myocardial infarction (NSTEMI), 86 (27.9%) with ST-elevation myocardial infarction (STEMI), and 22 (7.1%) with unstable angina. ACS was ruled out in 39 (12.7%) people hospitalized at the ED, associated with chest pain of non-ACS origin, due to clinical and laboratory data.

The study group's average age was 56.5±0.41 years. Among all the groups, we had no difference in age. The high-risk group presented an increased rate of hypertension, hyperlipidemia, diabetes mellitus, angiotensin receptor/angiotensin-converting enzyme blockers, antidiabetic agent, acetylsalicylic acid, statins, beta-blockers, calcium channel blockers, and diuretic drug use (Table 1).

There was no statistical difference between low- , moderate- and high-risk score groups regarding platelet count, serum creatinine, and eGFR. While hsTnI, neutrophil, monocyte, NLR, SII, SIRI, monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) were higher in the high-risk, lymphocyte levels were lower in the high-risk group compared to the low-risk group. While monocyte, lymphocyte, SIRI, and hsTnI levels were higher in the moderate-risk group, PLR levels were lower in the moderate-risk group compared to the low-risk group. While neutrophil, SII, SIRI, NLR, MLR, PLR, and hsTnI levels were higher in the high-risk group, lymphocyte levels were lower in the high-risk group compared to the moderate-risk group (Table 2).

While neutrophil, monocytes, SII, SIRI, NLR, MLR, and hsTnI levels were higher in ACS, no difference was found between the groups in platelets, lymphocytes, and PLR (Table 3).

In the ROC analysis for ACS, of the inflammation markers, the SIRI performed the highest AUC value was 0.858 (95% confidence interval [CI]=0.814–0.895), presenting 77.3% sensitivity and 79.5% specificity at a cutoff value of 1.19. In the ROC analysis for the HEART score, the AUC value is 0.991 (95% CI=0.972–0.998), offering 97% sensitivity and 100% specificity (Table 4).

The correlation analysis performed in all groups showed a significant relationship between SIRI, SII, NLR, MLR, PLR,

Table 2. Comparing laboratory data between the three groups, considering the HEART score level

Parameter	Low-score (n=47)	Moderate-score (n=108)	High-score (n=153)	p*
Neutrophil count (10^9/L)	4.90 (3.88–6.26)	5.29 (4.27–6.14)	7.15 (5.84–9.12)^{a***,b***}	**<0.001**
Platelet count (10^9/L)	248 (213–299)	261 (213–309)	261 (216–299)	0.774
Monocyte count (10^9/L)	0.53 (0.34–0.64)	0.77 (0.65–0.88)^{a***}	0.79 (0.63–1.04)^{a***}	**<0.001**
Lymphocyte count (10^9/L)	2.52 (1.94–2.76)	3.05 (2.35–3.62)^{a**}	1.87 (1.44–2.60)^{a**,b***}	**<0.001**
SII	520 (361–631)	441 (325–633)	878 (616–1383)^{a***,b***}	**<0.001**
SIRI	1.01 (0.62–1.31)	1.26 (0.94–1.83)^{a**}	3.02 (1.82–4.29)^{a***,b***}	**<0.001**
NLR	2.03 (1.59–2.57)	1.69 (1.32–2.29)	3.49 (2.58–5.15)^{a***,b***}	**<0.001**
PLR	107 (86.0–130)	84.0 (66.0–110)^{a**}	124 (96–178)^{a**,b***}	**<0.001**
MLR	0.20 (0.13–0.28)	0.26 (0.21–0.32)	0.41 (0.30–0.59)^{a***,b***}	**<0.001**
hsTnI (ng/L)	19.3 (15.7–24.1)	248 (48–2218)^{a***}	4402 (529–26553)^{a***,b***}	**<0.001**
eGFR (ml/min/1.73 m^2)	92.3 (64.4–103.1)	97.1 (88.5–108)	98 (82.9–105)	0.069
Creatinine (mg/dL)	0.84 (0.64–1.00)	0.85 (0.73–0.95)	0.83 (0.71–0.99)	0.811

**: p<0.01; ***: p<0.001; [a]: Low-score; [b]: Moderate-score. Data are presented median (25^{th}-75^{th} percentile). P*; for continuous variables, Kruskal Wallis test was utilised. SII: Systemic immune-inflammation index; SIRI: Systemic inflammation-response index; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio; hsTnI: High-sensitivity troponin I; eGFR: Estimate glomerular filtration rate. P<0.05: Statistically significant.

Table 3. Comparing laboratory data between the two groups, considering the ACS

Parameter	Non-ACS (n=39)	ACS (n=269)	p
Age (years)	58 (51–63)	57 (51–62)	0.543
HEART score	1 (1–2)	7 (5–9)	**<0.001**
Neutrophil count (10^9/L)	4.51 (3.73–5.84)	6.25 (4.84–7.86)	**<0.001**
Platelet count (10^9/L)	242 (213–292)	262 (216–304)	0.172
Monocyte count (10^9/L)	0.51 (0.25–0.63)	0.77 (0.63–0.94)	**<0.001**
Lymphocyte count (10^9/L)	2.52 (1.94–2.91)	2.34 (1.74–3.17)	0.768
SII	480 (349–616)	668 (442–1020)	**<0.001**
SIRI	0.78 (0.51–1.19)	1.96 (1.22–3.48)	**<0.001**
NLR	1.81 (1.56–2.43)	2.60 (1.73–3.79)	**<0.001**
PLR	99.0 (82.5–130)	107 (81.0–157)	0.285
MLR	0.19 (0.10–0.28)	0.32 (0.24–0.45)	**<0.001**
hsTnI (ng/L)	18.9 (15.9–22.7)	1276 (131–13435)	**<0.001**
eGFR (ml/min/1.73 m^2)	92.3 (61.7–103)	98 (85–107)	0.054
Creatinine (mg/dL)	0.84 (0.64–1.00)	0.84 (0.72–0.97)	0.583

Data are presented median (25^{th}-75^{th} percentile). For continuous variables, Mann-Whitney U test was utilised. ACS: Acute coronary syndrome; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation-response index; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio; hsTnI: High-sensitivity troponin I; eGFR: Estimate glomerular filtration rate. P<0.05: Statistically significant.

and HEART scores. The strongest correlations were found between the HEART score and SIRI (r=0.612; p<0.001), as shown in Table 5.

In ROC analysis of the low- and moderate-risk groups (Group 1 and Group 2) versus high-risk group (Group 3), we had NLR with the highest AUC value of 0.862 (95% CI = 0.818–0.898), presenting 69.3% sensitivity and 90.3% specificity at a cutoff value of 2.9. For SIRI at a cutoff value of 2.0, the AUC value appeared as 0.855 (95% CI=0.811–0.893), having 72.6% sensitivity and 85.2% specificity (Appendix 1 and Fig. 1). The pair-wise comparison of AUC levels showed no significant difference between NLR and SIRI, while NLR had a significantly higher performance than all other indices (Appendix 2).

NLR, PLR, SII, SIRI, and MLR had a significant relationship with the high-risk group in the univariate regression analysis. Furthermore, after adjusting for gender, age, diabetes, hyperlipidemia, and hypertension, all inflammation markers we studied remained statistically significant in multivariate regression analysis (Table 6).

Discussion

The HEART score is accepted for the cardiac risk category and recommended management strategy; patients with low HEART scores (<3) may be safely discharged from the ED with a very low risk of significant adverse cardiac events, thereby lowering needless hospital stays and hence expenditure on

Table 4. Receiver operating curve analysis of inflammation markers and HEART score in identifying ACS

Parameter	AUC	95 CI%	Cut-off value	Sensitivity	Specificity	p
NLR	0.674	0.618–0.726	>2.94	42.4	94.9	**<0.001**
SIRI	0.858	0.814–0.895	>1.19	77.3	79.5	**<0.001**
SII	0.688	0.633–0.739	>654	51.3	84.6	**<0.001**
MLR	0.778	0.727–0.823	>0.25	69.9	71.8	**<0.001**
HEART score	0.991	0.972–0.998	>3	97.0	100	**<0.001**

ACS: Acute coronary syndrome; AUC: Area under curve; CI: Confidence interval; NLR: Neutrophil to lymphocyte ratio; SIRI: Systemic inflammation-response index; SII: Systemic immune-inflammation index; MLR: Monocyte to lymphocyte ratio.

health [12]. The HEART score for ACP-admitted patients in the ED gives the physician a rapid and accurate prognosis prediction quickly after the patient is admitted, without requiring electronic computation [13]. Thrombolysis in myocardial infarction (TIMI), HEART, and the Global Registry of Acute Coronary Events (GRACE), which are frequently used for risk classification of ACP patients, are validated risk scores in order to predict adverse clinical results. In a study, while TIMI and HEART scores had better performance than GRACE in predicting MACEs, no significant difference was found between the scores TIMI and HEART [14]. In another study, the HEART score surpassed the GRACE and TIMI levels in discriminating MACEs in patients with ACP and determining the low-risk patient group [15]. In our study, the HEART scoring system was utilized, because it is a risk assessment tool that identifies high-risk patients requiring early invasive intervention for ACP [1].

Elevated troponin levels, measured by the immunochemistry method, may sometimes be misleading in favor of ACS. Macrotroponin or high-molecular-weight complexes may cause false troponin elevations [16–18]. However, the precise value of multiple biomarkers in place of or in addition to cardiac troponin in diagnosing ACS has yet to be established [19]. HsTn I or T will help for the early diagnosis and exclusion of AMI and the detection of cardiac cell death related to a variety of other pathophysiological events. Troponins will challenge clinicians to distinguish between these different events [20]. Concomitant use of inflammation and myocardial stress biomarkers improves this prediction.

Higher SII and SIRI were initially presented as markers of poor prognosis in cancer, as they potentially represent the body's systemic inflammatory response. Although its role in cancer patients is known, the role of SIRI in cardiovascular diseases has not been revealed, and there are very few studies on this subject in the literature [4, 21–25]. It was observed that higher monocytes, neutrophils, and lower lymphocyte levels, the three parameters of SIRI, were linked to elevated cardiovascular disease risk and mortality [4].

In our study, we found cutoff values for NLR (2.9), SIRI (2.0), SII (657), MLR (0.37), and PLR (119) to distinguish high-risk patients with ACP at ED admission. In determining the high-risk group, the highest AUC was observed in NLR, showing a significantly higher performance than all other indices. For SIRI at a cutoff value of 2.0, the AUC value was found as 0.855. Besides, the pair-

Table 5. Spearman correlation analysis between systemic inflammation markers and HEART score

In all groups (n=308)	HEART score	
Parameter	**r**	**p**
SIRI	0.612	**<0.001**
SII	0.461	**<0.001**
NLR	0.520	**<0.001**
PLR	0.268	**<0.001**
MLR	0.528	**<0.001**

SIRI: Systemic inflammation-response index; SII: Systemic immune-inflammation index; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio.

wise comparison of AUC levels showed no significant difference between NLR and SIRI. In comparing the non-ACS patients with those of ACS, while SII, SIRI, NLR, and MLR were higher, there was no difference in lymphocyte, platelet counts, and PLR. In the ROC analysis for ACS, the SIRI performed the highest AUC value of 0.858 at a cutoff value of 1.19. Some studies reported that NLR, PLR, SII, and MLR indices could be used to identify high-risk ACS patients [2, 26]. NLR had independently predicted ACS risk [27, 28]. In Turkish population, NLR was higher in STEMI compared to USAP. Moreover, NLR could be used at admission as an auxiliary parameter for predicting of ACS [29]. In a systemic review, NLR of 5.0 was suggested for ACS risk [30]. It was shown to be linked with the SYNTAX score in research conducted in NSTE-ACS [31]. There was a relationship between NLR and coronary lesion severity using the Gensini score [32]. Higher NLR was associated with cardiovascular events, in a meta-analysis [33]. Furthermore, it was stated that the NLR score refers to the complexity and degree of ACS as determined by the TIMI, SYNTAX, and GRACE scores [34]. In a report comparing individuals with stable CAD and MI, no difference in platelet counts, mean platelet volume, platelet distribution width and platelet large cell ratio was found [35]. In a systematic review, PLR was related to inhospital and long-term all-cause mortality and cardiovascular events in ACS [36]; the longer platelet half-life may lead to prognostic importance rather than diagnostic importance. In a study, PLR and NLR were shown as independent influencing variables for MACE following the coronary intervention [37]; in another study, NLR, MLR, and PLR had independent predictive

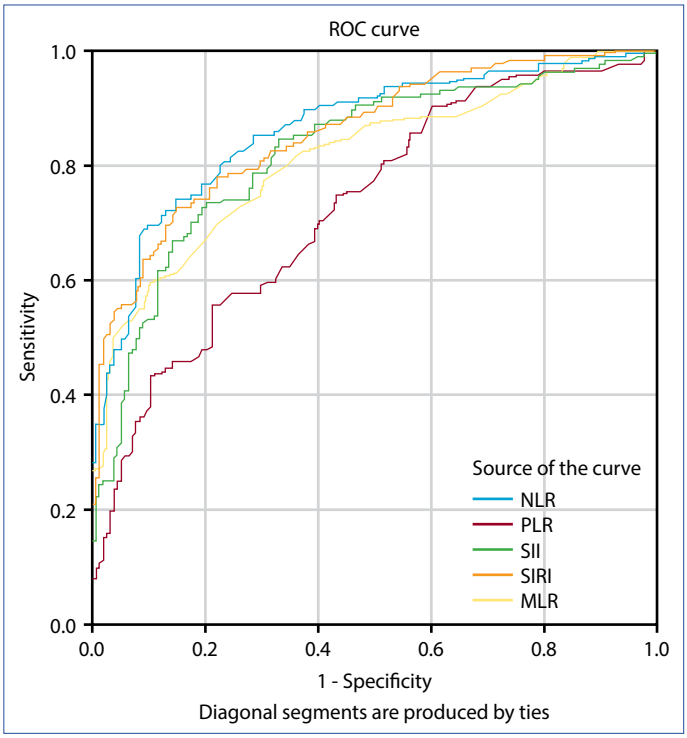

Figure 1. Receiver operating curve analysis for systemic immune-inflammation index, systemic inflammation-response index, platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, and monocyte to lymphocyte ratio in identifying high-risk patients.

ROC: Receiver operating characteristic; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation-response index; MLR: Monocyte to lymphocyte ratio.

values for MACE [2]. According to univariate regression analysis, NLR and MLR were found to be predictive of adverse cardiac events in another study [38]. Both PLR > 204.4 and NLR > 3.1 were linked to cardiovascular adverse events in CAD [39].

Patients with ACS showed significantly higher SIRI and SII compared to stable ischemic heart disease [21, 25]. In another study, SIRI was found to have the highest values in ACS and was significantly higher than in stable CAD [25]. In a study using the Gensini score, SII had an independent predictive value in predicting the occurrence and degree of CAD [40]. In addition to showing cardiac risk in ACS, another study showed that SII had an independent relationship to the extent of coronary stenosis in chronic coronary syndrome [41]. After a coronary intervention, SII showed a more robust prediction of MACE than conventional risk factors in CAD patients. A cohort study found high SIRI and SII index levels to predict stroke and all-cause mortality. SIRI, including the number of monocytes, was observed to have a predictive value for ACS [4]. SIRI combines monocytes, neutrophils, and lymphocytes to reflect the equilibrium of inflammation regulators. Composite markers such as SIRI are more stable and less sensitive to many factors than a single inflammatory marker. In a study, higher SIRI levels were associated with an increased risk of long-term clinical cardiovascular events. A high SIRI score indicated a robust pro-inflammatory response conducted by monocytes and neutrophils and a weak or suppressed anti-inflammatory response mediated by lymphocytes [23]. The aggregate index of systemic inflammation (AISI), SIRI, and neutrophil to lymphocyte × platelet ratio have been shown to have diagnostic values for MACE in ACS after the coronary intervention, and thus, AISI and SIRI are novel inflammatory indicators that can be used to predict prognosis [22, 23]. It was reported that the SIRI could increase the prognostic value of the GRACE risk score [22, 24]. In our study, it was observed to have relatively low diagnostic performance for SII and PLR. On the other hand, NLR or SIRI were noticed as prominent indices to distinguish high-risk patients with ACP at ED admission. SIRI, which includes the number of monocytes, may be helpful as a novel prognostic index for individuals with ACP.

To our knowledge, no one has studied the association between the SII and SIRI and the HEART risk score. Among the systemic inflammation markers in our study, SIRI (r=0.612), MLR (r=0.528), and NLR (r=0.520) correlated better with the HEART score (Table 5) than SII (r=0.461) or PLR (r=0.268). In a study with non-ST ACS patients, a significant relationship was shown between the HEART score and the NLR (r=0.452), PLR (r=0.539). In the same study, cut-off values of 3.95 for NLR and 115.5 for PLR were found to detect high risk patients [1]. Other studies showed associations of NLR with the TIMI score in STEMI [42] and of NLR with GRACE risk in ACS [43].

COVID-19 positivity emerges simultaneously in some patients with ACP during the pandemic. Myocardial injury may inde-

Table 6. Binary logistic regression analysis results for the high-risk patient group

Univariate regression (Unadjusted)				Multivariate regression (Adjusted)			
Parameter	**OR**	**%95 CI**	**p**	**Parameter**	**OR[a]**	**%95 CI**	**p**
NLR >2.90	21.05	11.17–39.67	**<0.001**	NLR >2.90	46.51	17.46–123.8	**<0.001**
SIRI >2.0	15.17	8.598–26.76	**<0.001**	SIRI >2.0	18.87	9.266–38.41	**<0.001**
MLR >0.37	12.75	6.929–23.46	**<0.001**	MLR >0.37	16.60	7.721–35.70	**<0.001**
SII >657	10.93	6.420–18.60	**<0.001**	SII >657	16.03	8.115–31.66	**<0.001**
PLR >119	1.013	1.009–1.017	**<0.001**	PLR >119	5.725	3.024–10.84	**<0.001**

[a]: Odds ratio adjusted for age, gender, diabetes, hyperlipidemia, and hypertension. OR: Odds ratio; CI: Confidence interval; NLR: Neutrophil to lymphocyte ratio; SIRI: Systemic inflammation-response index; MLR: Monocyte to lymphocyte ratio; SII: Systemic immune-inflammation index; PLR: Platelet to lymphocyte ratio.

pendently indicate progression to severe disease and adverse clinical outcomes such as mortality in patients with COVID-19 [44]. After viral infection, the hypoxia-inducible factor-1 signaling pathway is abnormally activated in the patient's peripheral blood mononuclear cells. Phenotypic transformation of vascular smooth muscle cells is the proposed mechanism in aneurysms and atherosclerosis, hence endothelial dysfunction [45]. We included patients who attended before the COVID-19 pandemic period. It may not be clear whether patients with ACP are infected with COVID-19 due to the poor performance of most COVID-19 diagnostic methods. Inflammation indices could lead to misleading results in patients with ACP accompanied by COVID-19. We think the pre-pandemic period increases the power of the study.

Study limitations

The limitation of our study is that it was conducted retrospectively at a single center.

Conclusion

The indices NLR, SIRI, SII, PLR, and MLR had independent positive predictive values for those with high-risk scores. When pre-pandemic data were evaluated, higher NLR or SIRI might help risk stratification for individuals with ACP, and it could be recommended for clinical benefit in ED. The strongest correlation was found between the HEART score and SIRI. SIRI, which includes the number of monocytes, may be helpful as a novel index in identifying individuals with ACS.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The University of Health Sciences Istanbul Training and Research Hospital Clinical Research Ethics Committee (No: 87, Date: 25/02/2022).

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – L.D., H.A.; Design – L.D., Y.Y., H.A.; Supervision – L.D., Y.Y., H.F.A., H.A., U.B.; Materials – L.D., Y.Y., H.A.; Data collection &/or processing – L.D., Y.Y.; Analysis and/or interpretation – L.D., Y.Y., H.F.A., H.A., U.B.; Literature search – L.D., Y.Y., H.F.A., H.A.; Writing – L.D., H.A.; Critical review – L.D., H.F.A., Y.Y., H.A., U.B.

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Appendix 1. Receiver operating curve analysis of inflammation markers in identifying high-risk

Parameter	AUC	95 CI%	Cut-off value	Sensitivity (%)	Specificity (%)	p
NLR	0.862	0.818–0.898	>2.9	69.3	90.3	**<0.001**
SIRI	0.855	0.811–0.893	>2.0	72.6	85.2	**<0.001**
SII	0.820	0.773–0.862	>657	73.2	80.0	**<0.001**
MLR	0.812	0.764–0.854	>0.37	59.5	89.7	**<0.001**
PLR	0.726	0.672–0.775	>119	55.6	78.7	**<0.001**

P significance level was accepted as <0.05. AUC: Area under curve; CI: Confidence interval; NLR: Neutrophil to lymphocyte ratio, SIRI: Systemic inflammation-response index; SII: Systemic immune-inflammation index; MLR: Monocyte to lymphocyte ratio; PLR: Platelet to lymphocyte ratio.

Appendix 2. The pair-wise comparison of area under curves among inflammation markers

Comparison	Area under curve		
	Difference	95 CI%	p
NLR-SIRI	0.007	–0.022–0.035	0.649
NLR-SII	0.042	0.014–0.069	**0.003***
NLR-PLR	0.136	0.089–0.184	**<0.001****
NLR-MLR	0.050	0.007–0.093	**0.024***
SIRI-SII	0.035	0.001–0.069	**0.045***
SIRI-PLR	0.130	0.072–0.188	**<0.001****
SIRI-MLR	0.043	0.009–0.078	**0.013***
SII-MLR	0.009	–0.044–0.061	0.753
SII-PLR	0.095	0.053–0.137	**<0.001****
MLR-PLR	0.086	0.031–0.142	**0.002***

*p<0.05; **p<0.001. CI: Confidence interval; NLR: Neutrophil to lymphocyte ratio; SIRI: Systemic inflammation-response index; SII: Systemic immune-inflammation index; PLR: Platelet to lymphocyte ratio; MLR: Monocyte to lymphocyte ratio.