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The relationship of systemic inflammatory parameters with mortality and prognosis in patients with COVID-19 and acute ischemic stroke

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Abstract

Aim: Inflammation plays a very important role in acute ischemic stroke (AIS) and many inflammatory markers are known to be associated with the prognosis of AIS. In this study, we aimed to evaluate the relationship of the systemic immune inflammation index (SII) and systemic inflammation response index (SIRI), which are two new inflammatory markers, with mortality and prognosis in patients with COVID-19 and AIS.

Materials and Methods: Ninety-five patients with COVID-19 who were followed up for AIS were included in the study. SIRI and SII values were calculated using laboratory data admission. The patients were divided into two groups according to prognosis and mortality. The modified Rankin scale (mRS) was used for prognosis at 3 months and mRS 0-2 was considered a good prognosis. Laboratory parameters neutrophil/lymphocyte ratio (NLR), SII, and SIRI values were compared between the groups according to prognosis and mortality.

Results: The NLR, SII, and SIRI values were found to be significantly higher in the poor prognosis group and the group with mortality ($p<0.001$). As NLR increased, the risk of poor prognosis increased 1.1 times. As the SII value increased, the risk of poor prognosis increased 2.9 times, and as SIRI increased, the risk of poor prognosis increased 1.8 times ($p<0.001$).

Conclusion: Our findings show that SIRI and SII are associated with prognosis and mortality in patients with COVID-19 and AIS. Low SIRI and SII values are associated with good clinical outcomes.

Introduction

Acute ischemic stroke (AIS) is one of the complications of COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes high mortality and morbidity [1]. Inflammation is related to the severity of stroke and plays a vital role in the prognosis of AIS. The mechanism of acute ischemia in COVID-19 is complex, and the role of thromboinflammation in the mechanism of coagulopathy and stroke remains a matter of debate [2]. In AIS, some inflammation factors such as interleukins (ILs), tumor necrosis factors (TNFs), as well as the neutrophil-lymphocyte ratio (NLR), serum bilirubin, C-reactive protein (CRP), and homocysteine play a role and have been proven to be associated with prognosis [3,4]. However, there are limited studies on these markers in patients with COVID-19 and AIS. In many studies, it has been shown that neutrophils, platelets, and lymphocytes, based on the systemic immune inflammation index (SII), can predict survival outcomes in various solid tumor types [5]. In addition, the SII index has been shown to be associated with poor prognosis in sinus vein thrombosis and acute ischemic stroke [6,7]. The systemic inflammatory response index (SIRI), based on a combination of neutrophils, monocytes, and lymphocytes, has been defined as a new inflammatory marker, and it has been stated that it may be prognostic in patients with malignancy, inflammatory and atherosclerotic diseases [8,9]. It was thought that SIRI and SII could be used to comprehensively evaluate the inflammatory state. To our knowledge, the prognostic significance of SIRI and SII in patients with COVID-19 and AIS has not yet been reported. It is important to understand the relationship between COVID-19 and its complication, AIS, more deeply. In this study, we aimed to evaluate the relationship of two new inflammatory markers, SII and SIRI, with mortality and prognosis in patients with COVID-19 and AIS.

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Material and Methods

In this study, prospectively collected data of 95 patients with a confirmed diagnosis of COVID-19 and AIS who were followed up between March 2020 and November 2021 were evaluated retrospectively. All patients with COVID-19 in this study were diagnosed according to the World Health Organization (WHO) guidelines, and patients with positive SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (rRT-PCR) tests in their nasopharyngeal swabs were included. Patients aged under 18 years, pregnant women, and patients with a history of malignancy, autoimmune disease, or hematologic disease were not included in the study. As part of the hospital admission policy, RT-PCR for SARS-CoV-2 was tested on the first day of admission and thereafter as needed. Patients were divided into two groups according to mortality and prognosis. The demographic and clinical characteristics, and laboratory and radiologic results of the patients were recorded. The diagnosis of AIS was confirmed using brain computed tomography (CT), magnetic resonance imaging (MRI), and clinical symptoms. The Causative Classification of Stroke algorithm was used for the etiologic classification of stroke [10]. The modified Rankin scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) scores were recorded at the time of admission and the 3rd month in all patients. The primary outcome was poor functionality 90 days, as reflected by an mRS score of 3–6. In-hospital mortality data were also recorded for all patients. Following hospital policy and expert opinion, low-dose thoracic CT was performed on an emergency basis in all acute patients. Laboratory parameters, NLR, SII, and SIRI values were compared between the groups according to prognosis and mortality. White blood cell (WBC), neutrophil, lymphocyte and platelet counts, CRP, D-dimer, troponin, activated partial thromboplastin (aPTT), prothrombin time (PT), and international correction ratio (INR) levels were recorded. NLR was calculated as the neutrophil count/lymphocyte count. SII was calculated as the neutrophil count x platelet count/lymphocyte count, and SIRI was calculated as the neutrophil count x monocyte count/lymphocyte count. Approval for the study was obtained from the ethics committee of Karatay University (Protocol No: 2021-044) and the Ministry of Health.

Statistical analysis

Data were analyzed using the IBM SPSS V23 (IBM Corp., Amrock, New York, United States). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used for groups and variables to determine the conformity of the data to normal distribution. The independent samples t-test and Mann-Whitney U test were used to compare variables according to NLR, SII, and SIRI values. Risk factors affecting mortality and prognosis were analyzed using logistic regression. Because the SII values contained extreme values, they were included in the analysis by performing LN transformation. The Chi-square test was used to evaluate categorical data. Analysis results are presented as mean ± standard deviation for quantitative data, median (min - max), and frequency (percent) for categorical data. Receiver operating characteristic curves (ROC) analysis was used to evaluate the effectiveness of SII and SIRI in detecting poor outcomes. The significance level was accepted as $p<0.05$.

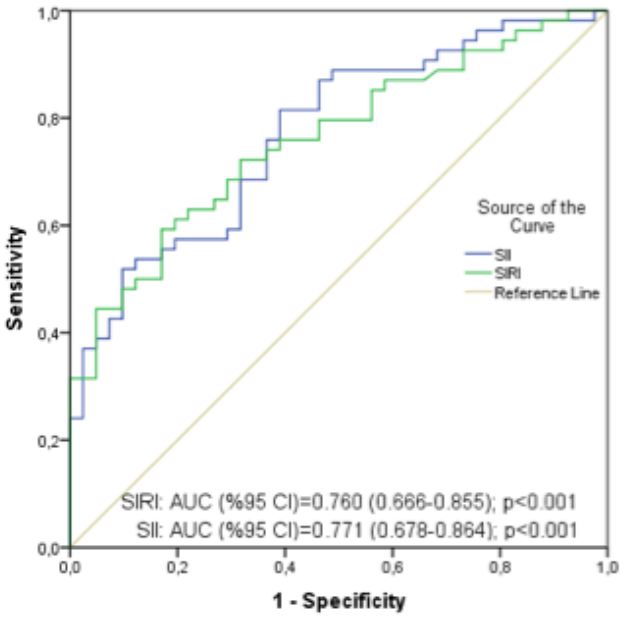

Figure 1. Receiver operating charasterictic curves of systemic inflammation response index (SIRI) and systemic immune-inflammation index (SII).

Results

In this study, 95 patients with positive nasopharyngeal swab rRT-PCR tests for COVID-19 who were followed up for AIS were included. Patients were divided into two groups according to mortality and prognosis. Of the patients included in the study, 40% (38/95) were female and 60% (57/95) were male, and the mean age was 71.88 ± 11.83 years in the good prognosis group and 72.30 ± 10.51 years in the poor prognosis group. There was no difference between the groups in terms of age and sex. When the accompanying risk factors and comorbidities were examined, hypertension was observed most frequently (55/95, 57.9%). Diabetes mellitus was observed in 39 (41%) patients, atrial fibrillation in 17 (17.9%), history of smoking in 16 (16.8%), history of stroke in nine (9.5%), and heart valve disease in five (5.2%). When grouped according to mortality and prognosis, no significant difference was found between the groups in terms of demographic characteristics and risk factors. The median values of the NIHSS score at admission were associated with mortality and poor prognosis, and as the NIHSS score increased, the rates of mortality and poor prognosis increased ($p<0.001$) (Table 1). The median NIHSS score was 6.0 for those with a good prognosis and 20.0 for those with a poor prognosis. When AIS was evaluated in terms of etiology, no statistically significant difference was observed between the groups according to mortality and prognosis (Table 1). When we evaluated the laboratory parameters, CRP and ferritin levels were significantly higher in the mortality group ($p=0.015$ and $p=0.011$, respectively). When evaluated according to prognosis, higher CRP, ferritin, and D-dimer levels were found to be associated with poor prog-

Table 1. Demographic data of mortality and prognosis groups.

	Mortality			Prognosis		
	No (n=58)	Yes (n=37)	P*	Yes (n=41)	No (n=54)	P*
Age, year (Mean±SD)	71.98 ± 12.25	72.32 ± 8.98	0.884a	71.88 ± 11.83	72.30 ± 10.51	0.856a
NIHSS (Mean±SD)	8.0 (0-25.0)	20.0 (3.0-28.0)	<0.001b	6.0 (0-25.0)	20.0 (3.0-28.0)	<0.001b
	n (%)			n (%)		
Sex						
Female	21 (55.3)	17 (44.7)	0.465	14 (36.8)	24 (63.2)	0.422
Male	37 (64.9)	20 (35.1)		27 (47.4)	30 (52.6)	
Smoking						
No	46 (58.2)	33 (41.8)	0.417	34 (43)	45 (57)	0.999
Yes	12 (75)	4 (25)		7 (43.8)	9 (56.2)	
Hypertension						
No	25 (62.5)	15 (37.5)	0.973	19 (47.5)	21 (52.5)	0.604
Yes	33 (60)	22 (40)		22 (40)	33 (60)	
Diabetes mellitus						
No	41 (62.1)	25 (37.9)	0.925	30 (45.5)	36 (54.5)	0.648
Yes	17 (58.6)	12 (41.4)		11 (37.9)	18 (62.1)	
Hyperlipidemia						
No	41 (64.1)	23 (35.9)	0.522	30 (46.9)	34 (53.1)	0.406
Yes	17 (54.8)	14 (45.2)		11 (35.5)	20 (64.5)	
Valvular heart disease						
No	55 (61.1)	35 (38.9)	0.999	38 (42.2)	52 (57.8)	0.649
Yes	3 (60)	2 (40)		3 (60)	2 (40)	
Atrial Fibrillation						
No	48 (61.5)	30 (38.5)	0.999	33 (42.3)	45 (57.7)	0.930
Yes	10 (58.8)	7 (41.2)		8 (47.1)	9 (52.9)	
Previous stroke						
No	55 (64)	31 (36)	0.147	40 (46.5)	46 (53.5)	0.073
Yes	3 (33.3)	6 (66.7)		1 (11.1)	8 (88.9)	
Stroke etiology						
Large vessel occlusion (LVO)	19 (48.7)	20 (51.3)	0.061	18 (46.1)	21 (53.8)	0.063
Small vessel disease	13 (76.5)	4 (23.5)		12 (70.6)	5 (29.4)	
Cardioembolic	15 (57.7)	11 (42.3)		12 (46.2)	14 (53.8)	
Other and undetermined causes	11 (84.6)	2 (15.4)		7 (53.8)	6 (46.2)	

*n(%); *Chi-square test (Yates correction); aIndependent samples t-test; b Mann Whitney U test; mean± standard deviation, median (min – max). Abbreviations: NIHSS- National Institute of Health Stroke Scale; mRS- Modified Rankin Scale.

nosis (p=0.005, p=0.032, and p=0.006, respectively) The median NLR value was 17 in the poor prognosis group, and NLR was significantly higher in the poor prognosis group (p<0.001). The median SII value was 7.1 in the poor prognosis group and was significantly higher in the poor prognosis group (p<0.001). The median SIRI value was 3370.7 in the poor prognosis group, and the SIRI value was significantly higher in the poor prognosis group (p<0.001) (Table 2). The risk factors affecting the mortality status were examined using logistic regression analysis and the results are presented in Table 4. As NLR increased, mortality risk increased 1.125 times (p<0.001). As the SII value increased, mortality risk increased 3.295 times (p<0.001). As the SIRI value increased, mortality risk increased 1.990 times (p<0.001) (Table 3)

The risk factors affecting the prognosis were analyzed using logistic regression analysis and the results are presented in Table 5. As NLR increased, the risk of poor prognosis increased 1.122 times (p<0.001). As the SII value increased, the risk of poor prognosis increased 2.978 times (p<0.001). As the SIRI value increased, the risk of poor prognosis increased 1.815 times (p<0.001) (Table 4). ROC analysis was used to determine the cut-off values for SII and SIRI values. As a result of the ROC analysis, the cut-off value was determined as 1962.94 and above for SII, and 6.07 and above for SIRI. The area under the ROC curve (AUC) (95%CI) for SII was 0.771 (0.678-0.864) and 0.760 (0.666-0.855) for SIRI (p<0.001). Sensitivity was 81.48%, specificity was 60.98%, the positive predictive value (PPV) was 73.33%, and the negative predictive value (NPV) was 71.43% for SII. When analyzed for SIRI,

Table 2. Relationship between laboratory findings and mortality and prognosis.

	Mortality			Prognosis		
	No	Yes	p	Good	Poor	p
Laboratory findings						
CRP, mg/L	70.0 (1-412)	91.0 (4.8.394.0)	0.015[b]	62.0 (1.0-227.0)	86.9 (4.8-412)	0.005[b]
Ferritin, ng/mL	250.0 (11.5-2584.0)	406.0 (16.4- 3109.0)	0.011b[b]	222.0 (11.5-1500.0)	396 (13.4-3109)	0.032[b]
Fibrinogen, mg/dL	485.75 (295.0-915.0)	613.0 (138.0-892.0)	0.414[b]	455.0 (295.0-759.0)	583 (138-915)	0.144[b]
D-dimer, ng/mL	580 (0.1-15000.0)	1590.0 (0.4-43412.0)	0.156b[b]	380.0 (0.1-8200.0)	1395 (0.4-43410)	0.006[b]
aPTT, s	26.4 (16.6-55.5)	28.9 (21.6-142.0)	0.052[b]	26.7 (19.6-55.5)	28.6 (16.6-142)	0.281[b]
LDH, U/L	11.9 (8.7-31.2)	12.1 (8.4-42.4)	0.373b[b]	11.7 (8.6-31.2)	12.5 (8.3-42.4)	0.216[b]
PT, s	317.0 (25.0-1382)	488.0 (116.0-2773.0)	0.061b[b]	299.0 (25.0-1382.0)	431.5 (116-2773)	0.063[b]
White Blood Cell, x103/µL	8.7 (3.5-21.8)	16.3 (11.2-30.0)	0.021[b]	8.49 ± 3.55	14.65 ± 5.13	0.041[a]
Neutrophil, x103/µL	7.09 ± 3.27	15.36±4.0	0.011[a]	6.22 ± 2.42	12.81 ± 5.18	0.021[a]
Lymphocyte, x103/µL	1.0 (0.2-15.9)	0.7 (0.3-3.6)	0.011[b]	1.1 (0.2-15.9)	0.8 (0.3-3.6)	0.022[b]
Monocyte, x103/µL	0.6 (0.1-1.3)	0.5 (0.1-1.7)	0.499[b]	0.6 (0.1-1.3)	0.5 (0.1-1.7)	0.654[b]
Platelet, x103/µL	249.5 (40.9-46.0)	211.0 (59.0-3367.0)	0.059[b]	258.0 (40.9-530.0)	215.0 (59.0-3367.0)	0.182[b]
SII x103/µL	1879.4 (50.9-12927.4)	5024.4 (476.8- 38832.7)	<0.001[b]	1203.5 (50.9-7079.2)	3715.0 (203.1- 38832.7)	<0.001[b]
SIRI x103/uL	3.8 (0.2-23.8)	10.6 (1.3-82.8)	<0.001[b]	2.9 (0.2-14.6)	7.8 (0.7-82.8)	<0.001[b]

a Independent samples t-test; *b* Mann-Whitney U test; mean± standard deviation; median (min – max).
Abbreviations: CRP- C-reactiveprotein; aPTT-partial thromboplastin Time; LDH-lactate dehydrogenase; PT-prothrombin time; NLR, neutrophil-to-lymphocyte ratio; SIRI, systemic inflammation response index; SII, systemic immune-inflammation index.

Table 3. Examination of risk factors affecting mortality.

	Mortality		Univariate	
	No	Yes	OR (%95 CI)	p
NLR	7.0 (0 – 41.0)	23.0 (4.0 – 64.0)	1.125 (1.069-1.185)	<0.001
SII	7.0 ± 1.0	8.0 ± 1.0	3.295 (1.838-5.906)	<0.001
SIRI	3.8 (0.2 – 23.8)	10.6 (1.4 – 82.8)	1.990 (1.092-1.297)	<0.001

*NLR-Neutrophil-lymphocyte ratio, SII- systemic immune inflammation index, SIRI- Systemic inflammation response index.

Table 4. Examination of risk factors affecting prognosis.

	Prognosis		Univariate	
	Good	Poor	OR (%95 CI)	p
NLR	6.0 (0 – 39.0)	18.0 (1 – 64.0)	1.122 (1.058-1.189)	<0.001
SII	7.0 ± 1.0	8.0 ± 1.0	2.978 (1.750-5.067)	<0.001
SIRI	2.9 (0.2 – 14.6)	7.8 (0.7 – 82.8)	1.815 (1.092-1.352)	<0.001

* NLR-Neutrophil-lymphocyte ratio, SII- systemic immune inflammation index, SIRI- Systemic inflammation response index.

sensitivity was 59.26%, specificity was 82.93%, PPV was 82.05%, and NPV was 60.71%. Analysis results are presented in Figure 1.

Discussion

In this study, we investigated the relationship between inflammatory markers such as SIRI and SII and the clinical outcomes of patients with COVID-19 and AIS. Lower SIRI and SII values were detected in patients with good clinical outcomes. Patients with lower SIRI and SII values had a better prognosis and lower mortality. In addition, SIRI and SII were thought to be independently prognostic predictors in patients with COVID-19. Studies published recently have shown that SIRI may be a prognostic indicator of various cancers. In a meta-analysis that included 6035 patients with solid cancers in which 14 articles were evaluated, SIRI was found to be associated with poor prognosis [11]. In another study evaluating patients followed for malignant intracranial masses, longer survival was found with lower SIRI levels [9]. In a study evaluating patients with AIS treated with endovascular treatment for the cause of proximal artery stenosis in the anterior circulation, high SIRI levels were associated with poor functional outcomes at 3 months [12]. Another study evaluating the clinical outcomes in patients with AIS undergoing mechanical thrombectomy with SIRI showed that better mRS scores and less symptomatic intracranial hemorrhage (ICH) were detected in patients with lower SIRI values (<2.9). In multivariate regression analysis, SIRI <2.9 was evaluated as an independent prognostic predictor associated with good clinical outcomes [13]. It is known that inflammation contributes to the progression of AIS, and it has been reported that leukocytes, including neutrophils, lymphocytes, and monocytes, cause different effects on the inflammatory reaction [14,15]. It has been shown that neutrophils activate the inflammatory pathway and cause neuronal injury by secreting a series of proinflammatory mediators such as inducible nitric oxide synthase (iNOS) and matrix metalloproteinases (MMPs) [15]. On the other hand, monocytes are known to play a role in the release of many inflammation-related cytokines and prothrombotic processes in atherosclerosis. Contrary to these cells, lymphocytes are known to have a downregulating effect on postischemic inflammation [16]. In experimental stroke

models, it has been shown that increased lymphocytes stimulate anti-inflammatory cytokines and reduce neuron damage by suppressing inflammatory cytokines [17]. In previous studies, it has been reported that inflammatory markers such as NLR and LMR are associated with prognosis in AIS, and it was shown that decreased NLR and high LMR predicted good clinical outcomes [18,19]. It was thought that SIRI could be a new inflammatory marker that could be used to better evaluate inflammation than NLR or LMR because it had three parameters. In our study, it was shown that SII and SIRI predicted prognosis and mortality better than NLR in patients with COVID-19 and AIS. Therefore, lower SIRI values were associated with a good prognosis and lower mortality rate; this situation was thought to reflect the suppression of the inflammatory process mediated by neutrophils and monocytes and the anti-inflammatory properties of lymphocytes. In addition to NLR and LMR, which are leukocyte-based inflammatory markers in patients with AIS, platelet-related inflammatory markers have also been studied [20]. In previous studies, it was reported that high PLR was associated with poor prognosis in patients with AIS [21]. It was shown that both leukocytes and platelets played an important role in inflammation and thrombosis through the release of chemokines during AIS [22,23]. Therefore, it was thought that SII, based on a combination of neutrophils, lymphocytes, and platelets, might better reflect the prognosis of patients with AIS than other inflammatory markers. The SII is a known prognostic factor in many malignancies [24]. In one study, increased SII values were associated with poor clinical outcomes in patients with supratentorial ICH [25]. Topcuoglu et al. showed that there was a correlation between the SII cut-off value of >1781 and the incidence of symptomatic ICH in patients with AIS who received intravenous thrombolytics [23]. In a study that included 362 patients evaluating the relationship of the SII index with the severity of the disease in patients with acute ischemic stroke, it was reported that the SII index was an independent risk factor in showing the severity of stroke [26]. In our study, SII values were found to be significantly lower in the good prognosis group than in the poor prognosis group. Although the number of patients with stroke seems to have decreased due to the decrease in hospital admissions and patient admissions other than COVID-19 infection in many countries, it has been suggested that COVID-19 infection may cause stroke by various mechanisms [27]. It is thought that the systemic proinflammatory mechanism and hypercoagulability that occur in patients with infection play a role in the etiopathogenesis of stroke [28]. Although there are many studies evaluating mortality in patients with COVID-19, a limited number of studies have evaluated the relationship of hematologic-based inflammatory parameters with mortality and prognosis. In a multicenter study in which 495 patients with COVID-19 were evaluated, the patients were grouped as ICU and non-ICU, the SII, SIRI, and NLR were found to be statistically significantly higher in the intensive care groups, and it was reported that the SII index predicted the need for intensive care with a specificity of 95.6% [29]. In another study evaluating serologic inflammatory markers in patients with COVID-19, the SII index was reported to have predictive value in predicting in-hospital mortality [30]. Our study revealed that SIRI and SII were associated with the prognosis of patients with COVID-19 and AIS. As NLR increased, the risk of poor prognosis increased 1.122 times, as SIRI value increased, the risk of poor prognosis increased 1.815 times, and as the SII value increased, the risk of poor prognosis increased 2.978 times. When evaluated in terms of mortality, it was shown that as NLR increased, mortality risk increased 1.125 times, as SIRI value increased, mortality risk increased 1.990 times, and as the SII value increased, mortality risk increased 3.295 times. The use of non-invasive, easily accessible, and cost-effective prognostic inflammatory markers such as SIRI and SII can be considered in these patients. However, there were some limitations of our study. The study was retrospective, other inflammatory markers such as plasma coagulation factors and interleukins were not studied, SIRI and SII were evaluated at the time of admission, and in addition to the atherosclerotic process, COVID-19 also had a potential impact on SIRI and SII. Although there are studies on hematologic-based inflammatory markers in patients with COVID-19 and AIS in the literature, no study has been found to evaluate the relationship of these markers with mortality and prognosis in COVID-19–positive patients with AIS. Although there are limitations, this is the first study to demonstrate the predictive value of SII and SIRI in the prognosis of COVID-19–positive patients with AIS.

Conclucion

In this study, SIRI and SII were shown to be associated with prognosis and mortality in COVID-19–positive patients with AIS. Low SIRI and SII values are associated with favorable clinical outcomes. SIRI and SII are noninvasive, easily available, and cost-effective serologic prognostic-predictive inflammatory markers in patients with AIS. Given that it is of great importance to discover the specific mechanism of the inflammatory response to be able to adopt immunomodulatory therapy, more studies are needed to confirm the findings and identify the underlying mechanisms.

Ethics approval

Approval for the study was obtained from the ethics committee of Karatay University (Protocol No: 2021-044) and the Ministry of Health.

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