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Prognostic Value of Systemic Immune-Inflammation Index and Systemic Inflammatory Response Index on Functional Status and Mortality in Patients with Critical Acute Ischemic Stroke

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Neuroinflammation plays an essential role in the pathogenesis of acute ischemic stroke (AIS). This study aims to investigate the predictive value of the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) on mortality and functional limitation in patients with critical AIS. Patients with critical AIS in a tertiary hospital's intensive care unit (ICU) between June 2020 and 2022 were retrospectively examined. Patients were classified according to their 28-day mortality (survivor and non-survivor group) and functional status (poor and good functional outcomes). The performances of SII and SIRI in predicting mortality and functional outcomes were compared. A total of 198 patients were included in the study. The median age of the entire population was 70 (56-86) years, and 52% (n = 103) were male. Coronary vascular disease/heart failure was found to be significantly higher in the mortality group (p = 0.025). While SII was found to be significantly higher in the mortality group (1,180 vs. 811, p = 0.038), SIRI did not show a significant difference (1.82 vs. 1.70, p = 0.257). SII and SIRI were significantly higher in the poor functional outcome group (p < 0.001 and p = 0.015). In the ROC analysis of the functional status prediction performances of SII and SIRI, the cut-off value of SII was ≥ 1,146, the area under the curve (AUC) = 0.645 (0.568-0.722), the cut-off value of SIRI was ≤ 2.54, AUC = 0.600 (0.520-0.680) was detected. SII helps predict 28-day mortality in patients with critical AIS. Both SII and SIRI can predict functional status at discharge.

Keywords: acute ischemic stroke; functional outcome; prognosis; systemic immune-inflammation index; system inflammation response index
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Introduction

Stroke is the second highest cause of death globally (11.6%). According to 2019 data, there were 12.2 million stroke cases worldwide, while 6.5 million deaths due to stroke were detected (GBD 2019 Stroke Collaborators 2021). Disability-adjusted Life Year (DALY) loss due to stroke worldwide is 143 million years. AIS is the third most common cause of disability and DALY loss. Strokes are divided into two groups: ischemic and hemorrhagic stroke. More than 70% of them are acute ischemic strokes (AIS) (Randolph 2016; Campbell et al. 2019; Zhu et al. 2021). The severe decrease in blood flow to the brain after AIS causes insufficient oxygen supply to the brain, leading to neuron death. Identifying patients with a poor prognosis as soon as possible may be beneficial in applying optimum treatment and shortening the length of hospital stay. For this purpose, rapidly determined and reliable biomarkers are essential in predicting poor prognosis.

The role of inflammatory response and immune cells in AIS pathogenesis is a promising area of research. Inflammatory interactions at the blood-endothelium interface, including cytokines, chemokines, and blood cells, are essential in the pathogenesis of tissue damage during cere-

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bral infarction (Zhu et al. 2022). In the experimental AIS model, immunoinflammatory cells, including neutrophils, lymphocytes, and monocytes, have been reported to infiltrate the ischemic brain tissue and play different roles (Zrzavy et al. 2018). Neutrophils enter the brain parenchyma immediately after the onset of ischemia and release free oxygen radicals. They can also directly exacerbate cell necrosis and apoptosis in the ischemic area (Herz et al. 2015). Similarly, the impact of monocytes as another vital inflammation trigger after AIS, migrating into ischemic brain tissue, leading to the expansion of the damaged area, is substantial. The systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI) can be easily calculated from the numbers of neutrophils, platelets, lymphocytes, and monocytes. It has been reported that SII and SIRI can reflect the inflammatory status and help predict prognosis in various clinical situations (Zheng et al. 2019; Zhang et al. 2024). However, more studies must be done on the predictive value of SII and SIRI on early mortality and functional outcomes of patients with critical AIS, which could significantly impact future AIS treatment.

This study aims to investigate the prognostic value of SII and SIRI on 28-day mortality and functional outcomes in patients with critical AIS in the intensive care unit (ICU) of a tertiary hospital.

Materials and Methods

This retrospective observational study, initiated after the approval of the local Clinical Trials Review Board and Ethics Committee (KAEK/2023.05.60, date: 17.05.2023), was conducted according to the principles of the Declaration of Helsinki. The study focused on patients with AIS who were under follow-up and treatment at the University of Health Sciences Turkey, Istanbul Kanuni Sultan Süleyman Training and Research Hospital between June 2020 and 2022. To ensure the accuracy of our findings, patient data were accessed through patient follow-up forms and the hospital information system. Written informed consent was obtained from the patients included in the study or their legal guardians.

Inclusion criteria are as follows: (1) ≥ 18 years of age, (2) AIS for the first time, and (3) presentation within 48 hours of first symptom onset. Exclusion criteria included: (1) history of infection, severe trauma, or surgery within two weeks before AIS diagnosis; (2) malignancy, autoimmune, and hematological disease; (3) severe liver and kidney diseases/failure; (4) use of medications that may affect platelet and lymphocyte counts (such as antiplatelet, glucocorticoids); (5) history of transient ischemic attack, cerebral infarction, intracranial hemorrhage, aneurysmal SAH, venous sinus thrombosis; (6) missing data.

According to the World Health Organization's Multinational Monitoring of Trends and Determinants in Cardiovascular Diseases (WHO-MONICA) criteria, AIS is defined as a "neurological deficit of cerebrovascular cause that persists for more than 24 hours or is interrupted by death within 24 hours" (WHO MONICA Project Principal Investigators 1988). Magnetic resonance imaging (MRI) or computed tomography (CT) within 24 hours of presentation confirmed the diagnosis of AIS.

Demographic data (age, gender, body mass index), comorbidity, need for thrombolytic therapy, length of stay in ICU and mechanical ventilator (Mv), GCS and Acute Physiology and Chronic Health Evaluation-II (APACHE-II) scores at the time of admission to ICU, 28-day mortality and functional outcome were recorded. The 28-day mortality and mRS scores of the discharged patients were obtained through the hospital information system and by calling their relatives.

modified Rankin Scale and functional outcome

The modified Rankin Scale (mRS), one of the most commonly used functional recovery scales, is renowned for its simplicity and ease of interpretation. It helps determine the degree of disability or dependency after a stroke. According to the mRS, a score of 0 to 2 indicates functional independence (good functional outcome), a score of 3 to 5 indicates dependency (poor functional outcome), and a score of 6 indicates death (Chalos et al. 2020). Functional independence (0-2 points) is defined as the patient walking on his own, unaided. In essence, the mRS, with its straightforward approach, highlights that the primary determinant of independence is walking without assistance. Our study, which evaluated functional outcomes on the 28th day after admission to ICU, further demonstrates the ease and clarity of the mRS in our research.

SII and SIRI values, which are inflammatory biomarkers, were obtained from blood results at admission to the hospital. SII was obtained from the formula platelet × (neutrophil count/lymphocyte count), and SIRI was obtained from the formula neutrophil count × (monocyte count/lymphocyte count). Patients were classified into the survivor and mortality groups according to 28-day mortality. It was also categorized as good functional outcome (mRS ≤ 2) and poor functional outcome (mRS > 2) according to 28-day mRS scores. SII, SIRI, and other clinical data were analyzed in groups.

The sample size was calculated using the G* Power 3.1 program. The study's primary purpose is to investigate the prognostic value of SII and SIRI values at admission to the ICU on 28-day mortality and functional outcomes in patients with critical AIS. For T-tests, when $p < 0.05$, the effect size is 0.5, and the power of the study is determined as 80%, 140 patients must be included in the study. All patients with AIS who were followed up in the ICU between the relevant dates and whose data were not missing were included in the study.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (SPSS Inc., Chicago, USA) software. The Shapiro-Wilks test and histogram were used to determine whether the data

conformed to a normal distribution. Descriptive data were expressed as the number of patients, percentage, median, and range. Quantitative variables that were not normally distributed were analyzed with the Mann-Whitney U test. The Chi-square and Fisher's exact tests were used to evaluate qualitative data. Multivariate regression analysis was used to determine whether SII and SIRI differed significantly between the groups and were independent predictors of mortality. Logistic regression analysis results were presented as odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristics (ROC) curve analysis was performed to determine the prognostic value of SII and SIRI. The significance level was accepted as $p < 0.05$.

Results

This comprehensive study encompassed 198 critically ill patients with AIS, all of whom were closely monitored in the ICU (Fig. 1). The median age in the entire population was 70 (56-86) years, and 52% were female (n = 103). Demographic data were meticulously collected and found to be similar between groups. The most common comorbid diseases in patients with AIS were hypertension (58.6%), diabetes mellitus (31.3%), and coronary vascular disease/heart failure (CVD/HF) (29.3%). The prevalence of CVD/HF was significantly higher only in the mortality group ($p = 0.025$). There was no significant difference between the groups regarding thrombolytic treatment (24.8% vs. 12.1%, $p = 0.111$). Half of the population had good clinical outcomes (mRS ≤ 2). In the mortality group, GCS scores were significantly lower at admission to the ICU, and APACHE-II scores were significantly higher ($p < 0.001$ for both). Platelet count at admission was significantly higher in the mortality group (289 vs. 230 ×109/L, $p = 0.008$). While SII was found to be significantly higher in the mortality group (1180 vs. 811, $p = 0.038$), SIRI did not show a significant difference (1.82 vs. 1.70, $p = 0.257$). The 28-day mortality in the entire population was 16.6% (Table 1).

The functional status of the patients (28th day after admission) was evaluated with the mRS scale. In patients with poor functional outcomes (mRS > 2), the GCS score was found to be significantly lower, and the APACHE-II score was significantly higher ($p < 0.001$ for both). In addition, lymphocyte levels were significantly lower in patients with poor functional outcomes (1.4 vs. 2.0, $p < 0.001$). SII (1162 vs. 743, $p < 0.001$) and SIRI (2.46 vs. 1.57, $p = 0.015$) were significantly higher in patients with poor outcomes (Table 2).

In the multivariate regression analysis of the factors that significantly affected mortality, GCS, APACHE-II scores, and platelet count at admission to the ICU were found to be independent predictors of mortality (Table 3).

Among the factors affecting functional outcomes between the groups, a low GCS score was an independent predictor of poor functional outcomes ($p < 0.001$). SII and SIRI were not independent predictors of functional outcome (Table 4).

In ROC Curve analysis of SII and SIRI showing significant difference between good and poor functional outcomes, a cut-off value of SII ≥ 1146, the area under the curve (AUC) = 0.645 (0.568-0.722), the cut-off value for SIRI ≤ 2.54, AUC = 0.600 (0.520-0.680) was detected (Table 5).

Discussion

This study investigated the prognostic value of SII and SIRI in critically ill patients with AIS followed up in the ICU. SII was found to help predict 28-day mortality. In addition, it was determined that both SII and SIRI values could be used to predict the functional outcomes of patients with AIS.

Stroke is a significant cause of functional disability and mortality in both developed and developing countries.

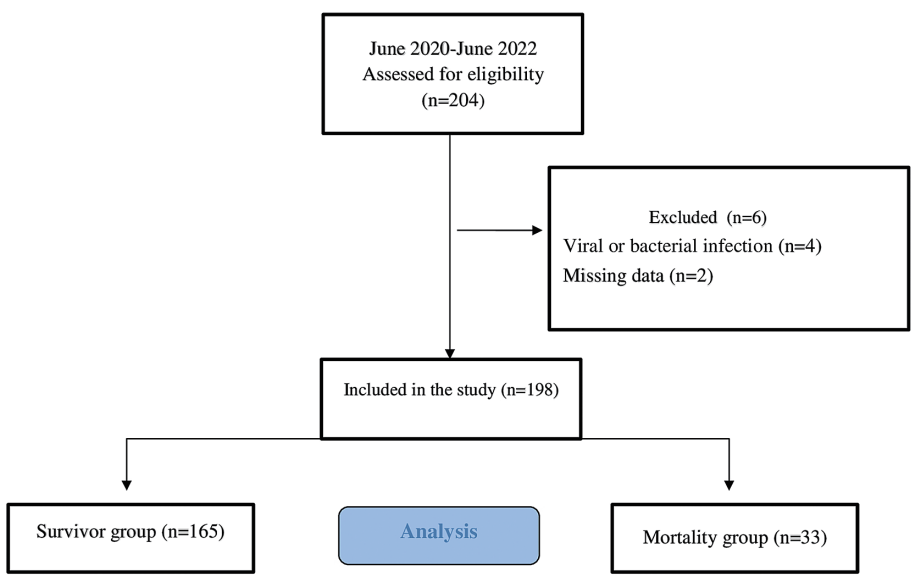

Fig. 1. Flow chart of the study.

Table 1. Demographic data of the groups and some clinical features.

	Overall (n=198)	Survivor Group (n=165)	Mortality Group (n=33)	*p*-value
Age (y)	70 (56-86)	69 (59-80)	77 (56-86)	0.110
Sex, n (%)				0.065
Female	103 (52)	81 (49.1)	22 (66.7)	
Male	95 (48)	84 (50.9)	11 (33.3)	
BMI	25.8 (23.8-27.7)	25.7 (23.8-27.7)	26.1 (23.2-28.2)	0.699
Comorbidity, n (%)				
Hypertension	116 (58.6)	94 (57)	22 (66.7)	0.302
Diabetes	62 (31.3)	51 (30.9)	11 (33.3)	0.784
CVD/HF	58 (29.3)	43 (26.1)	15 (45.5)	**0.025**
Atrial fibrillation	36 (18.2)	30 (18.2)	6 (18.2)	1.000
Asthma / COPD	15 (7.6)	13 (7.9)	2 (6.1)	1.000
Thrombolytic, n (%)	45 (22.7)	41 (24.8)	4 (12.1)	0.111
Functional outcome				**< 0.001**
Good (mRS ≤ 2)	99 (50)	99 (60)	0	
Poor (mRS 3-6)	99 (50)	66 (40)	33 (100)	
GCS	12 (9-15)	12 (10-15)	8 (7-9)	**< 0.001**
APACHE-II	13 (10-18)	12 (10-16)	22 (16-24.5)	**< 0.001**
Duration of ICU (days)	7 (3-12)	6 (3-11)	9 (7-19)	**0.009**
Duration of Mv (days)	0	0	8 (5-12)	**< 0.001**
Platelet, $\times 10^9$/L	233 (186-279)	230 (184-272)	289 (191-342)	**0.008**
Neutrophil, $\times 10^9$/L	6.31 (4.89-9.10)	6.28 (4.83-8.83)	6.48 (4.92-9.55)	0.447
Lymphocyte, $\times 10^9$/L	1.75 (1.10-2.30)	1.80 (1.20-2.30)	1.50 (0.80-2.40)	0.272
Monocyte, $\times 10^9$/L	0.54 (0.37-0.73)	0.54 (0.37-0.70)	0.55 (0.38-0.83)	0.450
SII	852 (555-1605)	811 (541-1442)	1180 (607-2297)	**0.038**
SIRI	1.73 (1.06-3.73)	1.70 (1.03-3.29)	1.82 (1.16-6.74)	0.257

Data are expressed as number of patients, percentage and median (interquartile range = Q1-Q3).
CVD/HF: Coronary vascular disease/heart failure, COPD: chronic obstructive pulmonary disease, GCS: Glasgow Coma Scale, APACHE-II: Acute Physiology and Chronic Health Assessment-II, ICU: Intensive care unit, Mv: Mechanical ventilation, SII: Systemic immune- inflammation index, SIRI: systemic inflammatory response index

Age is one of the most important non-modifiable risk factors for stroke. It has been reported that approximately 70% of stroke survivors are over the age of 65 (Altun et al. 2018). Gender does not significantly affect stroke (Altun et al. 2018; Huang 2023). It has been reported that the most important modifiable risk factor leading to both ischemic and hemorrhagic stroke is hypertension (Virani et al. 2020). It has been stated that the median age in patients with AIS is 69 years, 50% are male, and 70% of the patients have hypertension as a comorbid disease (Huang 2023). In another study, it was reported that ischemic stroke was detected in 90% of the patients in the stroke unit; the average age was 71 years, and 77% of the patients had hypertension (Kunt and Püllüm 2021). In our study, consistent with the literature, the median age was 70 years, and 52% of the patients were female. It was determined that the most common comorbid disease in the patients was hypertension. Among the comorbidities, only a history of coronary vascular disease/heart failure was found to have a significant effect on mortality.

Neuroinflammation is a critical factor in the development of ischemic stroke. At the onset of acute ischemic stroke, an intravascular inflammatory response is initiated. The literature reveals that the inflammatory cascade is activated immediately after the formation of vascular occlusion, leading to escalated brain damage and neurological dysfunction (Vidale et al. 2017). This has led to a surge in interest in neuroinflammation in recent years. It has been established that SII is a crucial determinant of prognosis in inflammatory events. It can be easily calculated from the number of platelets, neutrophils, and lymphocytes. SII holds significant potential as a marker to predict thrombus formation and inflammatory response in stroke (Xu et al. 2021).

A high SII can be seen in both prothrombotic events (higher platelets) and immune dysregulation (higher neutrophil and lower lymphocyte count). Neutrophils are among the earliest cells infiltrating the lesion a few hours after stroke. Thus, they cause the release of inflammatory mediators, leading to cell necrosis and apoptosis in the ischemic

Table 2. Analysis of patients according to their functional outcome.

	Good functional outcome mRS ≤ 2 (n=99)	Poor funtional outcome mRS >2 (n=99)	*p*-value
Age (y)	66 (55-77)	75 (63-85)	< 0.001
Sex, n (%)			0.064
Female	45 (45.5)	58 (58.6)	
Male	54 (54.5)	41 (41.4)	
BMI	25.3 (24.1-27.7)	26.1 (23.4-27.9)	0.905
Comorbidity, n (%)			
Hypertension	55 (47.4)	61 (61.6)	0.387
Diabetes	32 (32.3)	30 (30.3)	0.759
CAD/HF	24 (24.2)	34 (34.3)	0.118
Atrial fibrillation	14 (14.1)	22 (22.2)	0.140
Asthma/ COPD	8 (8.1)	7 (7.1)	0.788
GCS	15 (12-15)	9 (8-10)	**< 0.001**
APACHE-II	10 (9-13)	16 (13-24)	**< 0.001**
Platelet, $\times10^9$/L	233 (193-277)	230 (183-295)	0.792
Neutrophil, $\times10^9$/L	6.08 (4.94-7.97)	6.48 (4.84-9.57)	0.216
Lymphocyte, $\times10^9$/L	2.0 (1.5-2.4)	1.4 (0.9-2.1)	**< 0.001**
Monocyte, $\times10^9$/L	0.55 (0.40-0.67)	0.52 (0.35-0.79)	0.983
SII	743 (473-1116)	1162 (599-2242)	**< 0.001**
SIRI	1.57 (1.07-2.52)	2.46 (1.06-6.13)	**0.015**

Data are expressed as number of patients, percentage and median (interquartile range = Q1-Q3).
GCS: Glasgow Coma Scale, APACHE-II: Acute Physiology and Chronic Health Assessment-2, ICU: Intensive care unit, Mv: Mechanical ventilation, SII: Systemic immune-inflammation index, SIRI: systemic inflammatory response index

Table 3. Multivariate regression analysis of factors affecting mortality.

Variables	OR	95% CI (min-max)	*p*-value
CVD/HF	0.439	0.160-1.207	0.110
GCS	0.667	0.534-0.832	**< 0.001**
APACHE-II	1.091	1.002-1.188	**0.038**
Platelet	0.007	1.002-1.016	**0.004**
SII	1.000	1.000	0.970
Constant	0.459		0.659

OR: Odds ratio, CI: Confidence interval, CVD/HF: Coronary vascular disease/heart failure, Acute Physiology and Chronic Health Assessment-II, SII: Systemic immune-inflammation index

Table 4. Multivariate logistic regression analysis of functional outcome.

Variables	OR	95% CI (min-max)	*p*-value
GCS	0.469	0.370-0.596	**< 0.001**
APACHE-II	1.074	0.969-1.191	0.176
Lymphocyt	0.776	0.481-1.250	0.297
SII	1.000	0.999-1.000	0.752
SIRI	1.224	0.987-1.517	0.065
Constant	2456		0.848

OR: Odds ratio, CI: Confidence interval, GCS: Glasgow Coma Scale, APACHE-II: Acute Physiology and Chronic Health Assessment-II, SII: Systemic immune-inflammation index, SIRI: systemic inflammatory response index

Table 5. Functional outcome prediction performance of SII and SIRI.

	Cut-off	Sensitivity	Specificity	AUC (95% CI)
SII	1146	0.505	0.788	0.645 (0.568-0.722)
SIRI	2.54	0.495	0.758	0.600 (0.520-0.680)

AUC: Area Under Curve, CI: Confidence İnterval, SII: Systemic Immune-inflammation index, SIRI: systemic inflammatory response index

area (Jin et al. 2010). A higher neutrophil level in the early stage of AIS is associated with larger infarct volume, and neutrophil increase is an essential mediator of ischemic brain injury (Buck et al. 2008). It has been stated that platelets also play a role in brain damage after the development of AIS. In animal studies, the cerebral ischemia-

reperfusion model has been stated to disrupt cerebral blood flow by modulating harmful neutrophil accumulation in the brain and the formation of platelet neutrophil aggregates (Denorme et al. 2020). Another vital trigger of inflammation after AIS is monocytes. After the onset of ischemic stroke, peripheral monocytes increase and migrate to the ischemic brain tissue, expanding the injured area (Kaito et al. 2013). In a study by Huang (2023), which included a significant number of patients, it was found that SII was significantly higher in patients with moderate-severe AIS than those with mild severity. The author also stated that SII significantly predicted functional outcomes at discharge (Huang 2023). In another large-scale study, it was emphasized that high SII increased the risk of stroke and death from all causes (Jin et al. 2021). In our study, which focused on the association of SII with stroke severity, functional outcomes, and mortality, we found that SII was significantly higher in the mortality group (median 1,180 vs. 811, $p = 0.038$). Additionally, SII was significantly higher in patients with poor functional outcomes at discharge (median 1,162 vs.743, $p < 0.001$). However, SII was not an independent predictor of mortality and functional outcomes.

Our research focuses on the novel indicator of systemic inflammation, SIRI. This indicator has been found to effectively reflect the inflammatory state and predict the prognosis of various diseases, including aneurysmal subarachnoid hemorrhage and different cancers (Chen et al. 2019; Yi et al. 2021). A high SIRI is associated with high neutrophil/monocyte and low lymphocyte counts, indicating a strong pro-inflammatory response mediated by monocytes and neutrophils and an anti-inflammatory response mediated by lymphocytes. It has been suggested that high SIRI is an independent risk factor for death in AIS patients and is closely linked to prognosis (Dang et al. 2022). Huang (2023) found that SIRI was significantly higher in patients with moderate-severe AIS but was not associated with poor prognosis at discharge. In our study, SIRI showed no significant difference in the mortality and survivor groups. However, both SII and SIRI were found to be significantly higher in the poor functional outcome group. In the ROC analysis, SII's performance in predicting poor prognosis at discharge was superior to SIRI's (AUC 0.645 vs. 0.600). Our study includes patients with critical AIS who required ICU, and the differences in clinical conditions, disease levels, and comorbidities may explain the variations in the studies.

The study has some limitations. The first is retrospective and single-center. Multicenter, prospective studies involving more patients may reveal more impressive results. Second, although patients with AIS presented to the emergency department within 24 hours after the onset of ischemic stroke, the exact time of stroke onset could not be determined. Third, SII and SIRI values were obtained from blood results at admission to the ICU. Dynamic SII and SIRI at specific times were not determined.

In conclusion, SII, one of the inflammatory biomarkers calculated from the blood count at admission, helps predict mortality in patients with AIS followed in the ICU. Additionally, SII and SIRI can be used to predict functional outcomes in this patient group.

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