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Predictive value of systemic immune-inflammation index for cerebral reperfusion and clinical outcomes in patients with acute ischemic stroke undergoing endovascular treatment

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Abstract. – OBJECTIVE: The systemic immune inflammation (SII) index has been an excellent prognostic indicator in patients with acute ischemic stroke (AIS). In this study, we assessed the utility of the SII in predicting the prognosis and reperfusion status of patients with AIS who underwent endovascular treatment (EVT).

PATIENTS AND METHODS: 123 consecutive AIS patients were enrolled in our study. The receiver-operating characteristics (ROC) curve was used to determine the cut-off value of SII for predicting unsuccessful cerebral reperfusion. Multivariate logistic regression analysis analyzed the association between SII and unsuccessful reperfusion rate after EVT.

RESULTS: The median value of SII was significantly higher in patients with unsuccessful reperfusion compared to patients with successful reperfusion [2,029 (1,217-2,771) *vs.* 1,172 (680-2,145) respectively, *p*=0.003)]. A ROC curve analysis showed that the best cut-off value of SII for predicting unsuccessful reperfusion status was 1,690, with sensitivity and specificity of 71% and 69%, respectively. The area under the curve (AUC) was 0.673 (95% CI; 0.552-0.793). Multivariate analysis demonstrated that SII ≥ 1,690 value was an independent predictor of unsuccessful cerebral reperfusion and unfavorable clinical outcome after EVT (Hazard ratio – H.R.=3.713, 95% CI: 1.281-10.76, *p*=0.016, HR=2.28, 95% CI: 1.06-4.88, *p*=0.035, respectively).

CONCLUSIONS: We suggested that SII is a potential indicator to predict the unsuccessful cerebral reperfusion and unfavorable clinical outcome for patients with AIS undergoing EVT.

Key Words:
Acute ischemic stroke, Cerebral reperfusion, Endovascular treatment, Inflammation.

Introduction

Acute ischemic stroke (AIS) is the second leading cause of death and a major cause of disability worldwide and brings severe economic and social consequences[1]. The fundamental AIS treatment strategy is the earliest restoration of cerebral blood flow. Endovascular treatment (EVT) is the most efficient and gold standard treatment of choice for eligible patients with AIS, which significantly improves clinical outcomes[2]. Nevertheless, despite the technical modernization of reperfusion therapies, inadequate cerebral reperfusion has been observed in up to 40% of patients with EVT[3]. Early and individualized risk stratification to predict failed cerebral reperfusion after EVT can improve clinical outcomes by allowing physicians to make more precise decisions concerning the choice of pharmacologic and endovascular treatments, allocation of clinical resources, and triage among alternative levels of intensive care. Unfortunately, a widely accepted risk stratification method for predicting reperfusion status after EVT is not yet available. Therefore, finding a more reliable marker that could indicate the risk of impaired cerebral perfusion and poor outcome in patients with AIS who undergo EVT is crucial.

AIS is a complex multifactorial disease that has been reported to be associated with inflammatory and stress responses[4]. Neutrophils activate inflammatory reactions early in AIS and induce excessive brain injury by releasing proinflammatory destructive mediators[5]. In addition, higher platelet activation aggravates the release of inflammatory mediators and undesirable inflammatory processes[6]. Therefore, several studies have shown that

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these inflammatory reactions are associated with poor prognosis after AIS[7-9].

The systemic immune-inflammation index (SII) was recently developed[10] based on a combination of neutrophils, platelets, and lymphocytes to reflect the body's comprehensive immune and inflammation situation. Since then, SII has been a valuable marker for predicting clinical outcomes in various cancers, cardiovascular disease, and heart failure[11-13]. Furthermore, recent studies[14-17] revealed the association of SII with clinical outcomes of ischemic stroke. However, the relationship between SII and post-procedural cerebral perfusion status in patients with AIS has not been investigated. The present study evaluated the association of SII with angiographic cerebral reperfusion and investigated the prognostic value of SII in patients with AIS undergoing EVT.

Patients and Methods

Study Population

The retrospective cross-sectional study used the data of 123 patients with AIS who underwent EVT within 6 hours from symptom onset. Patients with a history of major surgery or trauma four weeks before hospital admission, active infections or inflammatory disease, severe kidney or liver dysfunction, hematologic disease, chronic inflammatory or autoimmune disease, and known malignancy were excluded from the study.

All patients were managed according to the guidelines for the early management of patients with AIS from the American Heart Association/ American Stroke Association[1]. A non-contrast computerized cranial tomography (C.T.) scan was performed to rule out the possibility of hemorrhagic stroke on admission to the Emergency Department. Intravenous thrombolysis with alteplase at a maximum dose of 0.9 mg/kg was administered in eligible patients within 4.5 hours after stroke onset. As identified by cervical and cranial CT-angiogram (CT-A), EVT was performed in patients with AIS caused by occlusion of the middle cerebral artery with or without the internal carotid artery or basilar artery. Digital subtraction angiography (DSA) was performed to determine the actual location of the occluded vessels. The two most common EVT techniques for reperfusion were used: direct aspiration alone or a combination of direct aspiration and mechanical thrombectomy with a stent retriever. The first line technique was manual aspiration with a SOFIA distal access catheter (MicroVention Europe, Saint-Germain-en-Laye-France). If it did not achieve an adequate recanalization, a combination of direct aspiration and a stent retriever was used with the NeVa thrombectomy device (Vesalio LLC, Lake Forest, CA, USA). Regarding EVT procedures, the choice of the particular device or intervention modality was left to the discretion of the interventionist. A routine cranial C.T. scan was performed 24 hours after the therapy or earlier in cases of changed or worsening neurological symptoms.

Clinical, Angiographic and Laboratory Data

The following data of baseline demographic and clinical characteristics were obtained from the hospital database: age and sex, history of hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation, dyslipidemia, prior stroke, smoking, prior use of antiplatelet or anticoagulant drugs, AIS characteristics including stroke etiology based on Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria, initial National Institutes of Health Stroke Scale (NIHSS), and symptom to puncture time[18]. Severe stroke was defined as an initial NIHSS score $^{3}10$. The following DSA data were also reviewed: arterial occlusion site, cerebral reperfusion status, and presence of first-pass reperfusion. Two interventional specialists (an expert interventional neurologist and an interventional cardiologist) analyzed the cerebral reperfusion status based on the Modified Thrombolysis in Cerebral Infarction (mTICI) grades[19]. Definition of the mTICI grades was as follows: grade 0 refers to no/minimal reperfusion; grade 1 refers to partial filling $< 50\%$ of territory; grade 2b refers to $\geq 50\%$ of territory; grade 2c refers to near-complete perfusion except slow flow or few distal cortical emboli, and grade 3 refers to complete perfusion. The unsuccessful reperfusion was identified in patients with antegrade mTICI grade $< 2c$ or 3[20]. Consequently, the patients were divided into two groups, according to their final mTICI grades: the successful reperfusion group and the unsuccessful reperfusion group. First-pass complete reperfusion was defined as achieving complete reperfusion (TICI $\geq 2c$) with a single thrombus aspiration without rescue treatment with intra-arterial thrombolytics or stent retriever. Collateral arterial supply was assessed based on CT-A using the TAN grading system, which ranges from 0 to 3 (0 for absent collateral circulation, 1 for collateral supply filling $> 0\%$ and $\leq 50\%$

of the occluded territory, 2 for collateral supply filling > 50% and < 100% of the occluded territory, and 3 for collateral supply filling 100% of the occluded territory)[21]. A poor collateral score refers to grades 0-1. A specialist neuro-interventionist evaluated the clinical outcome at three months with the modified Rankin Scale (mRS) score. A favorable clinical outcome was defined as mRS < 3, while an unfavorable outcome was described as an mRS score ≥ 3. Safety outcomes included symptomatic intracerebral hemorrhage (ICH) and the infarct's hemorrhagic transformation (H.T.). The symptomatic ICH was defined as any intracranial hemorrhage with an increase of ≥ 4 points on the total NIHSS score.

Laboratory analysis included the results of complete blood counts, creatinine, serum lipids, glucose, and CRP. Venous blood samples were collected from all patients at admission to the emergency department. The neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) was calculated as the neutrophils and platelets to lymphocytes. The SII and systemic inflammation response index (SIRI) values were calculated as follows: SII = platelet count × (neutrophil count/lymphocyte count) and SIRI = neutrophil count × (monocyte count/lymphocyte count), respectively.

The Local Ethics Committee approved the retrospective analyses of anonymized patient data in accordance with the declaration of Helsinki (Approval number: 71522473-050.01.04-128385-137). Each patient or their family member had signed written informed consent.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 21.0, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on normality, assessed using the Kolmogorov-Smirnov test.

According to normality, group means for continuous variables were compared using the independent samples *t*-test or the Mann-Whitney U test. The categorical variables were presented as counts (n) and percentages and compared with the Chi-square test. Spearman's correlation coefficients were used to determine the correlations between SII and the failed cerebral reperfusion. Receiver operating characteristic (ROC) curve analysis was performed to define thresholds for SII for predicting the unsuccessful reperfusion status with corresponding specificity and sensitivity. Multivariate stepwise logistic regression was used to identify independent predictors of unsuccessful reperfusion and clinical outcome after EVT, and odds ratios (O.R.s) with 95% confidence intervals (CI) were calculated. Covariates with $p<0.10$ in univariate analysis were entered into a backward multivariate model. A two-tailed p-value < 0.05 was considered statistically significant.

Results

123 patients with AIS were enrolled in our study, including 65 (52.8%) females and a mean age of 66.5±12 years. 24 (19.5%) patients demonstrated unsuccessful reperfusion among the study population. The patients' demographics, laboratory, and clinical data are summarized in Table I. The median value of SII was significantly higher in patients with unsuccessful reperfusion, compared to patients with successful reperfusion [2,029 (1,217-2,771) *vs.* 1,172 (680-2,145), $p=0.003$] (Figure 1). The neutrophil count, SIRI value, and NLR were also higher in patients with unsuccessful reperfusion, while lymphocyte counts were lower in the unsuccessful reperfusion group. The PLR and hs-CRP levels did not differ between the two groups. Patients in the unsuccessful reperfusion group had significantly higher mortality, less favorable clinical outcomes (mRS score < 3) at three months, and an increased incidence of hemorrhagic transformation ($p<0.001$, $p=0.017$, and $p<0.001$, respectively). All patients underwent EVT by direct aspiration, with the clot aspirated with a large-diameter distal access catheter. In 26 patients, primary suction failed, and a rescue treatment was performed with a stent retriever coaxially introduced through the same distal access catheter. The DSA results showed 64.2% MCA occlusion, 27.7% ICA-MCA tandem occlusion, and 8.1% basilar artery occlusion. There was no difference between the two groups regarding the arterial occlusion site. Patients with unsuccessful reperfusion were more likely to have a poor collateral supply regarding the CTA findings (33.3% *vs.* 11.1%, $p=0.01$).

Table II indicates the angiographic and procedural characteristics of the study population. The ROC curve analysis showed that the best cut-off value of SII for predicting unsuccessful reperfusion was 1,690, with sensitivity and specificity of 71% and 69%, respectively. A ROC curve analysis was also performed to compare the SII with SIRI, NLR, and PLR. As shown in Figure 2 the

Table I. Demographic, laboratory, and clinical characteristics of the study population.

Characteristics	Successful reperfusion n= 99	Unsuccessful reperfusion n=24	*p*-value
Age (years)	66±12	67.6±11	0.63
Gender, female, n (%)	50 (50.1)	15 (62)	0.36
Hypertension, n (%)	73 (73.7)	19 (79.1)	0.79
Dyslipidemia, n (%)	72 (72.7)	15 (62.5)	0.60
Coronary artery disease, n (%)	34 (34.3)	10 (41.6)	0.63
Diabetes mellitus, n (%)	19 (30)	6 (36)	0.57
Obesity, n (%)	19 (19.1)	9 (37.5)	0.06
Smoking, n (%)	32 (32.3)	3 (12.5)	0.08
Prior stroke, n (%)	19 (19.1)	4 (16.7)	1.00
Prior use of antiplatelets, n (%)	28 (28.3)	9 (37.5)	0.46
Prior use of anticoagulants, n (%)	34 (34.3)	8 (33.3)	1.00
Initial NIHSS score*	15/17/19	17/17.5/19.8	0.58
Systolic blood pressure, (mmHg)*	150 (130-175)	160 (132-186)	0.47
ASPECT score*	9/10/10	8/9/10	0.09
Stroke etiology			
Atherosclerosis, n (%)	14 (14.1)	3 (12.5)	
Cardioembolic, n (%)	57 (57.6)	13 (54.2)	0.78
Other or undetermined, n (%)	28 (28.3)	8 (33.3)	
Atrial fibrillation, n (%)	48 (48.5)	10 (41.6)	0.65
Laboratory findings			
LDL-C (mg/dl)	124±36	120±31	0.63
HDL-C (mg/dl)	42±11	42±10	0.90
Triglyceride (mg/dl)*	90 (64-137)	115 (69-182)	0.15
Total cholesterol (mg/dl)	177±46	179±40	0.80
hs-CRP (mg/dl)*	8.5 (4-17.3)	15.4 (7.2-39.8)	0.06
Admission glucose (mg/dl)*	125 (103-173)	141 (112-162)	0.40
Creatinine (mg/dl)*	0.8 (0.6-1.0)	0.8 (0.7-1.0)	0.28
WBC count (mL)*	8,700 (7,000-10,900)	10,500 (7,600-12,500)	0.73
Hemoglobin (g/dl)	12.9±2.1	12.8±1.6	0.91
Platelet count ('10^9/L)*	222 (179-260)	191 (165-256)	0.28
Monocytes (mL)*	490 (339-652)	571 (326-912)	0.16
Neutrophil count (mL)	7.821±3.130	10.135±3.862	**0.002**
Lymphocyte count (mL)*	1,300 (1,000-1,840)	1,055 (657-1,532)	**0.04**
Neutrophil/lymphocyte ratio*	5.8 (3.1-9.0)	9.7 (5.6-17.3)	**0.001**
Platelet/lymphocyte ratio*	161 (99-244)	200 (157-251)	0.11
SII ('10^9/L)*	1,172 (680-2,145)	2,029 (1,217-2,771)	**0.003**
SIRI ('10^9/L)*	2,583 (1,331-4,183)	5,446 (2,712-9,147)	**<0.001**
Clinical outcomes			
3-month mRS score 0-2, n (%)	65 (65.6)	3 (12.5)	**<0.001**
3-month mortality, n (%)	20 (20.2)	11 (45.8)	**0.017**
Hemorrhagic transformation, n (%)	13 (13.1)	15 (62.5)	**<0.001**
Symptomatic ICH, n (%)	5 (5)	4 (16.7)	0.63

Successful reperfusion is defined as modified Thrombolysis in Cerebral Infarction Score TICI 2c or 3.
Data were shown as mean ±standard deviation and number (%). * Data are presented as median (IQR: interquartile range). ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; ICH, intracerebral hemorrhage; mRS, modified Rankin score; hs-CRP, high-sensitivity C-reactive protein; HDL, high-density lipoprotein; LDL, low- density lipoprotein; WBC, White blood cells; SIRI, systemic inflammation response index; SII, systemic immune-inflammation index.

predictive accuracy of SII was greater than PLR but quite lower than SIRI and NLR (SII AUC, 0.673; 95% CI: 0.552-0.793, PLR AUC, 0.604; 95% CI: 0.491-0.716, SIRI AUC, 0.748; 95% CI: 0.639-0.858, and NLR AUC, 0.717; 95% CI: 0.595-0.838).

We established a multivariate logistic regression model using unsuccessful cerebral reperfusion as the dependent variable with adjustments for significant variables (as identified from the univariate regression analysis**)**. The SIRI, NLR, and PLR were interpreted due to similar variables

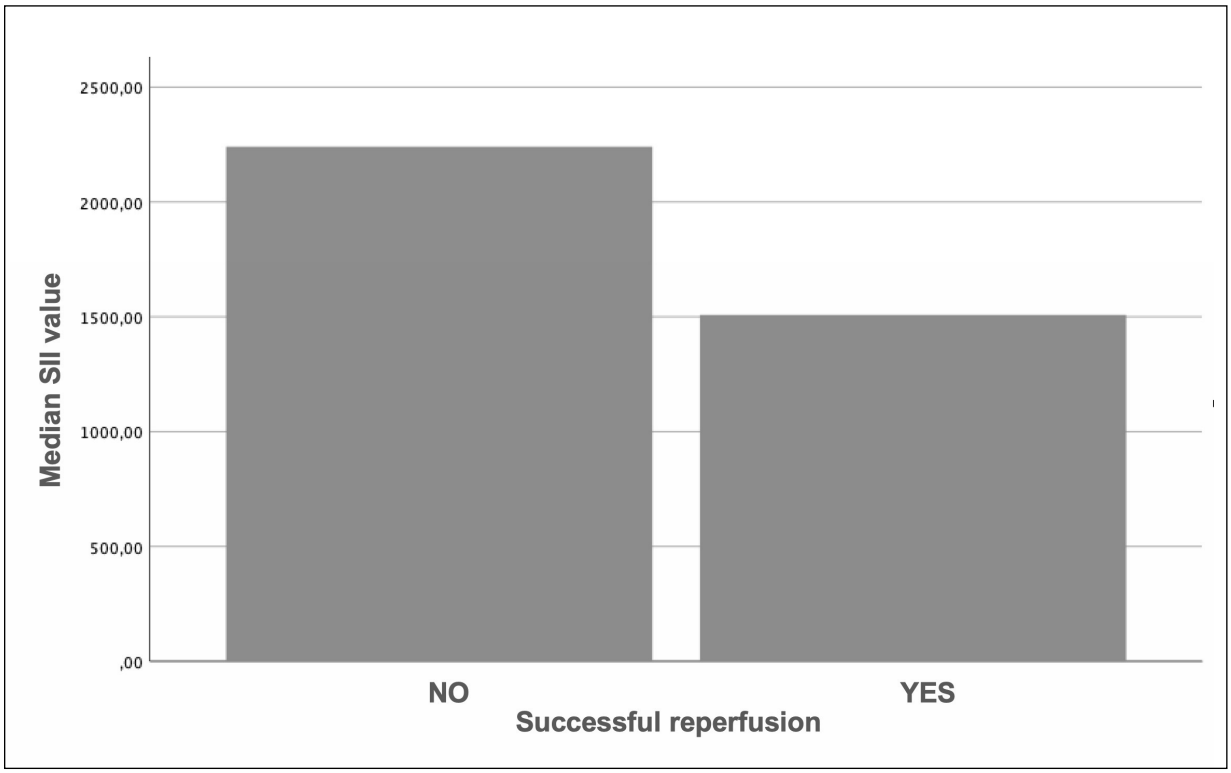

Figure 1. Median systemic immune inflammation index (SII) levels between the groups.

and were not included in the regression analysis. Multivariate analysis showed that SII ≥1,690 value (HR=3.713, 95% CI: 1.281-10.76, p=0.016), poor collateral supply (HR=0.213, 95% CI: 0.062-0.735, p=0.014), and obesity (HR=0.304, 95% CI: 0.092-0.974, p=0.045) were independent predictors of unsuccessful cerebral reperfusion after EVT in patients with AIS (Table III).

Binary univariate and multivariate logistic regression analyses were also performed to identify the relationship between SII and clinical outcome. Variables with a p-value <0.10 were analyzed using a multivariate logistic regression model in univariate analysis. Upon multivariate regression analysis, the predictors of unfavorable clinical outcome (mRS≥3) were SII ≥1,690 (HR=2.28, 95% CI: 1.06-4.88, p=0.035) and serum glucose levels on admission (HR=0.99, 95% CI: 0.98-1.00, p=0.024) (Table IV).

Discussion

The present study showed that SII was an independent predictor of unfavorable clinical outcomes and unsuccessful cerebral reperfusion of patients who underwent EVT for AIS. This study is, to our knowledge, the first to demonstrate the association between SII and unsuccessful cerebral reperfusion status. Patients with failed cerebral reperfusion and unfavorable clinical outcomes had higher levels of SII.

Prompt reperfusion of cerebral infarct-related occluded artery by EVT is the best strategy for managing selected patients with AIS. The achieved reperfusion grade after EVT is crucial in this new era of ischemic stroke care. The current American Stroke Association guidelines recommend modified Thrombolysis in Cerebral Infarction (mTICI) grades of 2c or 3 for EVT, referring to successful reperfusion[1]. Even though technical development in reperfusion therapy, unsuccessful cerebral reperfusion is encountered in a sizeable number of patients with AIS[3]. Numerous clinical studies[22,23] have demonstrated the prognostic significance of impaired cerebral reperfusion. Predicting unsuccessful cerebral reperfusion and adverse clinical outcomes in patients with AIS who will undergo EVT may enable physicians to choose the best treatment strategy. Therefore, the patients who would benefit most from reperfusion therapy can be determined.

Table II. Angiographic and procedural characteristics of the study population.

Characteristics	Successful reperfusion n=99	Unsuccessful reperfusion n=24	*p*-value
Symptom to puncture time (minute) *	185 (127-260)	233 (155-305)	0.18
Symptom to recanalization time (minute) *	235 (177-314)	311 (204-372)	0.06
Arterial occlusion site			
Middle cerebral artery, n (%)	65 (65.6)	14 (58.3)	0.49
Internal carotid artery and middle			
Cerebral artery tandem lesion, n (%)	24 (24.4)	10 (41.7)	0.12
Posterior circulation, n (%)	10 (10)	0 (0)	0.35
Poor collateral supply, n (%)	11 (11.1)	8 (33.3)	**0.01**
Bovine arch, n (%)	14 (48.5)	3 (41.6)	1.00
First pass recanalization, n (%)	57 (57.6)	5 (20.8)	**0.001**
Procedure technique			
Direct aspiration, n (%)	99 (100)	24 (100)	-
Direct aspiration and stent retriever, n (%)	16 (16.2)	10 (41.7)	**0.01**
IVT and EVT, n (%)	2 (2)	4 (14.3)	0.78
IAT, n (%)	0(0)	1 (4.1)	0.19

Successful reperfusion is defined as modified Thrombolysis in Cerebral Infarction score TICI 2c or 3. Data were shown as mean ±standard deviation and number (%). * Data are presented as median (IQR: interquartile range). IVT, intravenous thrombolysis; EVT, endovascular treatment; IAT, intraarterial thrombolysis.

Clinically, inflammatory, and immune circulatory cells, including neutrophils, platelets, and lymphocytes, have significant roles in the development of cerebrovascular disease[8]. Various individual biomarkers of inflammation to predict the clinical prognosis of patients with AIS have been widely evaluated in literature. Ying et al[24] reported that increased NLR levels are positively associated with 3-month poor functional outcome and 3-month mortality in AIS patients undergoing reperfusion treatments. Previous studies[25-28] involving AIS patients undergoing EVT have revealed that NLR and PLR were associated with the functional outcome, hemorrhagic transfor-

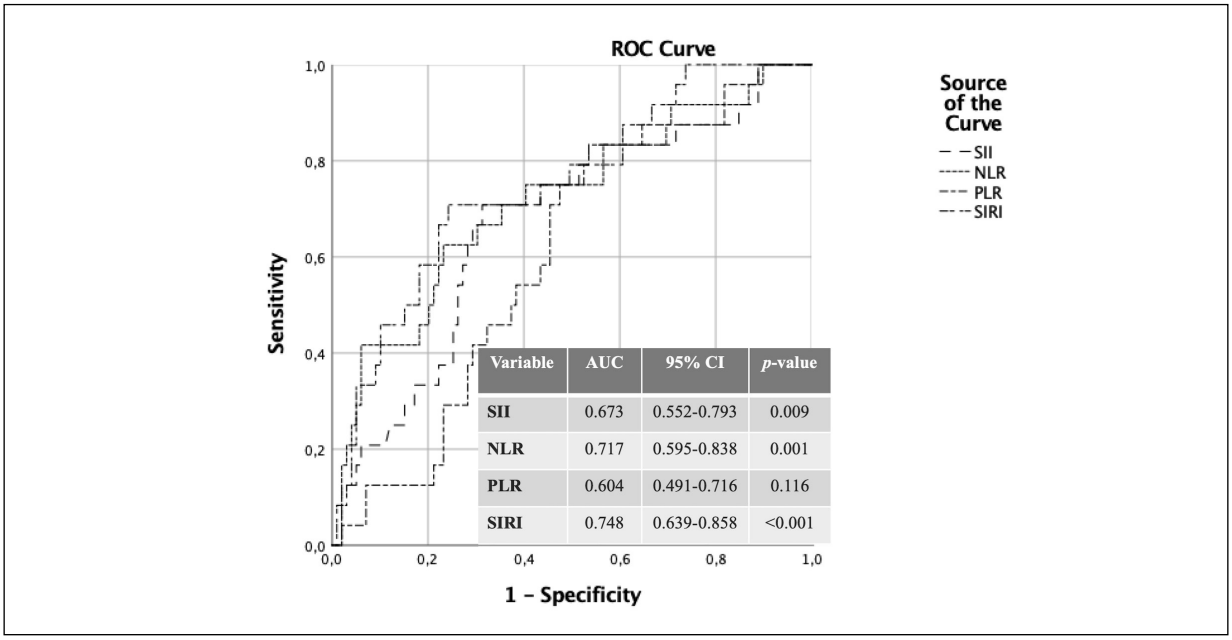

Figure 2. Receiver operating characteristics (ROC) curve analysis for systemic immune inflammation index (SII), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte index ratio (PLR), and systemic inflammation response index (SIRI) regarding unsuccessful reperfusion. AUC, the area under the curve; CI, confidence interval.

Table III. Predictors of unsuccessful reperfusion in univariate and multivariate logistic regression analyses.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	0.99	0.95-1.03	0.62	-	-	-
Sex (Female)	1.63	0.65-4.08	0.29	-	-	-
Diabetes mellitus	1.16	0.36-3.78	0.79	-	-	-
Smoking	3.27	0.89-12.04	0.07	2.98	0.602-14.80	0.181
Prior stroke	1.34	0.39-4.57	0.63	-	-	-
Dyslipidemia	1.16	0.38-3.54	0.14	-	-	-
Hypertension	0.71	0.24-2.12	0.54	-	-	-
Obesity	0.39	0.14-1.14	0.09	0.30	0.092-0.974	**0.045***
Atrial fibrillation	1.35	0.54-3.36	0.51	-	-	-
SBP on admission	0.99	0.98-1.01	0.62	-	-	-
Initial NIHSS score >10	0.98	0.88-1.08	0.68	-	-	-
Poor collateral status	0.25	0.08-0.77	0.01	0.21	0.062-0.735	**0.014***
ICA occlusion	0.75	0.25-2.20	0.59	-	-	-
Prior use of antiplatelets	0.53	0.19-1.44	0.21	-	-	-
IVT	1.34	0.42-4.36	0.62	-	-	-
Serum glucose	1.00	0.99-1.01	0.64	-	-	-
GFR	1.00	0.99-1.01	0.58	-	-	-
hs-CRP	1.00	0.99-1.01	0.89	-	-	-
SII ≥1,690	5.53	2.01-14.15	0.001	3.71	1.281-10.76	**0.016***

HR, hazard ratio; CI, confidence interval; NS, no statistical significance; SBP, systolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; ICA, internal carotid artery; GFR, glomerular filtration rate; hs- CRP, high sensitive C-reactive protein; SII, systemic immune inflammation index.
Covariates with $p<0.10$ in univariate analysis were entered into a backward multivariate model.
* Statistically significant. Unsuccessful reperfusion is defined as Thrombolysis in Cerebral Infarction score < mTICI 2c or 3.

mation, and mortality. Contrary to these studies, Inanc and Inanc[29] showed that NLR and PLR did not correlate with clinical outcome parameters in AIS who underwent mechanical thrombectomy. Yan et al[30] conducted a systematic literature search and pooled data from individual studies to assess the relationship between PLR and functional outcomes and mortality in stroke patients. Their analysis of eight studies concluded that PLR might not be a useful prognostic marker to predict functional outcomes and mortality after AIS. Although many studies have investigated how these inflammatory markers affect the clinical outcomes of patients receiving EVT, the impact of these markers on the reperfusion rate after EVT has been evaluated in a limited number of studies. Lee et al[31] reported that higher NRL and PLR were associated with unsuccessful reperfusion after EVT. In contrast to this study, Inanc and Inanc[29] also found no significant association of recanalization rates after mechanical thrombectomy with NLR and PLR.

According to the conflicting results in the literature, the validity of the risk stratification models, such as NLR and PLR, is controversial. These measurable inflammatory models integrate one or two cell types and only represent local immune and inflammatory status. However, the inflammation is often systemic.

The SII, a composite indicator integrating platelet, neutrophil, and lymphocyte counts which can reflect the body's comprehensive immune and inflammation situation, has been proven to be a promising prognostic predictor in cardiovascular disease[12,13]. Recent clinical studies on patients with AIS showed that elevated SII had a greater risk of poor clinical outcomes[14-17]. Yang et al[14] reported that SII was independently associated with hemorrhagic transformation in patients with AIS. Topcuoglu et al[15] also reported that a SII threshold > 1,781 was associated with an increased incidence of symptomatic ICH in patients with AIS treated with intravenous thrombolysis. Weng et al[16] evaluated the predictive value of the SII for 3-month functional outcome in patients with AIS treated with IVT. They demonstrated that SII was an independent risk factor for poor prognosis at three months (OR=3.953, 95% CI: 1.702-9.179, p=0.001). Yi et al[17] recently assessed the utility of the SII in estimating clinical outcomes in AIS patients treated with mechanical thrombectomy. They concluded that SII was an independent predictor of favorable clinical outcomes after mechanical thrombectomy (OR=1.82, 95% CI: 1.16-

Table IV. Predictors of favorable 3-month functional outcome in univariate and multivariate logistic regression analyses.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.01	0.98-1.04	0.68	-	-	-
Sex (Male)	0.76	0.37-1.55	0.45	-	-	-
Diabetes mellitus	0.45	0.17-1.21	0.10	-	-	-
Smoking	1.37	0.60-3.14	0.46	-	-	-
Prior stroke	0.90	0.35-2.32	0.83	-	-	-
Dyslipidemia	0.97	0.43-2.21	0.95	-	-	-
Hypertension	1.41	0.59-3.38	0.17	-	-	-
Obesity	0.52	0.20-1.33	0.10	0.50	0.20-1.25	0.143
Atrial fibrillation	1.46	0.71-3.02	0.30	-	-	-
Systolic blood pressure	0.99	0.98-1.00	0.15	-	-	-
Initial NIHSS score <10	0.29	0.03-2.73	0.28	-	-	-
ICA occlusion	1.12	0.32-3.91	0.85	-	-	-
Middle cerebral artery occlusion	1.31	0.42-4.12	0.64	-	-	-
Good collateral status	0.40	0.14-1.11	0.18	-	-	-
Prior use of antiplatelets	1.18	0.53-2.64	0.69	-	-	-
Symptom to puncture time	1.00	0.99-1.00	0.05	1.00	0.99-1.00	0.172
IVT	1.57	0.63-3.89	0.33	-	-	-
First-pass reperfusion	1.63	0.79-3.34	0.10	1.62	0.75-3.55	0.223
Serum glucose	0.99	0.98-1.00	0.02	0.99	0.98-1.00	**0.024***
GFR	1.00	0.98-1.02	0.86	-	-	-
hs-CRP	1.00	0.99-1.00	0.12	-	-	-
SII ≥1,690	2.49	1.18-5.23	0.01	2.28	1.06-4.88	**0.035***

Legend: H.R., hazard ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; ICA, internal carotid artery; IVT, intravenous thrombolysis; GFR, glomerular filtration rate; hs- CRP, highly sensitive C-reactive protein; SII, systemic immune inflammation index

Covariates with $p<0.10$ in univariate analysis were entered into a backward multivariate model.

* Statistically significant.

A favorable 3-month functional outcome is defined as a modified Rankin score of 0-2.

3.10, $p=0.031$). According to our results, a SII value ≥ 1,690 was independently correlated with a 3-month functional outcome, compatible with previous literature.

Although previous data have shown that SII can be used to predict clinical outcomes in patients with AIS, the predictive value of SII for cerebral reperfusion status after EVT has not been previously evaluated. Our novel finding revealed that a SII threshold ≥ 1,690 is independently associated with impaired cerebral reperfusion in AIS patients treated with EVT. Thus, we tentatively propose that SII may represent a promising biomarker for predicting unsuccessful cerebral reperfusion after EVT.

Why is SII associated with impaired cerebral reperfusion and clinical outcomes in patients with AIS? We do not have a clear answer yet; however, we will highlight possible explanations in the following text.

It has been suggested that an inflammatory cascade is activated in all stages of AIS[4]. Neutrophils infiltrate ischemic cerebral tissue within the first hour of the vessel occlusion in acute stroke and release the proteolytic enzymes, such as arachidonic acid derivates, superoxide radicals, and matrix metalloproteinase[5]. This early inflammation promotes cellular damage, increases capillary permeability, initiates the breakdown of the blood-brain barrier (BBB), and further expands cerebral infarct areas by invading brain tissue *via* secreted proinflammatory mediators. Moreover, neutrophils can plug capillaries in the cerebral microcirculation, facilitating further infarct development and extending the infarcted size[7]. Neutrophils also engage with platelets to form neutrophil-platelet aggregates that block the microcirculation, thereby mechanically blocking the flow. The neutrophil-driven proinflammatory process also causes a prothrombotic state due to upregulation of the production and activation of platelets[6]. Activated platelets further activate other platelets by releasing inflammatory mediators into the microcirculation, promoting the entrapment of more platelets, thus creating a vicious cycle of inflammation and coagulation. The prothrombotic state due to thrombocytosis may also contribute to the development of impaired reperfusion at the capillary level[32]. As

for lymphocytes, stress during the acute phase activates the hypothalamic-pituitary-adrenal axis when AIS occurs. As a result, increased cortisol secretion and sympathetic tone promote lymphocyte apoptosis, leading to lymphopenia[33]. Some studies demonstrated that neutrophils could promote lymphocyte apoptosis by releasing proinflammatory cytokines[34]. As a part of the adaptive immune response, lymphocytes play an essential element in the immune regulatory pathway. Schwartz and Moalem[35] have shown that lymphocytes have a critical role in healing and repair effects on inflammation. With respect to AIS, Kim et al[8] reported that lower lymphocyte counts correlated with the poor functional outcome at three months. In this context, due to high neutrophil and platelet levels and low lymphocyte concentration, a high SII may be associated with increased inflammatory activity and lead to impaired cerebral reperfusion and poor clinical outcomes.

Limitations

There are several limitations to consider in this study. First, this study is a single-center, retrospective design with limited sample size. Second, we evaluated only admission SII levels. The dynamic changes of SII might be more objective in predicting clinical outcomes. Finally, we did not assess other inflammatory markers such as fibrinogen, myeloperoxidase, and TNF-α. Therefore, prospective studies in larger populations are needed to validate our conclusions.

Conclusions

We found that a higher value of SII was independently associated with poor clinical outcomes and unsuccessful cerebral reperfusion in AIS patients undergoing EVT. SII might be a potential indicator for predicting clinical prognosis and cerebral reperfusion status.

Conflict of Interests

The authors declare no potential conflicts of interest concerning this article's research, authorship, and/or publication.

Authors' Contributions

All authors have substantial contributions to research conception and design, or the acquisition of data, analysis, and interpretation of data; drafting the article or revising it critically for important intellectual content, and final approval of the version to be published. MBV designed and supervised the study. T.A. drafted the manuscript. BAA performed statistical analyses and reviewed the manuscript. YGA, S.B., HAE, ŞD participated in data collection, interpretation, and manuscript review. A.P.Z., O.T., A.V., P.V., T.K. contributed to data management, quality control, and manuscript review. The authors had access to all data and shared responsibility.

Ethics Approval

The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine in accordance with the Declaration of Helsinki and good clinical practice (Approval number: 71522473-050.01.04-128385-137).

Informed Consent

Each patient or their family member had signed written informed consent.

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