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ORIGINAL RESEARCH

Systemic Immune-Inflammation Index (SII) and Neutrophil-to-Lymphocyte Ratio (NLR): A Strong Predictor of Disease Severity in Large-Artery Atherosclerosis (LAA) Stroke Patients

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Background: Systemic immune-inflammation index (SII) and neutrophil-to-lymphocyte ratio (NLR) are novel inflammatory markers based on neutrophil, platelet and lymphocyte counts. Atherosclerosis is a chronic inflammatory vascular disease. This study aimed to verify the predictive value of the clinical parameters such as systemic immune-inflammation index (SII) and neutrophil-to-lymphocyte ratio (NLR) for the severity in Large Artery Atherosclerosis (LAA) stroke patients.

Methods: The SII is defined as platelet × (neutrophil count/lymphocyte count), the NLR is defined as neutrophil count/lymphocyte count. Univariate logistic regression was used to analyze the association between SII and NLR and NIHSS score in patients with LAA stroke. Multiple logistic regression was used to analyze the risk factors for the severity of LAA stroke. We plotted receiver operating characteristic curves to determine the diagnostic role of SII and NLR in differentiating stroke disease severity.

Results: We included 283 LAA stroke patients, the SII and NLR in the moderate-to-severe stroke group were significantly higher than the mild stroke group. Multiple logistic regression analysis showed that SII (OR 1.051 95% CI (1.035–1.066), $P < 0.001$), NLR (OR 1.077,95% CI (1.032–1.123), $P < 0.001$) were significantly associated with stroke severity. The SII values under the receiver operating characteristic curve (0.701, 95% CI (0.649–0.791, $P < 0.001$, cut-off value 912.97) and NLR values under the receiver operating characteristic curve (0.604,5% CI (0.519–0.689), $P < 0.01$, cut-off value 1.461), and SII values had high discrimination ability. Both SII and NLR had high diagnostic and predictive value for stroke severity, and SII was better than NLR.

Conclusion: The higher SII and NLR, the more severity in LAA stroke patients. SII and NLR are independent risk factors for LAA stroke, and they can also effectively predict stroke severity; moreover, SII has a higher diagnostic efficacy than NLR. However, multicenter studies with large sample size are still needed to confirm this conclusion.

Keywords: large-artery atherosclerosis stroke, systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, stroke severity, predictor

Introduction

Globally, stroke is the second leading cause of death in persons older than 60 years. Stroke is the first cause of adult death and disability in China, which brings huge medical and economic burden to the society and family.[1–3] Ischemic stroke (IS) accounts for 70%−85% of all strokes, of which artery atherosclerosis-artery atherosclerosis (LAA) accounts for about 37.3%, Atherosclerosis is one of the most important causes of ischemic stroke.[2] Atherosclerosis is a chronic inflammatory disease

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characterized by the formation of plaques containing lipids, connective tissue, and immune cells in the intima of large and medium-sized artery.[4] Immunoinflammatory response plays an important role in the pathophysiology of cerebrovascular disease and is one of the main factors in stroke prognosis.[5,6] Studies have shown that SII and NLR, as a new type of inflammatory markers, are convenient to obtain, low cost, and can more comprehensively reflect the level of local immune and systemic inflammatory response.[7] Previous studies have suggested that SII associated with the severity and functional prognosis of IS, as well as with post-stroke cognitive dysfunction, stroke-associated pneumonia and other complications.[8–10] However, there is no clear study on whether SII is related to the severity of LAA stroke patients. Therefore, this study intends to explore the diagnostic and predictive value of SII in the severity of LAA stroke, so as to help clinicians assess patients' conditions earlier and more accurately and improve patient prognosis.

Methods

Study Population

Data of patients with first-episode acute ischemic stroke treated in Chengdu Seventh People's Hospital from February 2023 to February 2024 were retrospectively collected. Patients were included if they met the following criteria: (1) Admission within 24 hours of stroke onset; (2) LAA stroke; (3) Han nationality, aged 18 years or older. The exclusion criteria were as follows: (1) history of previous transient ischemic attack, cerebral infarction, intracranial hemorrhage, aneurysmal subarachnoid hemorrhage and venous sinus thrombosis; (2) patients with malignant tumors, autoimmune diseases and hematological diseases; (3) patients with severe hepatic and renal insufficiency or unstable vital signs; (4) patients with infection or fever within two weeks before stroke; (5) patients with chronic inflammation (including rheumatoid arthritis, vasculitis, inflammatory bowel disease.). The criteria for acute ischemic stroke were based on the diagnostic criteria of the Guidelines for the Diagnosis and Treatment of Acute ischemic Stroke in China 2023,[3] and were confirmed by head CT or MRI. The diagnosis and classification of ischemic stroke are performed by professional neurologists. Before conducting this study, the sample size had already been estimated using the sample size calculation method.[11] This study was approved by the Ethics Committee of Chengdu Seventh People's Hospital, all procedures were conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki, and all participants agreed to enrollment and signed informed consent.

Study Protocol and Data Collection

General data of patients were collected, including age, sex, hypertension, diabetes, history of coronary heart disease, admission blood pressure, etc. Collect the red blood cell count, white blood cell count, neutrophil count, lymphocyte count and platelet count within 24 h of admission to calculate the SII and NLR values of the same blood sample.

The National Institutes of Health Stroke Scale (NIHSS) score assessed on the day of admission was used to evaluate the severity of neurological deficits. The NIHSS score 5 was identified as mild stroke and the NIHSS score >5 as moderate-to-severe stroke.[8]

Statistical Analysis

Statistical analysis was performed using the SPSS 22.0 software. Normally distributed data were expressed as mean ± SD and nonnormally distributed data as medians and interquartile range. Comparison between group was performed using Mann Whitney *U*-test, chi-square test where appropriate. Multiple Logistic regression was used to screen for risk factors of LAA stroke outcomes. Receiver operating characteristic (ROC) curve analysis was used to evaluate the prognostic indicators of cerebral infarction, and $P \leq 0.05$ was considered statistically significant.

Results

Comparison of the Clinical Characteristics of Patients with Different Degrees of Stroke

This study finally included 283 patients with acute LAA stroke, including 177 males and 106 females, 210 mild stroke and 73 moderate-to-severe stroke. Comparing the moderate-to-severe stroke group with the mild stroke group, age, SII, NLR, platelet-to-lymphocyte ratio (PLR), C-reactive protein, APTT, D-dimer, hyperlipidemia and other indicators showed significant differences ($P < 0.05$), as shown in Table 1.

Table 1 Comparison of Clinical Characteristics of Patients in the Mild and Moderate-to-Severe Stroke Groups

Variants	NIHSS≤5 (n=210)	NIHSS>5(n=73)	χ^2/t	*P*
Sex			8.950	**0.003**
Male (n=177)	142 (80.2%)	35 (19.8%)		
Female (n=106)	68 (64.2%)	38 (35.8%)		
Hypertensive			0.256	0.6613
Yes (n=189)	142(75.1%)	47(24.9%)		
No (n=94)	68 (72.3%)	26(27.7%)		
Diabetes			1.927	0.183
Yes (n=84)	67(79.8%)	17(20.2%)		
No (n=199)	143(71.9%)	56(28.1)		
Hyperlipidemia			10.105	**0.001**
Yes (n=93)	80(86%)	13(14%)		
No (n=190)	130(68.4%)	60(31.6%)		
Years	66.39±12.86	70.81±12.51	−2.546	**0.011**
Platelet	183.10±60.45	195.19±67.37	−1.429	0.154
Neutrophil	6.69±8.88	9.09±10.90	−1.875	0.062
Lymphocyte	1.55±0.96	1.65±1.21	−0.683	0.495
SII	750.36±650.00	2507.06±3727.69	−6.568	**<0.001**
NLR	5.51±9.33	9.39±14.89	−2.588	**0.010**
PLR	143.29±85.61	171.81±118.94	−2.204	**0.028**
CRP	12.62±37.60	25.22±67.04	−1.977	**0.049**
Albumin	40.92±4.67	39.89±4.30	1.657	0.099
Triglyceride	1.94±1.48	1.56±1.15	1.959	0.051
Cholesterol	4.72±1.37	4.71±1.01	0.067	0.947
HDL	1.36±0.36	1.43±0.36	−1.341	0.181
LDL	2.46±0.85	2.41±0.73	0.391	0.696
Uric acid	363.02±115.34	368.73±109.42	−0.369	0.713
Urea nitrogen	7.06±7.73	7.66±6.55	−0.593	0.553
Glycosylated hemoglobin	6.75±2.14	7.19±1.96	−1.573	0.117
PT	16.38±19.00	13.67±1.072	1.216	0.225
INR	1.12±0.13	1.13±0.97	−0.700	0.484
APTT	28.57±3.62	30.39±5.39	−3.224	**0.001**

(*Continued*)

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Table 1 (Continued).

Variants	NIHSS≤5 (n=210)	NIHSS>5(n=73)	χ^2/t	*P*
TT	17.47±6.60	18.00±8.79	−0.534	0.594
FIB	3.31±0.91	3.82±1.96	−2.992	**0.003**
D-D	1.87±3.56	3.22±4.21	−2.671	**0.008**

Notes: Bold for p-values less than 0.05.
Abbreviations: SII, Systemic Immune-Inflammation Index; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; CRP, C-reactive protein; HDL, High-Density Lipoprotein Cholesterol; LDL, Low-Density Lipoprotein Cholesterol; PT, Prothrombin Time; INR, International Normalized Ratio; APTT, Activated Partial Thromboplastin Time; TT, Thrombin Time; FIB, Fibrinogen; D-D, D-Dimer.

Analysis of the Risk Factors Related to Stroke Severity

NIHSS score of LAA stroke patients at admission was used as the dependent variable, age, SII, NLR, PLR, APTT, hyperlipidemia, C-reactive protein, D-dimer and FIBC were used as independent variables, and other clinical data levels were adjusted for multiple Logistic regression analysis. The results showed that age, SII, NLR, APTT, and hyperlipidemia were independent risk factors for predicting disease severity in patients with LAA stroke, as shown in Table 2.

ROC Analysis

Both SII and NLR could effectively predict the severity of LAA stroke patients, and the area under ROC curve (AUC) of SII was (0.701,95% CI (0.649–0.791, P < 0.001, cut-off value 912.97) NLR was (0.604,5% CI (0.519–0.689), P < 0.01, cut-off value 1.461, as shown in Figure 1and Table 3. It shows that when LAA stroke patients had SII index greater than 912.97 and NLR greater than 1.461, their condition was more severe and needed more aggressive treatment.

Table 2 Logistic Regression Analysis Results of Risk Factors for Moderate-to-Severe Stroke in Patients with LAA Stroke

Variants	*OR*	95% CI	*P*
Year	1.044	1.014–1.075	**0.004**
SII	1.051	1.035–1.066	**<0.001**
NLR	1.077	1.032–1.123	**0.001**
APTT	1.125	1.042–1.214	**0.003**
Hyperlipidemia	0.340	0.149–0.777	**0.011**
PLR	0.996	0.991–1.001	0.111
CRP	1.002	0.996–1.008	0.579
D-D	1.073	0.986–1.168	0.103
FIB	1.280	0.892–1.837	0.180

Notes: Bold for p-values less than 0.05.
Abbreviations: SII, Systemic Immune-Inflammation Index; NLR, Neutrophil-to-Lymphocyte Ratio; APTT, Activated Partial Thromboplastin Time; PLR, Platelet-to-Lymphocyte Ratio; CRP, C-reactive protein; FIB, Fibrinogen; D-D, D-Dimer.

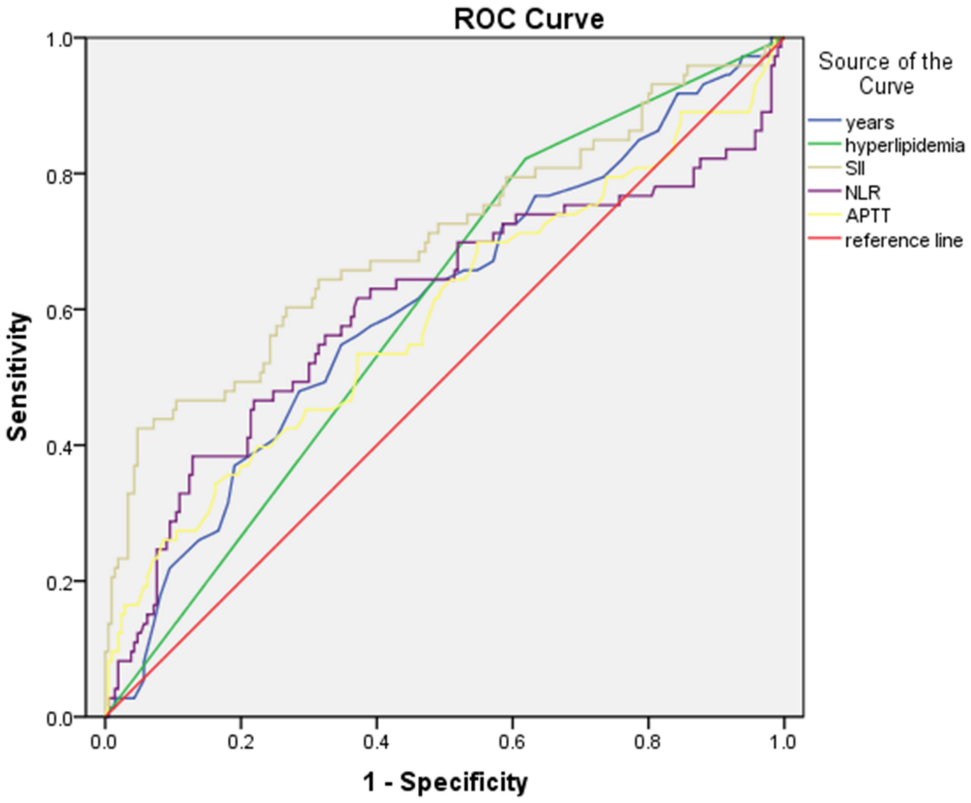

Figure 1 ROC curves for predicting the disease severity in patients with LAA stroke.

Discussion

In this study, we evaluated the relationship between SII, NLR and the severity of LAA stroke. According to the NIHSS score, statistically significant differences in SII, NLR, PLR, and C-reactive protein were observed between mild and moderate-to-severe subgroups. In addition, SII and NLR are independent risk factors for LAA stroke, which can effectively judge the severity of stroke, and SII has a higher diagnostic efficacy compared with NLR.

Atherosclerosis is an important cause of ischemic stroke, and LAA stroke is the main subtype of ischemic stroke.[2] Inflammation plays an important role in the pathogenesis of atherosclerosis. Damage or activation of the arterial endothelium can attract circulating inflammatory cells such as monocytes, lymphocytes and neutrophils to gather locally. After local aggregation, inflammatory cells can infiltrate through the endothelium and transform into foam cells, promoting the formation of plaque. Inflammatory cells such as macrophages can release cytokines and growth factors to promote smooth muscle cells proliferation and anterior migration, leading to plaque growth. Meanwhile, the activation

Table 3 Area Under the ROC Curve for Each Indicator

Variants	AUC	P	95% CI	Cutoff value	Sensitivity (%)	Specificity (%)
Year	0.606	0.007	0.529–0.683	73.50	54.8	65.2
Hyperlipidemia	0.601	0.010	0.530–0.673	1.5	82.2	38.1
SII	0.701	0.000	0.649–0.791	912.97	57.5	21.4
NLR	0.604	0.008	0.519–0.689	1.461	83.6	95.7
APTT	0.591	0.021	0.509–0.673	32.05	34.2	83.8

Abbreviations: SII, Systemic Immune-Inflammation Index; NLR, Neutrophil-to-Lymphocyte Ratio; APTT, Activated Partial Thromboplastin Time.

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of T cell and B cells also participate in the inflammatory process of atherosclerosis. Activation of inflammasomes such as NLRP3 can lead to the release of inflammatory mediators, promoting plaque development and unstable.[12–14]

Inflammatory process plays a key role in the pathogenesis of atherosclerosis[15]. Chronic, low-grade inflammation seems to be critical for the progression of LAA.[16] Mohamed G Zeinhom et al suggest that inflammatory burden may play an interactive role in the effectiveness of antiplatelet therapy.[17] The assessment of systemic inflammation by blood cell count (including neutrophils, lymphocytes and platelets) is a low-cost, effective, and easy to implement method that can provide important biological markers for inflammatory processes related to the pathogenesis of LAA.[18]

SII is a new biomarker, SII, and NLR values can reflect the number of peripheral blood lymphocytes, neutrophils and platelets and can be a more balanced and comprehensive assessment of individual immune and inflammatory responses.[19] Previous studies have shown that hypertensive patients with higher SII have an increased risk of stroke,[18] SII is positively correlated with post-stroke depression,[20] and SII and NLR values are correlated with ischemic stroke severity and functional prognosis.[21] A meta-analysis also showed that a higher SII levels were associated with a higher risk of poor prognosis in IS.[22] It has been shown that SII independently predicts of early neurological deterioration in acute atherosclerotic stroke.[23]

In this study, the SII index had higher predictive value of LAA stroke severity than NLR. The difference between SII and NLR is that SII adds the platelet count. Platelet activation is the core initiating link of thrombotic diseases. Platelets can adhere to the vessel wall to promote[24] of atherosclerotic plaque formation. Further more, the activation of platelets promotes inflammation and thrombosis.[24,25] Platelet can adhere to the damaged vascular wall, release a variety of inflammatory mediators and growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) and epidermal growth factor (EGF), these factors can promote the proliferation and migration of vascular smooth muscle cells (VSMC), and then promote the formation and development of plaque.[24] The activated platelets can also amplify the role of pro-inflammatory cytokines by releasing (such as serotonin, adenosine diphosphate), accelerate the coagulation process, and promote the formation of thrombosis.[24] Thus, SII can better reflect the systemic inflammation situation of LAA stroke patients than NLR, and has a higher predictive value.

At present, the theory of neuroinflammation has attracted much attention, and the anti-inflammation and brain protection therapy of stroke have also shown a crucial position. Annaelle Zietz et al[12] proposed the positive effect of anti-inflammatory treatment on stroke recurrence and secondary prevention. One study demonstrated that natalizumab can reduce infarct volume after cortical stroke and reduce white blood cell invasion of the brain after cortical stroke.[26] Fingolimod reduces infarct volume in a mouse transient ischemia-reperfusion model.[27] In animal models of local cerebral ischemia, D-camphorol can significantly reduce the expression of tumor necrosis factor-α, inducible nitric oxide synthase, interleukin-1β, and cyclooxygenase-2 after cerebral ischemia reperfusion.[28] The results of the TASTE study published in the journal STROKE showed a significant anti-inflammatory effect of edaravone dextrocamphorol injection in patients with IS.[29]

Conclusions

This study showed that SII and NLR are independent risk factors for the severity of LAA strokes and can be used to assess the severity of LAA stroke patients at an early stage. Therefore, SII and NLR may help clinicians to assess patients' conditions earlier and more accurately and improve their prognosis. In addition, monitoring SII and inflammation levels and controlling them early in high-risk populations may help to interrupt the onset and progression of atherosclerotic disease in at-risk populations and may play a positive role in reducing the severity of LAA stroke and coronary atherosclerotic heart disease.

There are several limitations to this study. First, it is a single-center study that may limit the general applicability of the results. Second, the sample size was small, which may affect the power of the statistical analysis. In addition, the patients we selected were patients within 24 hours of the onset of stroke, and blood samples were drawn as soon as possible after admission. However, over time, the level of inflammation will change accordingly, and it is still difficult to better control confounders. In future studies, we plan to cooperate with other hospitals to conduct multicenter studies to expand the sample size and control the time of blood drawing. Further clinical and basic studies are needed to explore and establish the exact relationship between inflammatory indices such as SII and LAA stroke severity.

Disclosure

The authors report no conflicts of interest in this work.

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