Neurology Asia 2025; 30(2) : 377 – 382

The importance of panimmune inflammation value and systemic immuno-inflammation index in patients with acute cerebrovascular infarction

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Abstract

Background: Stroke is a condition that negatively affects the quality of life in all societies and is one of the leading causes of mortality in adults. It is the second most common cause of death and disability worldwide. Acute ischemic stroke leads to severe physical, social, psychological, and economic devastation. Early and accurate diagnosis of these patients in the emergency department is crucial for timely treatment. This study aimed to investigate the course of the pan-immune inflammation value (PIV), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI), which has been identified as new inflammatory markers in patients diagnosed with acute stroke. *Methods:* This retrospective study compared inflammatory markers obtained from the complete blood count results of patients diagnosed with acute ischemic stroke in the emergency department between 01.01.2022 and 01.03.2024 with those of healthy individuals. *Results:* In our study, 201 patients with acute ischemic stroke and 100 healthy individuals were compared. The results demonstrated that inflammatory markers, including the PIV, SII, and SIRI, were significantly higher in the stroke group compared to the control group ($p<0.05$). Specifically, neutrophil, CRP, PIV, SII, SIRI, and NLR values were elevated in the ischemic stroke group, while lymphocyte and hemoglobin levels were higher in the control group. *Conclusion:* This study highlights the potential of PIV, SII, and SIRI as novel biomarkers for predicting inflammation and prognosis in acute ischemic stroke patients. These markers may serve as cost-effective and practical tools for early diagnosis and risk stratification in clinical settings. Further studies with dynamic evaluations are needed to explore the long-term prognostic value of these markers.

Keywords: Stroke, emergency department, pan-immune inflammation value, systemic inflammatory response index, systemic immune-inflammation index

INTRODUCTION

Acute ischemic stroke (AIS) is a clinical emergency that leads to high morbidity, mortality, and disability. With an increasing trend and a tendency to occur at younger ages, it is one of the leading causes of death and disability worldwide.

Due to ischemia and hypoxia in stroke, brain tissues rapidly undergo a series of pathological processes such as excitotoxicity, oxidative stress, neuroinflammation, apoptosis, and blood-brain barrier damage. Accurate predictive, diagnostic, and prognostic biomarkers and effective therapeutic targets for acute ischemic stroke have not yet been determined.[1]

Recently, there has been growing interest in research related to the inflammatory response after stroke. Understanding the role of the primary effector cells involved in the inflammatory response and the immune reactions following stroke is crucial for developing effective treatment strategies.[2]

Numerous studies have shown that the neuroinflammatory response plays an important role in the pathophysiology of ischemic stroke. Recent research has demonstrated that the inflammatory response plays a role in the development and prognosis of AIS. Systemic immune inflammation markers, which combine levels of neutrophils, lymphocytes, and platelets,

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Date of Submission: 12 December 2024; Date of Acceptance: 27 December 2024

https://doi.org/10.54029/2025vke

have emerged as predictors of inflammation and prognosis.

Recently, several inexpensive, easy-to-measure, white blood cell-based inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), and systemic inflammation response index (SIRI), have been introduced.[3-5]

The pan-immune-inflammation value (PIV) has recently gained more attention as a novel indicator of inflammation. It has been reported as a comprehensive measure of the inflammatory and immune status.[6] The PIV index has shown promising results in identifying patients with poor prognosis in various diseases related to inflammation and the immune system, such as myocardial infarction[7], malignancy[8], and antineutrophil cytoplasmic antibody-associated vasculitis.[9]

The SII is a biomarker that combines platelet count, neutrophil count, and lymphocyte count. It reflects systemic inflammatory response and immune activation. Some studies have shown that the SII is effective in predicting inflammation and prognosis in various disease groups.[10] A new inflammatory biomarker, the systemic inflammation response index (SIRI), has not yet been explored in cerebrovascular diseases.

In this study, we aimed to compare these new parameters in patients with acute cerebrovascular stroke and healthy individuals.

METHODS

Patients and data collection

This retrospective study was conducted at the Emergency department of a second-line hospital between November 1, 2021 and February 1, 2022. The study was conducted in accordance with the principles of the Helsinki Declaration and written informed consent was obtained from all participants. The study was approved by the university's local ethics committee (Protocol NO: KA23/175).

This study was conducted retrospectively by reviewing the medical records of patients diagnosed with acute cerebral ischemia between June 2022 and June 2024. It was planned to include patients over the age of 18. Patient data were obtained retrospectively from the hospital system. A group of patients who visited our center's check-up clinic for a general examination and were found to be normal was selected as the control group. The complete blood count values of this group were also accessed from the records.

Calculation of systemic inflammation markers

Laboratory parameters, neutrophil/lymphocyte ratio, PIV, SII and SIRI indices were compared. White blood cell (WBC), neutrophil, lymphocyte, platelet, and hemoglabin levels were recorded. PIV, SII, SIRI, NLR were calculated according to the following formulas.

PIV = Neutrophil, $x10^3$/uL × Platelet, $x10^3$/uL × Monocyte $x10^3$/uL / lymphocyte $x10^3$/uL
SII Neutrophil, $x10^3$/uL × Platelet, $x10^3$/uL / lymphocyte $x10^3$/uL
SIRI Neutrophil, $x10^3$/uL × Monocyte $x10^3$/uL / lymphocyte $x10^3$/uL
NLR Neutrophil, $x10^3$/uL / Platelet, $x10^3$/uL

Statistical analysis

All statistical analyses were conducted using R 4.1.3 (https://www.r-project.org/). The Kolmogorov-Smirnov test was utilized to assess the normal distribution of the data. Variables were presented as mean± standard error, median, minimum, maximum, and interquartilerange (IQR), and differences between variables were assessed using the Mann–Whitney U test forcases, as normality assumptions were not met for all variables. Additionally, Spearman correlation analysis was conducted to examine the relationship between variables. A p-value of <0.05 was considered statistically significant.

RESULTS

This study involved a total of 301 patients, with 100 in the Normal group and 201 in the acute ischemic stroke (AIS) group. Among them, 164 were women (52 in the Normal group and 112 in the SVO group), and 137 were men (48 in the Normal group and 89 in the AIS group). The median age was 40 for the Normal group and 74 for the AIS group. The demographic and laboratory findings of the patients for each group are presented in Table 1 and Figure 1.

Statistically significant differences were observed between the Normal and AIS groups regarding most variables, except for White Blood Cell, Monocyte, and Platelets, at a 95% confidence level. Specifically, Age, Neutrophils, CRP, PIV, SII, SIRI, and NLR values were higher in the AIS group ($p<0.05$), while Hemoglobin and Lymphocyte values were higher in the Normal group.

Table 1: Comparison of groups according to the demographic and laboratory finding

Variables	Group	Mean	Median	Minimum	Maximum	IQR	p value
Age	Normal	39.4±1.33	40.00	20.00	72.00	17.00	0.000*
	AIS	71.9±0.90	74.00	23.00	95.00	15.75	
Hemoglobin	Normal	14.06±0.12	14.10	11.50	17.20	2.13	0.000*
	AIS	13.42±0.12	13.40	7.34	17.90	2.28	
White Blood Cell	Normal	9.40±0.20	9.10	5.86	16.00	2.32	0.060
	AIS	10.75±0.32	9.90	4.60	40.40	4.46	
Neutrophils	Normal	6.45±018	5.94	3.64	11.30	2.98	0.000*
	AIS	8.81±0.29	8.17	2.73	26.00	5.66	
Lymphocyte	Normal	2.04±0.07	1.97	0.50	4.03	0.68	0.000*
	AIS	1.47±0.05	1.30	0.35	4.62	0.83	
Monocyte	Normal	0.67±0.03	0.65	0.04	1.71	0.42	0.050
	AIS	0.76±0.02	0.72	0.10	2.34	0.41	
Platelets	Normal	262.62±8.65	249.00	153.00	600.00	67.00	0.088
	AIS	287.20±7.04	260.50	119.00	560.00	162.50	
CRP	Normal	4.49±0.35	3.85	0.50	13.20	6.10	0.000*
	AIS	28.95±3.06	12.40	0.50	272.00	30.35	
PIV	Normal	624.37±45.48	511.89	14.41	2350.11	462.14	0.000*
	AIS	13607.68±1238	6807.80	100.98	82907.41	15444.77	
SII	Normal	959.38±65.49	815.13	239.87	4268.88	435.27	0.000*
	AIS	2960.80±230.62	1519.43	209.33	15093.75	3180.78	
SIRI	Normal	2.50±0.17	2.08	0.05	7.51	2.33	0.000*
	AIS	7.98±0.75	3.89	0.37	86.62	8.02	
NLR	Normal	3.82±0.27	3.10	1.10	18.48	1.86	0.000*
	AIS	8.90±0.60	5.92	0.93	63.69	8.14	

*: $p<0.05$

AIS: acute ischemic stroke; PIV: pan-immune inflammation value; SII: systemic immune-inflammation index; SIRI: systemic inflammatory response index; NLR: neutrophil-lymphocyte ratio

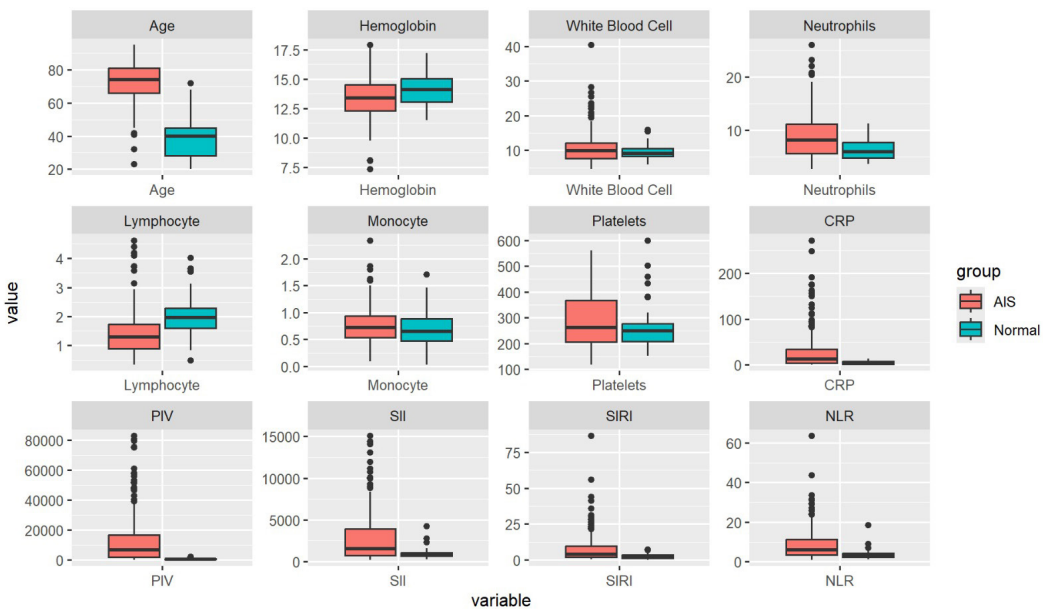

Figure 1. Comparison of groups according to the demographic and laboratory findings

AIS: acute ischemic stroke; PIV: pan-immune inflammation value; SII: systemic immune-inflammation index; SIRI: systemic inflammatory response index; NLR: neutrophil-lymphocyte ratio

The results of the Spearman correlation analysis, aimed at examining the relationships between variables, are depicted in the correlation matrix shown in Figure 2. In this matrix, the distribution of each variable is displayed along the diagonal. Below the diagonal, there are bivariate scatter plots with a fixed line. The correlation values and their significance levels, represented by stars, are presented above the diagonal. Each significance level is denoted by a corresponding symbol: p-values of (0.001, 0.01, 0.05) correspond to symbols ("***", "**", "*")

As illustrated in Figure 2, age exhibits inverse relationships of 20% and 39% with Hemoglobin and lymphocyte, respectively. Additionally, age demonstrates positive relationships of 17%, 35%, 45%, 33%, 36%, and 40% with monocyte, CRP, PIV, SII, SIRI, and NLR, respectively.

Hemoglobin displays a positive relationship of 12% with lymphocyte. Furthermore, hemoglobin manifests negative relationships of 14%, 16%, 25%, and 15% with platelets, CRP, PIV, and SII, respectively.

White blood cell demonstrates positive relationships of 56%, 33%, 15%, 29%, 23%, 31%, 38%, and 32% with neutrophils, monocyte, platelets, CRP, PIV, SII, SIRI, and NLR, respectively.

Neutrophils exhibit an inverse relationship of 53% with lymphocyte. Additionally, neutrophils showcases positive relationships of 33%, 36%, 31%, 26%, 80%, 78%, and 84% with monocytes, platelets, CRP, PIV, SII, SIRI, and NLR, respectively.

Lymphocyte demonstrates inverse relationships of 23%, 34%, 27%, 22%, 83%, 76%, and 89% with monocyte, platelets, CRP, PIV, SII, SIRI, and NLR, respectively.

Monocyte exhibits 24%, 21%, 14%, 30%, 69%, and 31% positive relationships with platelets, CRP, PIV, SII, SIRI, and NLR, respectively.

Platelets demonstrate positive relationships of 64%, 39%, and 37% with SII, SIRI, and NLR, respectively.

CRP exhibits positive relationships of 83%, 30%, 34%, and 33% with PIV, SII, SIRI, and NLR, respectively.

PIV demonstrates positive relationships of 23%, 26%, 26%, and 33% with SII, SIRI, and NLR, respectively.

SII exhibits 83% and 93% positive relationships with SIRI and NLR, respectively.

SIRI demonstrates a positive relationship of 88% with NLR.

DISCUSSION

Stroke is one of the most common fatal diseases worldwide. It is also one of the leading causes of chronic disability and dementia.[11] In recent years, the inflammatory response after stroke has become a focus of research, as understanding the role of inflammation in tissue damage is thought to play a significant role in the repair and treatment of ischemic stroke. To diagnose patients and determine appropriate treatment, it is necessary to conduct tests on inflammation markers, basic hematological parameters, and serum biochemistry.[2]

Neutrophils are the first subset of leukocytes to accumulate in the brains of ischemic stroke patients.[12] In an experimental study on permanent middle cerebral artery occlusion, it was found that neutrophils constituted approximately 30% of the total cell population entering the brain within the first 3 hours after the occlusion.[13] In our study, it was observed that neutrophil levels were higher in patients with acute ischemic stroke, which was consistent with the literature.

Inflammation plays an important role in the occurrence, progression, and plaque instability of stroke, increasing the risk of plaque rupture and thromboembolic events, which can eventually lead to major arterial occlusion.[14]

C-reactive protein (CRP) plays a significant role in the pathogenesis of stroke and has been shown to have strong independent predictive value regarding stroke outcomes. Several studies have emphasized a significant relationship between high CRP levels and impaired endothelial vascular reactivity.[15,16] A study investigating strokes reported that plasma CRP levels were more elevated in cases of large cerebral artery occlusions compared to those caused by small artery occlusions.[17,18] In our study, CRP levels were found to be higher in acute stroke patients compared to the control group.

The inflammatory response is regulated by numerous immune cells, such as lymphocytes, granulocytes, and monocytes, and the cell counts of these immune cells provide vital information about inflammatory conditions.[19]

Previous clinical studies have shown that the neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) are associated with the functional outcomes of acute ischemic stroke. In line with these studies, NLR and SII have also been shown to be early predictors of prognosis. These studies concluded that the NLR ratio increases in the acute phase, decreases

in later stages, and is associated with worse prognosis in the group with higher values.[20-22] In our study, consistent with the literature, the NLR value was significantly higher in the stroke group.

The PIV is a novel and comprehensive biomarker that includes measurements of neutrophils, platelets, monocytes, and lymphocytes. Fuca and colleagues initially developed the PIV as a predictive biomarker for metastatic colon cancer, based on the possible inflammatory effects of neutrophil, platelet, and monocyte levels, using peripheral blood count features generally associated with systemic inflammation.[23]

Following ischemia in acute stroke, damage-associated molecular patterns released by necrotic cells trigger the activation of resident immune cells within the central nervous system, including microglia and astrocytes. This activation subsequently leads to the recruitment of peripheral immune cells to initiate adaptive immune responses.[24,25] In one study, a strong and statistically significant correlation was found between high PIV values and delayed ischemic stroke in patients who experienced delayed ischemic stroke after aneurysm-related intracranial hemorrhage. There is currently no clear information in the literature regarding changes in PIV values in acute stroke. In our study, the PIV value was found to be significantly higher in the stroke group compared to the healthy control group.

The SII is a new biomarker that indicates a prothrombotic state (increased platelet count) and immune dysfunction (elevated neutrophil count with neutrophilia and/or low lymphocyte counts). To date, few studies have investigated the use of SII as a prognostic or diagnostic biomarker in acute stroke. Weng and colleagues reported that SII levels were higher in patients with acute ischemic stroke compared to healthy controls. The same study found that SII values were also significant in terms of predicting prognosis.[26] In our study, consistent with the literature, SII values were found to be higher in the acute ischemic stroke group compared to the control group.

A new inflammatory marker, the SIRI has begun to be recognized as an effective reflection of the inflammatory state in recent studies. It has been shown to predict the prognosis of multiple diseases, including aneurysmal subarachnoid hemorrhage and various cancers.[27,28] In a study conducted on patients with acute cerebral ischemia, it was found that SIRI values were elevated during acute ischemia. The same study concluded that SIRI could be more useful in predicting prognosis in ischemic patients.[29] Similarly, in our study, SIRI values were found to be higher in the ischemic group compared to the control group during acute stroke. SIRI may be an important inflammatory marker both for diagnosis and prognosis prediction.

This study still has some potential limitations. First, this is a single-center retrospective study and the sample size and study population limits the results. The study did not include frequently known markers such as interleukins, or plasma factors. We evaluated inflammatory markers such as PIV, SII, SIRI, and NLR, according to blood parameters taken at admission and did not analyze the fluctuation behavior of markers with repeated dynamic measurements. We think the dynamic evaluation of parameters with repeated measurements during hospitalization in future studies will contribute to the literature.

In conclusion, this study is the first to compare PIV, SII, and SIRI between patients diagnosed with acute ischemia and a healthy control group. According to the results obtained from our study, these markers could be predictive tools for both diagnosis and prognosis. Our study provides clinical evidence for foundational research on the relationship between inflammation and AIS (acute ischemic stroke). Most importantly, our study offers an economical and practical approach to improving risk stratification for poor AIS outcomes, especially in primary healthcare settings.

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