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Prognostic Value of Systemic Immune Inflammation Index in Malignant Ischemic Stroke: A Study on Patient Selection and Timing of Surgical Decompression

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ABSTRACT

Background: Ischemic stroke is a substantial health concern with long-term neurological consequences and economic implications. Inflammation worsens secondary brain injury, prompting the search for prognostic biomarkers. The optimal approach for treating malignant ischemic stroke, patient selection, and intervention timing remain intricate due to patient diversity.

Methods: We investigate the systemic immune inflammation index (SII) predictive value for surgical decompression timing and patient selection in malignant ischemic stroke. We include patients who underwent surgical decompression for ischemic stroke-induced malignant brain edema in the past five years. Retrospective data were collected, including demographics, history, laboratory results, imaging, and surgical details. SII was calculated using platelet, neutrophil, and lymphocyte counts. Descriptive statistics and multivariate regression models were used.

Results: In this study involving 80 patients, we evaluated the impact of decompressive craniectomy on ischemic stroke outcomes. Patients were divided into the Decompression Group (n=39) and Non-Decompression Group (n=41). Gender distribution, hypertension, diabetes mellitus, atrial fibrillation, and hemorrhage occurrence showed no significant differences between the groups. However, the Decompression Group had higher NIHSS scores at presentation (18.1±4.6 vs. 14.8±4.7, P=0.02) and discharge (17±5 vs. 11.2±4, P=0.001). SII at presentation and control were significantly higher in the Decompression Group (P=0.04 and P=0.05, respectively). Hospitalization duration on the 10th day was longer in the Decompression Group (39.5±28.8 vs. 11.8±5.6, P=0.001).

Conclusions: Our study examines SII's potential as a prognostic marker for surgical decompression timing and patient selection in malignant ischemic stroke. Despite limitations, we highlight the complex relationship between systemic inflammation, stroke severity, and post-surgical outcomes. Further research with larger cohorts must validate SII's utility and refine its application in ischemic stroke management. Continued investigation is crucial to establish SII's role as a predictive tool in guiding clinical decisions.

Keywords: Decompressive craniectomy, ischemic infarct, malign cerebral edema, systemic immune inflammation index

INTRODUCTION

Ischemic stroke, particularly occlusive ischemic stroke, represents a severe health concern beyond a life-threatening condition, often leading to permanent neurological disabilities and affecting a broad spectrum of society. This challenging scenario exerts detrimental impacts not only on individuals' quality of life but also on the societal economic equilibrium.

Ischemic stroke is characterized by inflammation as a pivotal contributor to its pathology and outcome. Inflammation exacerbates secondary brain injury by deteriorating the blood-brain barrier, compromising microvascular function, inducing brain edema and oxidative stress, and directly causing neuronal cell death (1,2). This recognition has prompted the exploration of inflammation as a primary target for advancing

novel stroke therapies. Among the goals is utilizing inflammatory biomarkers to enhance mortality prediction and functional outcomes in stroke patients.

Despite advancements, the existing options for acute ischemic stroke treatment remain limited and costly. The queries of which treatment approaches to apply, when, and for whom continue to lack comprehensive answers. Notably, in the case of malignant ischemic stroke, selecting appropriate candidates and optimal timing for interventions such as surgical decompression pose challenges (3-5). These challenges are compounded by the heterogeneous nature of stroke patients, characterized by diverse demographic profiles and comorbidities.

Various inflammatory indicators, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and red blood cell distribution width (RDW), have been investigated as potential prognostic markers in ischemic stroke (6-7). However, their predictive values have shown inconsistent levels of significance. A newly emerging inflammatory index, known as the Systemic Immune Inflammation Index (SII), is calculated by combining three immune-inflammatory cell types (lymphocytes, neutrophils, and platelets), providing a comprehensive reflection of the inflammatory status (8). Elevated SII levels have been shown to increase the risk of stroke in hypertensive patients and impact the prognosis of these patients (9). Based on these findings, the purpose of our study was to calculate SII based on the initial routine blood test at the time of admission and SII obtained from the blood test during neurological deterioration in patients presenting with acute large vascular occlusion that subsequently develops malignant cerebral edema. We aimed to establish a model for predicting the requirements of decompressive craniectomy (DC) and further validate the predictive value of SII in estimating the prolonged prognosis of patients who undergo DC treatment.

METHODS

Study Design

The study aims to investigate the prognostic utility of the SII in determining the optimal timing for DC and selecting suitable patients with malignant brain edema resulting from ischemic stroke.

Data Source and Patient Selection

Patients in our hospital within the last five years who developed malignant brain edema after ischemic stroke and patients who underwent DC due to malignant brain edema will be included in the study. Patient data will be derived from electronic health records, surgical reports, and medical imaging studies. The data collection process will be retrospective and include demographic information, medical history, laboratory results, imaging findings, and surgical details.

Patient Management: The AHA-ASA standard protocol for acute ischemic stroke treatment (10) was administered in patients displaying clinical symptoms of acute ischemic stroke. Upon admission, all patients underwent Brain Computed Tomography (CT) or, in suitable cases, CT angiography. Patients with symptom onset within the first 4.5 hours and no contraindications received intravenous thrombolysis; those with treatable large vessel occlusion within the first 6 hours after symptom onset, according to CT angiography, were subjected to endovascular treatment All 80 patients received standardized conservative management, including measures such as controlling blood pressure, administering hyperosmolar treatment, utilizing hypertonic saline solutions, and implementing hyperventilation techniques. Following confirmation of space-occupying hemispheric infarction on follow-up CT, similar to the HAMLET (11) study protocol, DC was performed when the Glasgow Coma Scale (GCS) score dropped to ≤13 for right hemispheric lesions or ≤9 for left-sided lesions. There was no strict time limit of 48 hours between stroke onset and DC. Other HAMLET exclusion criteria, such as age >60, hemorrhagic transformation, and involvement of other vascular territories, were not applied; a neurologist and a neurosurgeon discussed the clinical course and overall condition of such patients, and the decision regarding DC was made after obtaining informed consent from the patient and their family.

During DC, a large skin incision was made in the shape of a question mark based on the ear base. Subsequently, a bone flap containing frontal, temporal, and parietal bones with a diameter of at least 120 mm was created. The craniectomy was extended to the temporal skull base. The dura was opened widely in a cross-shaped manner. The cortical surface was covered with non-approximated dural flaps and absorbable hemostatic cellulose. Finally, the skin was closed. Postoperatively, all patients were admitted to the Intensive Care Unit (ICU) for supportive care purposes.

Calculation of Systemic Immune Inflammation Index (SII): SII was calculated by multiplying the platelet (P) count by the neutrophil (N) count and then dividing the result by the lymphocyte (L) count (SII = P x N/L), with platelet, neutrophil, and lymphocyte counts extracted from laboratory results.

STATISTICAL ANALYSIS

The study data were analyzed in SPSS (Statistical Package for the Social Sciences) 23.0 and MedCalc 23.110. Numeric data were expressed as median (interquartile range (IQR)) and frequent data as rates. Comparison of two independent groups with numeric data was carried out by Mann Whitney U test, and the Chi-square test was used for frequent data. The Kolmogorov-Smirnov test conducted the normality analysis. Logistic regression

Table 1. Characteristics of the patients at baseline

Variables	Decompression Group (n=39)	Non-decompression Group (n=41)
Age, years	71 (67 to 75)	75 (69 to 80)
Gender, n Female Male	 13 (33.3) 26 (66.7)	 21 (51.2) 20 (48.8)
Hypertension, n	31 (79.5)	28 (68.3)
Diabetes Mellitus, n	12 (30.8)	17 (41.5)
Atrial Fibrillation, n	22 (56.4)	16 (39)
Hemorrhage, n	16 (41)	19 (46.3)
NIH Stroke Scale	18 (15 to 22)	14 (11 to 18)
NIH Stroke Scale Mild (1-10) Moderate (1-18) Severe (≥19)	 2 (5.1) 19 (48.7) 18 (46.2)	 9 (22) 22 (53.7) 10 (24.4)

SII; systemic immune-inflammation index; IQR; interquartile range *Data are expressed as n (%) and median (IQR) unless otherwise stated.

analysis was used for multivariate analysis to ascertain the independent variables predicting the 3rd month mortality. All the hypotheses were constructed as two-tailed, and an alpha critical value of 0.05 was accepted as significant.

RESULTS

Baseline Characteristics of Patients: **Table 1** presents the baseline characteristics of patients in the Decompression Group (n=39) and the Non-decompression Group (n=41). The Decompression Group had a median age of 71 years (IQR: 67 to 75), while the Non-decompression Group had a median age of 75 years (IQR: 69 to 80). Gender distribution showed that most patients in the Decompression Group were male (66.7%), whereas the Non-decompression Group had a slightly higher proportion of females (51.2%). The prevalence of comorbidities such as hypertension, diabetes mellitus, atrial fibrillation, and hemorrhage varied between groups. Notably, the median NIH Stroke Scale score at baseline was higher in the Decompression Group (18, IQR: 15 to 22) compared to the Non-decompression Group (14, IQR: 11 to 18).

Primary and Secondary Outcomes: **Table 2** outlines both groups' primary and secondary outcomes. Mortality in the third month was significantly higher in the Decompression Group (38.5%) compared to the Non-decompression Group (17.1%), with a p-value of 0.03. Additionally, the Modified Rankin Scale (mRS) score was higher in the Decompression Group (median: 5, IQR: 4 to 6) than in the Non-decompression Group (median: 4, IQR: 3 to 5), with a p-value of 0.00. Hospitalization duration was notably longer in the Decompression Group (median: 29 days, IQR: 19 to 56) compared to the Non-decompression Group (median: 10 days, IQR: 8 to 14). Moreover, NIH Stroke Scale scores at discharge were also higher in the Decompression Group (median: 18, IQR: 13 to 20) than in the Non-decompression Group (median: 12, IQR: 9 to 14), with p-values of 0.00.

Table 2. Primary and secondary outcomes in decompression and non-decompression groups

Variable	Decompression Group (n=39)	Non-decompression Group Value (n=41)	P value
Mortality*	15 (38.5)	7 (17.1)	0.03
mRS	5 (4 to 6)	4 (3 to 5)	0.00
SII control	887 (487 to 1190)	950 (504 to 1206)	0.55
Hospitalization (days)	29 (19 to 56)	10 (8 to 14)	0.00
NIH Stroke Scale (at discharge)	18 (13 to 20)	12 (9 to 14)	0.00
SII Difference	19 (-516 to 278)	39 (-328 to 531)	0.40

SS; standard deviation; NIH Stroke Scale; SII; systemic immune-inflammation index
*Mortality in the 3rd month, ^Data are expressed as n (%) and median (IQR) unless otherwise stated

Table 3. Univariate comparison of patients with and without mortality at the 3rd month regarding the co-morbidities, NIHSS and systemic immune-inflammation index

Variable	Mortality (n=22)	No Mortality (n=58)	P Value
Age, years	75 (68 to 77)	71.5 (68 to 75)	0.49
Diabetes Mellitus, n	9 (40.9)	20 (34.5)	0.59
Hypertension, n	16 (72.7)	43 (74.1)	0.89
NIH Stroke Scale*	19.5 (16 to 24)	15 (11 to 18)	0.00
SII*	1019 (663 to 1347)	693 (458 to 1209)	0.22
SII difference	-209.7 (-357 to 100)	130.4 (-213 to 522)	0.01

SS; standard deviation; NIH Stroke Scale; SII; systemic immune-inflammation index
*NIH Stroke Scale and SII at presentation, ^Data are expressed as n (%) and median (IQR) unless otherwise stated.

Table 4. Logistic regression analysis in order to establish the independent variables predicting mortality at the 3rd month

Variable	Odds Ratio	95% CI	P Value
Age	0.96	0.9 to 1.3	0.29
Diabetes Mellitus	3.7	0.9 to 16	0.07
NIH Stroke Scale	1.4	1.17 to 1.7	0.00
SII at presentation	1	0.99 to 1	0.40
Hemorrhage	5	1.24 to 20	0.02
Hypertension	0.67	0.15 to 3	0.60
Decompression	1.68	0.4 to 7	0.47

CI; confidence interval; SII; systemic immune-inflammation index

Univariate Comparison of Mortality: **Table 3** explores the univariate comparison of patients with and without mortality in the third month. Age, comorbidities (diabetes mellitus and hypertension), baseline NIH Stroke Scale scores, systemic immune-inflammation index (SII) at presentation, and SII difference were assessed. Notably, patients who experienced mortality had significantly higher baseline NIH Stroke Scale scores (median: 19.5, IQR: 16 to 24) than survivors (median: 15, IQR: 11 to 18) with a p-value of 0.00. The SII difference was also significantly different between the two groups (p-value: 0.01).

Logistic Regression Analysis: Table 4 presents the logistic regression analysis results to identify independent variables predicting mortality in the third month. The analysis revealed that higher baseline NIH Stroke Scale scores (Odds Ratio: 1.4, 95% CI: 1.17 to 1.7) and the presence of hemorrhage (Odds Ratio: 5, 95% CI: 1.24 to 20) were associated with increased odds of mortality. However, decompression did not significantly influence mortality (Odds Ratio: 1.68, 95% CI: 0.4 to 7).

These results suggest that baseline stroke severity, as measured by the NIH Stroke Scale and the presence of hemorrhage are significant predictors of mortality in the third month. At the same time, the choice of decompression did not independently impact mortality outcomes.

DISCUSSION

In recent years, studies focusing on the post-stroke inflammatory response have steadily increased. It is believed that inflammation plays a role in initiating post-stroke recovery and repair processes, but certain aspects of the inflammatory response in stroke patients can have detrimental effects (12). A novel inflammatory index, SII, is calculated by combining three immune-inflammatory cell types (lymphocytes, neutrophils, and platelets), comprehensively reflecting the inflammatory status (8). Elevated SII levels have been shown to increase the risk of stroke in hypertensive patients and impact the prognosis of these patients (9). Therefore, the purpose of our study was to calculate SII based on the initial routine blood test at the time of admission, establish a model for predicting the requirements of DC, and validate the predictive value of SII to aid in selecting patients for DC.

Treating patients with malignant cerebral edema following ischemic stroke remains quite challenging. Decompressive craniectomy can reduce brain herniation and prevent death by reducing the mass effect on infarcted brain tissue (13). The current consensus suggests that after identifying brain herniation through imaging, DC can be performed as soon as possible without waiting for neurological deterioration (14). Various studies have shown that decompressive surgery can reduce the mortality rate from 80% to 30% in cerebral edema following ischemic stroke cases. Oliver and colleagues suggested that monitoring the optic nerve sheath diameter with ultrasound in patients with large vessel occlusion could predict severe intracranial hypertension and help select appropriate candidates for DC (15). However, it is still unclear which patients with extensive middle cerebral artery occlusion will develop severe cerebral edema necessitating decompressive surgery or which group will benefit the most from the procedure. Given the long-term effects of chronic physical disability and psychosocial problems following DC in treating ischemic stroke-related malignant cerebral edema, it is challenging to decide which patients are suitable for early or preventative surgery or to defer surgery until clear evidence of improvement or deterioration emerges. Over the past few years, an increasing number of studies have highlighted the significance of inflammation in the pathogenesis of ischemic stroke (16,17). Inflammatory pathways activated during acute and reparative stages of ischemic stroke involving cytokines, chemokines, and damage-associated molecular patterns play a crucial role in tissue damage and prognosis after ischemic stroke (18). The pro-inflammatory signals arising from endothelial and cerebral tissue damage within minutes of cerebral ischemia can exacerbate brain damage by influencing the infiltration of various inflammatory cells (neutrophils, monocytes/macrophages, different subtypes of T cells, and other inflammatory cells) into the ischemic region (19). Studies have shown neutrophils are the first cells to respond to cerebral ischemia (20). Neutrophils, part of the innate immune system, can intensify brain parenchymal inflammation by activating numerous pro-inflammatory cytokines. Inflammatory reactions following neutrophil endothelial adhesion can damage secondary brain tissue (21,22).

Additionally, cerebral ischemia and hypoxia can induce monocytes to produce inflammatory mediators like interleukin-6 (IL-6) and tumor necrosis factor (TNF), further exacerbating secondary injury after cerebral ischemia and hypoxia, aggravating comprehensive brain tissue damage, and suggesting that the detrimental effects of white blood cells are not limited to neutrophils (23). Platelet-monocyte aggregates (PMA) formed by

monocyte activation of platelets following ischemic brain injury contribute to vascular thrombosis and occlusion, intensifying post-ischemic inflammation by releasing vasoactive mediators and worsening ischemia (24). Given the complex nature of inflammation, simply counting the number of white blood cells is insufficient to indicate the severity of inflammation. Therefore, new biomarkers have been designed by combining different subtypes of white blood cells, such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), SIRI, or SII, based on various inflammatory parameters associated with stroke (25,26). For example, Zhang and colleagues investigated the impact of the systemic inflammatory response index (SIRI) on prognosis in patients with acute ischemic stroke, finding a positive correlation between NLR and three-month mortality risk and an independent association between low lymphocyte-monocyte ratio and increased risk of hemorrhagic transformation in stroke patients (27).

The newly introduced SII, calculated by combining three immune-inflammatory cell types (lymphocytes, neutrophils, and platelets), comprehensively reflects the inflammatory status (8). Previous studies have reported that SII predicts prognosis in myocardial infarction, breast cancer, and small-cell lung cancer patients (28,12). Luo and colleagues included 76 patients with aneurysmal subarachnoid hemorrhage in their prognostic analyses, showing that SII at admission was closely related to their six-month clinical outcomes (29). Chen and colleagues (30) also demonstrated that SII was an independent predictor for delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. In our study, SII calculated from the admission blood test was significantly lower in patients with malignant ischemic stroke who experienced neurological deterioration. This situation suggests that changes in SII in ischemic malignant cerebral edema could be a predictive parameter for DC.

Results from studies have indicated that biomarkers related to systemic inflammation are associated with the development of malignant cerebral edema and all-cause mortality following acute ischemic stroke (27). However, no data in the literature shows the contribution of high SII during acute ischemic stroke and increasing SII values during follow-up to the development of malignant cerebral edema and their relevance in the selection of the appropriate patient group for DC. Our study observed that increased SII in the first days of middle cerebral artery occlusion-related ischemic stroke was strongly associated with malignant cerebral edema development and mortality in patients who underwent decompression.

It is widely accepted that the higher the NIHSS score, the more severe the stroke is. In our study, there was a positive correlation between SII and NIHSS; based on these findings, it can be concluded that there is a positive correlation between SII and stroke severity. As far as we know, no study has previously documented the role of SII in stroke prognosis. Therefore, there is great potential to use SII to predict stroke prognosis.

The Study Limitations

1. The subjects in this study were selected from a single center, which may have led to selection bias or geographically biased results. The next step would be to conduct a multi-center study.
2. The number of standard variables related to stroke prognosis was extraordinarily high and collected quately in our study. More data on other parameters are required to enhance the robustness of our results.
3. The sample size in our study was relatively small; larger sample sizes are needed to confirm our findings.

CONCLUSION

Our study contributes to the growing body of literature elucidating the intricate relationship between systemic inflammation biomarkers, stroke severity, the development of malignant brain edema, and post-surgical outcomes. Further research, incorporating larger samples and broader variables, is warranted to validate the utility of SII as a prognostic tool and to refine patient selection criteria for decompressive surgery in ischemic stroke. Our findings underscore the potential of SII to aid in predicting outcomes and guiding clinical decision-making. However, continued investigation is imperative to cement its role in the stroke management paradigm.

DECLARATIONS

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Conflict of interest: None

Informed consent form: Informed consent was waived due to the retrospective nature of the study.

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Authors' contributions: All authors contributed equally to the conduction and finalizing of the study.

Ethical Considerations: We secured ethical approval from the institutional review board (Health Sciences University Antalya Training and Research Hospital Clinical Research Ethics Committee, Approval Number and date: 11/24, 24/08/2023). Informed consent was waived due to the retrospective nature of the study. This study was conducted in agreement with the Declaration of Helsinki-Ethical principle for medical research involving human subjects.

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