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Original Research Article

THE PREDICTIVE ROLE OF SYSTEMIC INFLAMMATORY RESPONSE INDEX (SIRI) IN PROGNOSIS OF CRITICALLY ILL PATIENTS WITH SPONTANEOUS INTRACEREBRAL HEMORRHAGE

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ABSTRACT

Background: Intracerebral hemorrhage (ICH) is often associated with high morbidity and mortality. The body's inflammatory response plays a major role in determining both immediate and long-term outcomes following ICH. Inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), red cell distribution width (RDW), and systemic inflammatory response index (SIRI) are commonly used to assess this response. This study aimed to evaluate and compare the prognostic utility of SIRI against other commonly used markers—NLR, PLR, LMR, and RDW—in patients with acute ICH admitted to intensive care.

Materials and Methods: This retrospective cohort study included 140 patients diagnosed with acute ICH and admitted to the ICU between September 2023 and September 2024. The correlation between SIRI and stroke severity, measured by the NIH Stroke Scale (NIHSS), was assessed using Spearman's correlation coefficient. Prognostic performance for in-hospital outcomes, including mortality and sepsis, was analyzed using receiver operating characteristic (ROC) curves for SIRI, NLR, PLR, LMR, and RDW.

Results: SIRI demonstrated a statistically significant positive correlation with NIHSS scores. Higher SIRI values were associated with increased mortality. ROC analysis, adjusted for relevant confounders, showed that SIRI had superior predictive accuracy for mortality (AUC = 0.722) and sepsis (AUC = 0.606) compared to PLR and LMR. However, no significant difference was found when comparing SIRI with NLR and RDW.

Conclusion: Elevated SIRI levels were linked to more severe strokes and higher mortality risk in ICH patients. Among the inflammatory markers studied, SIRI emerged as a strong and independent predictor of poor outcomes in ICU-admitted ICH cases, supporting its potential role in clinical risk stratification.

Keywords: Intracerebral hemorrhage, Systemic Inflammatory Response Index, Prognosis, Neurocritical Care, 30-day Mortality, Cohort Study.

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) is a fatal form of stroke, accounting for approximately 15% of all stroke cases.[1] It is associated with high mortality and poor clinical outcomes.[2] Despite advances in medical care and management, ICH remains a significant health concern, with 30-day mortality rates approaching 40%.[3]

The systemic and local inflammatory responses in stroke are essential in understanding the pathophysiology and is a vital factor in determining the mortality of stroke cases.[4] Inflammation triggers microglial activation, leading to secretion of

cytokines and chemokines that promote neutrophil and monocyte infiltration, worsen the perihemorrhagic edema, compound the hemorrhagic injury, worsening the prognosis.[5,6] Studies have shown that inflammatory biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) play crucial roles in predicting the systemic inflammatory response after a hemorrhagic stroke occurs.[6]

Among all these markers, SIRI (systemic inflammatory response index), stands out as a novel inflammatory marker which is a chronic low-grade inflammatory index. SIRI uses peripheral blood monocytes and the neutrophil-to-lymphocyte ratio (NLR) to provide a comprehensive understanding of the inflammatory state in various conditions.[7] Previously applied for prognosis of cancer,[8] SIRI has shown possibilities of being a more comprehensive indicator of systemic inflammation in stroke.[9] It has also been shown as better in representing the status of inflammatory response in the body compared to the standard peripheral blood cell ratios like NLR, LMR, and PLR.[9] Various studies have shown that high SIRI levels can be useful indicator for predicting other complications in stroke patients like atrial fibrillations and stroke associated pneumonia (SAP).[10,11]

In previous studies on glioma,[12] breast cancer,[13] and cervical cancer,[14] high levels of SIRI indicated poor mortality and morbidity and as such could be integrated as a prognostic tool in the future development of treatment for stroke patients.[15] Given the established role of inflammation in stroke and ICH, this study aims to evaluate the prognostic value of SIRI in predicting outcomes in acute spontaneous intracerebral haemorrhage and compare its efficacy with other known biomarkers.

MATERIALS AND METHODS

Study Design and Participants

This study was approved by the Kempegowda Institute of Medical Sciences Institutional Ethics Committee. Informed consent was waived by the review board as this study was observational, retrospective and all data was anonymized. In this single-center, retrospective observational study, a blind outcome evaluation was performed. This study was carried out in compliance with the Declaration of Helsinki.

We screened adult patients with spontaneous intracerebral hemorrhage admitted to the intensive care unit (ICU) of KIMS Hospital, a university-affiliated academic hospital, between September 2023 to September 2024. The inclusion criteria were as follows: 1. Patients at or above the age of 18 years; 2. Patients who have suffered from a spontaneous, acute intracranial hemorrhage; 3. Patients who are hospitalised for atleast 48 hours; 4. Hospitalisation in an intensive care unit (ICU). To minimize confounding, we excluded: 1. Individuals under the age of 18 upon initial admission; 2. Patients with ICH as a result of traumatic brain injury, brain tumor, cerebral aneurysm, cerebral arteriovenous malformation, or other structural abnormalities; 3. Patients with a diagnosis of acute ischemic stroke as confirmed by a non- contrast CT scan; 4. Patients with known/existing severe kidney and liver conditions, leukemia, lymphoma, other hematological diseases, malignant tumors, on anticoagulant medication; 5. Patients lacking sufficient data on first day of admission.

Study variables and Outcomes

Medical records were meticulously reviewed to collect patient demographics, previous medical histories, laboratory values and ICD-10 based final diagnoses. National Institute of Health Stroke Scale (NIHSS) and GCS scores were extracted from the neurological examination performed within an hour of ICU admission. Risk factors like diabetes mellitus, hypertension, alcoholism, smoking, coronary artery disease was documented. Besides, hematological parameters included haemoglobin (Hb), white blood count (WBC), neutrophil count (N), lymphocyte count (L), monocyte count(M), platelet count (P), red blood cell distribution width (RDW), serum albumin, lactate levels assessed within 24 hours of admission. These values were used to calculate inflammatory markers like: neutrophil to lymphocyte ratio (NLR=N/L), platelet to lymphocyte ratio (PLR=P/L), lymphocyte to monocyte ratio (LMR=L/M) and SIRI (SIRI=N×[M/L]).

The primary outcome was the 30-day all-cause mortality, correlation analysis of SIRI and NIHSS and comparative analysis of SIRI with NLR, LMR and PLR. The 30-day outcome including complications such as pneumonia and sepsis was the secondary outcome

Statistical Analysis

Continuous variables are expressed as Mean ± Standard Deviation (SD), whereas categorical variables are presented as numbers and percentages. They were compared using t-tests and Chi Square or Fisher exact tests, when appropriate. Multivariable Logistic Regression analysis was used to analyse the independent effect of SIRI on mortality in patients. The adjusted variables included age, sex, risk factors such as hypertension, diabetes mellitus, coronary artery disease, smoking and alcohol consumption, GCS, hemoglobin, platelets. These factors were considered as they have been documented to be associated with stroke prognosis. To analyse the correlation between NIHSS and SIRI, Spearman's correlation method was used with a p-value less than 0.05 considered statistically significant. Receiver Operating Characteristic (ROC) curve analysis was used to compare the predictive ability of SIRI with NLR, LMR, PLR and RDW for mortality in patients with ICH.

RESULTS

Patient demographics: A total of 261 patients with intracerebral hemorrhage were identified, of whom 140 patients met the inclusion criteria for the study. The median age was 57 (range 19-94 years) and 67.8% of the study group constituted of males. A total of 24 patients (17.1%) succumbed within 30 days of admission to the ICU. Additionally, 9 patients (6.4%) developed sepsis and 8 patients (5.7%) developed pneumonia within 30 days of suffering from ICH. Close to half the patients (N=67; 47.9%) had predisposing hypertension, 30 patients (21.4%) had diabetes, 7 patients (5%) had a prior diagnosis of coronary artery disease. 12 patients (8.6%) had a history of alcohol consumption, while 7 patients (5%) were known smokers.

Univariable analysis: Baseline demographics and clinical characteristic between survivors and non-survivors, patients with sepsis and without sepsis; and patients with SAP and without SAP within 30 days, were summarised in Tables 1, 2 and 3 respectively. Survivors and non-survivors exhibited statistically significant differences in several laboratory parameters, including total leukocyte count ($p = 0.011$) and neutrophil count ($p = 0.009$). SIRI was noted to be significantly higher in non-survivors as compared to survivors ($p = 0.015$). Survivors had significantly higher GCS scores (median: 11 vs. 6, $p < 0.001$) and lower NIHSS scores (median: 14 vs. 27, $p < 0.001$).

Multivariable logistic regression: Multivariable logistic regressions were performed to further confirm the association of inflammatory markers on 30-day mortality, where NLR, LMR, PLR and SIRI were included as binary values (dichotomized at their median value). None of the inflammatory markers showed independent influence for 30-day mortality.

Association between SIRI and NIHSS: Spearman's correlation analysis suggested a positive correlation between SIRI and NIHSS; correlation coefficient was 0.219 ($p = 0.009$).

ROC curve analysis for 30-day mortality: ROC curves were plotted to evaluate the efficiency of SIRI and NLR, PLR, LMR and RDW in predicting outcomes in haemorrhagic stroke. In predicting mortality, we found that SIRI (AUC = 0.722) was more accurate than other inflammatory biomarkers including NLR, PLR, LMR and RDW (AUC = 0.651, 0.521, 0.426, 0.609) (Figure1). With adjusted covariates, SIRI was a better predictor of sepsis outcomes (AUC = 0.606), with no significant differences compared to other markers (NLR AUC = 0.55; PLR AUC = 0.531; LMR AUC = 0.504; RDW AUC = 0.534) (Figure 2). However, SIRI did not demonstrate any discriminatory ability in patients with SAP.

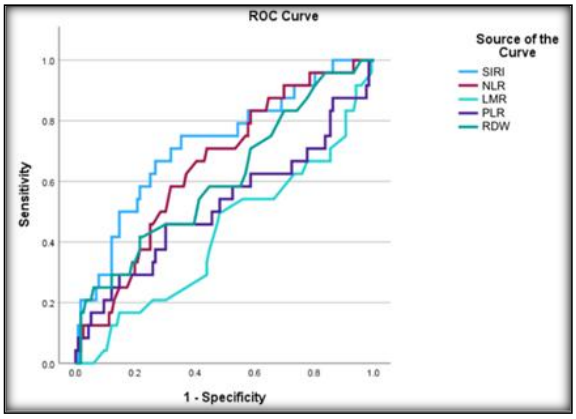

Figure 1: Receiver Operating Curve (ROC) for prediction of mortality in patients with ICH using SIRI

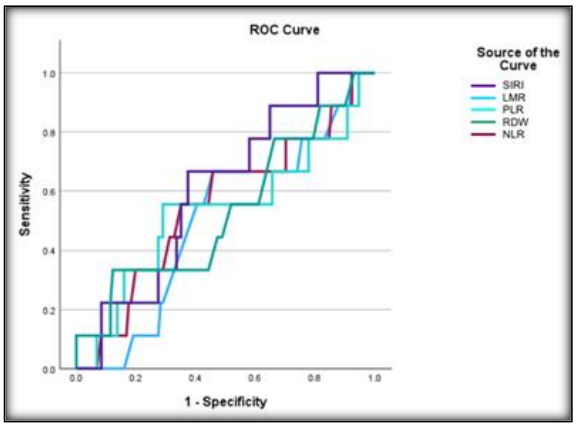

Figure 2: Receiver Operating Curve (ROC) for prediction of sepsis outcomes in patients with ICH using SIRI

Table 1: Comparison of baseline demographics vs clinical characteristics between survivors and non- survivors.

Variable	Survivors (N=116)	Non-survivors (N=24)	p-value
Demographics			
Age, y	57 (45-65)	53 (37-67.5)	0.302
Male, N (%)	81 (69.8%)	14 (58.3%)	0.678
Comorbidities, N(%)			
Hypertension	57 (49.1%)	10 (41.7%)	0.505
Diabetes Mellitus	26 (22.4%)	4 (16.7%)	0.532
Coronary Artery Disease	6 (5.2%)	1(4.2%)	0.837
Smoking	7(6.0%)	0	0.217
Alcohol	12 (10.3%)	0	0.099
Laboratory Indicators at ICU Admission, median (IQR)			
Haemoglobin g/dl	12.6 (11.1 – 14.2)	11.75 (10.1 – 11.8)	0.559
Total Leucocyte count x 109/L	11.2(8.8-14)	14.9(10.9-21.3)	0.011
Neutrophils x 109/L	9.4 (7.3 – 12.2)	13.3 (8.8-18.8)	0.009
Lymphocytes x 109/L	1.3 (0.9- 1.9)	1.4 (0.7-2.0)	0.910
Monocytes x 109/L	0.3 (0.2- 0.5)	0.4 (0.3- 0.5)	0.280

Platelets x 109/L	259.5 (203.5 – 303.8)	259.0 (172 – 310.3)	0.378
RDW	13.6 (12.9-14.6)	13.9 (12.8 – 17.6)	0.123
Albumin g/L	3.9 (3.5- 4.4)	4.2 (3.3- 4.9)	0.950
Lactate mmol/L	1.3 (1.0 – 2.0)	1.7 (1.3 – 3.2)	0.055
Inflammatory marker, median (IQR)			
NLR	7.2 (4.4 – 12.5)	10.5 (6.8 – 15.2)	0.009
LMR	4 (2.7 – 6.0)	4.2 (1.8 – 5)	0.267
PLR	196.5 (138.3 – 269.6)	205.4 (121.2 – 354.3)	0.292
SIRI	2.2 (1.4-3.7)	3.6 (2.0-9.8)	0.015
Scoring Systems, median (IQR)			
GCS	11 (7.3 – 15.0)	6 (5.0-9.0)	<0.001
NIHSS	14 (6.0-21.0)	27 (17.3 – 28.0)	<0.001

Table 2: Comparison of baseline demographics vs clinical characteristics between patients with and without sepsis

Variable	Patients with no Sepsis (n= 131)	Patients with Sepsis (n=9)	p-value
Demographics			
Age, y	57 (45-65)	45 (36-60)	0.112
Male, N (%)	87 (66.4%)	8 (88.9%)	0.163
Comorbidities, N(%)			
Hypertension	64 (48.9%)	3 (33.3%)	0.367
Diabetes Mellitus	29 (22.1%)	1 (11.1%)	0.435
Coronary Artery Disease	7 (5.3%)	0	0.477
Smoking	7 (5.3%)	0	0.342
Alcohol	12 (9.2%)	0	0.477
Laboratory Indicators at ICU Admission, median (IQR)			
Haemoglobin g/dl	12.6 (10.9-14.2)	12.1 (11.4-14.6)	0.587
Total Leucocyte count x 109/L	11.5 (8.8-14.7)	15.1 (11.4-17.7)	0.060
Neutrophils x 109/L	9.4 (7.3 -12.6)	13.4 (9.4-16.1)	0.084
Lymphocytes x 109/L	1.3 (0.8-1.9)	1.6 (0.9-2.0)	0.516
Monocytes x 109/L	0.3 (0.2-0.5)	0.4 (0.3-0.6)	0.310
Platelets x 109/L	258.0 (200.0 -302.0)	364.0 (204.0-401.5)	0.112
RDW	13.6 (13.0 – 14.7)	13.9 (13.0-16.7)	0.731
Albumin g/L	3.9 (3.4- 4.4)	3.8 (3.5-4.7)	0.546
Lactate mmol/L	1.37 (1.1-2.0)	1.85 (1.2 – 2.5)	0.155
Inflammatory marker, median (IQR)			
NLR	7.7 (4.7-12.9)	9.9 (4.7-15.0)	0.566
LMR	4.0 (2.7 – 6.0)	5.0 (2.3 – 5.3)	0.966
PLR	199.0 (137.4 -271.8)	243.7 (118.6 – 365.3)	0.737
SIRI	2.3 (1.4-4.1)	3.3 (1.7-5.5)	0.298
Scoring Systems, median (IQR)			
GCS	11 (7-15)	7 (4.5-12)	0.109
NIHSS	14 (6-24)	24 (11-28)	0.164

Table 3: Comparison of baseline demographics vs clinical characteristics between patients with and without pneumonia

Variable	Patients without SAP (n = 132)	Patients with SAP (n=8)	p-value
Demographics			
Age, y	56.5 (43.5 -65.0)	60.5 (49.8 – 74.8)	0.226
Male, N (%)	88 (66.7%)	7 (87.5%)	0.221
Comorbidities, N(%)			
Hypertension	63 (47.7%)	4 (50.0%)	0.901
Diabetes Mellitus	27 (20.5%)	3 (37.5%)	0.254
Coronary Artery Disease	7 (5.3%)	0	0.504
Smoking	6 (4.5%)	1 (12.5%)	0.316
Alcohol	11 (8.3%)	1 (12.5%)	0.683
Laboratory Indicators at ICU Admission, median (IQR)			
Haemoglobin g/dl	12.6 (10.9 – 14.3)	12.1 (10.6 – 13.5)	0.553
Total Leucocyte count x 109/L	11.9 (9.0 – 14.9)	13.3 (9.4 – 15.8)	0.578
Neutrophils x 109/L	9.5 (7.5 – 13.2)	11.1 (6.5-13.7)	0.654
Lymphocytes x 109/L	1.3 (0.9 – 1.9)	1 (0.6 – 1.8)	0.273
Monocytes x 109/L	0.3 (0.2 – 0.5)	0.3 (0.2 – 0.5)	0.936
Platelets x 109/L	258.5 (200.5 – 303.0)	266.0 (203.5 – 307.0)	0.914
RDW	13.6 (13.0 – 14.8)	13.25 (12.5 – 23.5)	0.529
Albumin g/L	3.9	3.5	0.047
Lactate mmol/L	1.45	1.26	0.330
Inflammatory marker, median (IQR)			
NLR	7.7 (4.7 – 12.9)	10.9 (7.2 – 17.4)	0.234
LMR	4.3 (2.7 – 5.9)	3.3 (2.0 – 6.25)	0.310
PLR	199.4 (136.2 – 262.0)	252.2 (163.8 – 449.2)	0.483
SIRI	2.3 (1.43 – 4.0)	3.5 (1.1 – 9.4)	0.404
Scoring Systems, median (IQR)			
GCS	10.0 (7.0 – 14.8)	11.5 (8.0-14.8)	0.441
NIHSS	15.0 (3.5- 21.0)	9.50 (3.5-21.0)	0.176

Table 4: Receiver Operating Curve (ROC) for Prediction of Mortality in ICH

Inflammatory Markers	AUC	95% CI Low	95% CI Upp
NLR	0.651	0.538	0.765
PLR	0.521	0.377	0.665
LMR	0.426	0.295	0.557
RDW	0.609	0.481	0.737
SIRI	0.722	0.606	0.838

DISCUSSION

Recent studies have shown the prognostic value of the Systemic Inflammation Response Index (SIRI) in patients with intracerebral hemorrhage (ICH). The pathophysiology of intracerebral hemorrhage (ICH) involves both primary injuries, due to the hematoma's mass effect, and secondary injury, which arises from neuroinflammatory processes. Following hematoma formation, inflammation is initially driven by the M1 microglia, secreting cytokines (e.g., interleukin-1β [IL-1β] and tumor necrosis factor-α) that are involved in the breakdown of the extracellular matrix, cellular integrity, and the blood brain barrier. Additionally, inflammatory factors recruit and induce differentiation of A1 reactive astrocytes and T helper 1 (Th1) cells, which contribute to the secretion of inflammatory cytokines, augmenting M1 polarization and potentiating inflammation. This cascade results in the recruitment of peripheral immune cells, including neutrophils and monocytes, which exacerbate blood-brain barrier breakdown and perihematomal edema.[16]

The systemic immune-inflammation index (SIRI) integrates neutrophilic inflammation, monocyte activation, and lymphocyte suppression, capturing the interplay between systemic and localized inflammatory responses. Elevated neutrophil and monocyte count in the early stages of ICH are critical in amplifying secondary brain injury through the release of proteases and free radicals, while lymphopenia reflects immune exhaustion, increasing susceptibility to infections such as sepsis.

A meta-analysis by Huang et al. (2023) demonstrated a robust association between elevated SIRI levels and adverse functional outcomes in stroke patients.[17] This study, which analyzed data from over 12,000 patients, highlighted SIRI's superior predictive ability compared to other inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR).

Similarly, Li et al. (2021) focused on spontaneous ICH patients, showing that higher admission SIRI values were independently associated with poor 3-month functional outcomes and increased 1-month mortality.[18] This finding underscores SIRI's utility in early risk stratification and its stronger predictive power compared to NLR. Furthermore, Wang et al. (2023) explored the relationship between SIRI and in-hospital infections among acute ICH patients.[19] Elevated SIRI levels were associated with a higher incidence of infections and unfavorable outcomes during hospitalization, emphasizing its role in identifying patients at increased risk of complications.

Research by Ma et al. (2023) evaluated SIRI alongside other inflammatory indices, such as the systemic immune-inflammation index (SII), in ischemic stroke patients15. This study highlighted the relative strengths of SIRI as a prognostic marker for long-term outcomes, further supporting its applicability across different stroke subtypes. Additional studies, such as those by Feola et al. (2023), have shown the prognostic value of SIRI in patients with minor ischemic strokes and in elderly patients with hypertension, further broadening the scope of SIRI's utility in stroke management.[20,21]

Collectively, these studies corroborate the findings of the current analysis, affirming that elevated SIRI is associated with higher stroke severity, increased mortality risk, and greater susceptibility to complications in critically ill ICH patients. The consistent evidence across diverse cohorts and settings highlights SIRI's potential as a valuable prognostic marker, aiding clinicians in tailoring interventions and improving patient management strategies.

While SIRI shows significant promise, its limitations must also be acknowledged. For instance, its predictive value for specific complications such as pneumonia remains limited, as indicated in the current study. Thus, while SIRI is a useful tool for overall prognosis, it should be used in conjunction with other clinical assessments and biomarkers to comprehensively evaluate patient risk profiles.

Despite its potential, several limitations persist. Many studies on SIRI are retrospective, introducing potential selection bias. Blood sample collection timing significantly impacts SIRI values, necessitating standardized protocols for accurate measurement. Furthermore, although elevated SIRI values are consistently associated with poor outcomes, universal cutoff values for clinical decision-making remain undefined. Future research should also explore the integration of SIRI with advanced imaging biomarkers, such as perihematomal edema volume and hematoma expansion, to enhance its predictive accuracy. Investigating the temporal dynamics of SIRI, including serial measurements during the disease course, could provide valuable insights into its evolving role in ICH pathophysiology and prognosis.

CONCLUSION

Systemic Inflammatory Response Index (SIRI) is a valuable predictor of outcomes in patients with spontaneous intracerebral hemorrhage (ICH). Elevated SIRI levels were strongly associated with

increased 30-day mortality and stroke severity. SIRI outperformed other inflammatory biomarkers such as NLR, PLR, and LMR in predicting mortality.

Clinical significance: SIRI represents a promising prognostic marker in ICH, offering insights into stroke severity and patient outcomes. Elevated SIRI levels were significantly associated with increased 30-day mortality, stroke severity and complications like sepsis, emphasizing its role in early risk stratification. This biomarker provides a comprehensive assessment of systemic inflammation by integrating neutrophil, monocyte and lymphocyte counts, offering improved predictions compared to its traditional counterparts such as NLR, PLR and LMR. Integrating SIRI into routine clinical practice, in conjunction with other assessments, could enhance prognostic accuracy and informed therapeutic decision-making. Prospective studies should aim to establish standardized thresholds and explore its utility in combination with other indices to optimize patient care.

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