

The Predictive Role of Systemic Inflammation Response Index (SIRI) in the Prognosis of Stroke Patients

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Purpose: Stroke is a disease associated with high mortality. Many 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 documented to predict stroke prognosis, their predictive power is limited. A novel inflammatory indicator called systemic inflammatory response index (SIRI) has been advocated to have an essential role in the prognostic assessment of cancer and infectious diseases. In this study, we attempted to assess the prognosis of stroke by SIRI. Moreover, we compared SIRI with other clinical parameters, including NLR, PLR, LMR and RDW.

Methods: This was a retrospective cohort study. We obtained data of 2450 stroke patients from the Multiparametric Intelligent Monitoring in Intensive Care III database. We used the Cox proportional hazards models to evaluate the relationship between SIRI and all-cause mortality and sepsis. Receiver operating curve (ROC) analysis was used to assess the predictive power of SIRI compared to NLR, PLR, LMR and RDW for the prognosis of stroke. We collected data of 180 patients from the First Affiliated Hospital of Wenzhou Medical University, which used the Pearson's correlation coefficient to assess the relationship between SIRI and the National Institute of Health stroke scale (NIHSS).

Results: After adjusting multiple covariates, we found that SIRI was associated with all-cause mortality in stroke patients. Rising SIRI accompanied by rising mortality. Besides, ROC analysis showed that the area under the curve of SIRI was significantly greater than for NLR, PLR, LMR and RDW. Besides, Pearson's correlation test confirmed a significant positive correlation between SIRI and NIHSS.

Conclusion: Elevated SIRI was associated with higher risk of mortality and sepsis and higher stroke severity. Therefore, SIRI is a promising low-grade inflammatory factor for predicting stroke prognosis that outperformed NLR, PLR, LMR, and RDW in predictive power.

Keywords: systemic inflammation response index, stroke, NIHSS, mortality

Introduction

Stroke is an acute cerebrovascular disease caused by the sudden rupture of vessels in the brain or the inability of blood to flow to the brain due to the occlusion of vessels.¹ Stroke is the second leading cause of death and a major contributor to disability in China.² It is characterized by high morbidity, mortality, and disability and greatly burdens society and families.³ Ischemic stroke is highly predominant, being one of the most important causes of neurological morbidity and mortality. It is multifactorial in origin and influenced by

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multiple genetic and environmental risk factors. No definite mechanism has been found so far.⁴⁻⁶

Inflammation is a major factor in the pathology and outcome of acute ischemic stroke.⁷ Inflammation can induce secondary brain injury by exacerbating blood-brain barrier damage, microvascular failure, brain edema, oxidative stress, and directly inducing neuronal cell death. Accordingly, inflammation is currently considered a prime target for developing new stroke therapies.⁵ Inflammatory biomarkers are expected to help predict mortality and functional outcomes in stroke patients.⁸ As inflammatory indicators, the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR) and red blood cell distribution width (RDW) have been reported to be predictive of stroke prognosis, but their formulations are relatively homogeneous and not comprehensive.^{9,10} It has been reported that the novel chronic low-grade inflammatory index systemic immunity-inflammation index (SIRI) has excellent predictive power in glioma,¹¹ breast cancer¹² and nasopharyngeal carcinoma;¹³ however, no studies have attempted to investigate its role in prediction in stroke prognosis.

SIRI is a more comprehensive marker for chronic low-grade inflammation based on monocyte, neutrophil, and lymphocyte counts.¹⁴ Neutrophils are the forerunners to brain lesions after ischemic stroke and perform elaborate functions. After the onset of stroke, the neutrophil composition of peripheral blood increases shortly, and higher neutrophil counts have been associated with unfavorable stroke outcomes.^{15,16} Peripheral monocytes infiltrate the lesion site within 24 hours after ischemic stroke, and traditionally, monocytes are thought to play a deleterious role in ischemic stroke.¹⁷ The role of lymphocytes in stroke is complicated; in some settings, T cells still seem to aggravate neuronal damage late after the ischemic insult, while regulatory B cells were beneficial in mouse models of stroke.^{18,19}

Interestingly, a recent study confirmed that SIRI was independently associated with ischemic stroke in patients with rheumatoid arthritis.²⁰ Therefore, we aimed to assess the prognostic impact of SIRI on the mortality and severity of stroke patients.

Materials and Methods

Data Acquisition

Data for the study were obtained from the publicly available Multiparametric Intelligent Monitoring in Intensive

Care III (MIMIC-III) database, version 1.4. MIMIC-III includes identifiable health data for >50,000 critically ill patients enrolled to Beth Israel Deaconess Medical Center (Boston, MA, USA) from 2001 to 2012.²¹ An Institutional Review Board endorsement was obtained from the Massachusetts Institute of Technology (Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (Boston, MA, USA). All personal information was deleted to preserve the privacy of the patients.

The inclusion criteria were as follows: 1. Patients who suffered from acute stroke; 2. Hospitalization in an intensive care unit (ICU); 3. Hospitalization of at least 48 hours; 4. Age 16 years or older. Patients with more than 20% of missing data were excluded.

In addition, we collected data of 180 patients from the First Affiliated Hospital of Wenzhou Medical University between August 2019 and August 2021 to analyze the correlation between SIRI and NIHSS. This retrospective cohort study was approved by the Ethics Committee in Clinical Research of the First Affiliated Hospital of Wenzhou Medical University (registration number: KY2021-R104). The data were anonymous, and thus, the requirement for informed consent was discarded. This study was conducted in accordance with the Declaration of Helsinki.

Study Variables and Outcomes

The data included age, gender, race, vital signs, laboratory characteristics, comorbidities and metric scores. Vital signs included heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate and temperature. Complications included acute atrial fibrillation, coronary artery disease (CAD), chronic liver disease, chronic obstructive pulmonary disease (COPD), respiratory failure, peripheral vascular disease, sepsis, diabetes mellitus (DM) and hypertension. Besides, laboratory data included neutrophil count, monocyte count, lymphocyte count, white blood cell (WBC) count, hemoglobin, platelet count, red blood cell volume distribution width (RDW), glucose, serum creatinine and blood urea nitrogen (BUN) collected for the first 24 hours in the ICU. Metrics included the National Institute of Health stroke scale (NIHSS), Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA). The primary outcomes were the 90-day all-cause mortality, correlation analysis of SIRI and NIHSS and comparative analysis of SIRI with NLR, PLR and LMR. The 30-day, one-year and in-

hospital all-cause mortality of stroke patients were secondary outcomes.

Statistical Analyses

The value of SIRI is continuous. Mean \pm SD was used to portray continuous variables, and categorical variables were presented as numbers and percentages. Multivariable cox regression and smooth curve fitting were used to analyze the independent effects of the SIRI levels and mortality in patients. The adjusted variables encompassed age, sex, ethnicity, systolic blood pressure, diastolic blood pressure, heart rate, glucose, anion gap, temperature, platelet counts, atrial fibrillation, liver disease, respiratory failure, serum creatinine, hemoglobin GCS, and SOFA. These confounders were selected since they have been documented to be associated with stroke prognosis, and had an estimated change in association with outcome of more than 10%. Receiver Operating Characteristic (ROC) curve analysis was applied to compare the predictive power of SIRI with NLR, PLR, LMR and RDW for mortality in stroke patients. The Pearson correlation method was used to analyze the correlation between SIRI and NIHSS; a p-value less than 0.05 was considered statistically significant. All statistical analyses were performed with R software 4.0.0 (<https://www.r-project.org/>).

Results

Demographic

2450 patients from the MIMIC-III database were enrolled in this study. They were classified into three levels based on SIRI values. Tables 1 and S1 demonstrate the features of these participants. As shown in Table 1, there were significant differences in heart rate, SBP, DBP, MAP, respiration rate, temperature, WBC, platelet, glucose, BUN, anion gap, respiratory failure, pneumonia SOFA and SAPS II, but no differences in atrial fibrillation, CAD and liver disease. Moreover, the all-cause mortality (in-hospital, 30-days, 90-days and one year) of stroke patients increased with SIRI.

Association Between SIRI and Clinical Outcomes

The smooth curve fit in Figure 1 visually illustrates that all-cause mortality at 30 days, 90 days and one year escalated significantly with increasing SIRI. The 90-day mortality was 21.9% (536/2450) (Table S1). Table 2 shows that a high SIRI was associated with the risk for 30-day, 90-day, one year and in-hospital all-cause mortality in stroke

patients. For model 1, for 90-day mortality, the HR (95% CI) for the second (1.6–3.8) and third (>3.8) tertiles were 1.21 (0.99, 1.48) and 1.80 (1.49, 2.18), respectively, compared to the first tertile (<1.6). For Model 2, which was adjusted for age, sex and ethnicity, the HR (95% CI) of 90-day mortality for the second (1.6–3.8) and third (>3.8) tertiles were 1.19 (0.97, 1.46) and 1.75 (1.45, 2.11) respectively, compared to the first tertile (<1.6).

A similar trend was found for model 3, after adjusting age, sex, ethnicity, systolic blood pressure, diastolic blood pressure, heart rate, glucose, anion gap, temperature, platelet counts, atrial fibrillation, liver disease, respiratory failure, serum creatinine, hemoglobin, GCS, and SOFA. The HR (95% CI) for the second (1.6–3.8) and third (>3.8) tertiles were 1.31 (1.04, 1.65) and 1.42 (1.13, 1.78) respectively, compared to the reference (<1.6). A similar trend was observed for the 30-day, one-year and in-hospital all-cause mortality.

We observed another similar result to the mortality. As seen in Table 3, higher SIRI values were associated with a higher incidence of sepsis. For model 1, the OR (95% CI) for the second (1.6–3.8) and third (>3.8) tertiles were 1.28 (1.03, 1.60) and 2.19 (1.77, 2.71), respectively, compared to the first tertile (<1.6). For Model 2, which was adjusted for age, sex and ethnicity, the OR (95% CI) for the second (1.6–3.8) and third (>3.8) tertiles were 1.32 (1.06, 1.65) and 2.26 (1.82, 2.81) respectively, compared to the first tertile (<1.6). For model 3, after adjusting systolic blood pressure, diastolic blood pressure, system inflammatory response syndrome, serum creatinine, hemoglobin, white blood cell count, platelet count, red cell volume distribution width, atrial fibrillation, coronary artery disease, chronic kidney disease, respiratory failure, pneumonia, GCS and SOFA. The OR (95% CI) for the second (1.6–3.8) and third (>3.8) tertiles were 1.20 (0.92, 1.57) and 1.45 (1.10, 1.91) respectively, compared to the first tertile (<1.6).

We performed a subgroup analysis and found that the results were stable (Table 4).

ROC Curve Analysis for 90-Day Mortality

ROC curves were plotted to assess the efficiency of SIRI and NLR, PLR, LMR and RDW in predicting mortality in stroke patients in Figure 2 and Table 5. We found that SIRI was more accurate than other biomarkers of inflammation including NLR, PLR, LMR and RDW (AUC 0.6216 vs

Table I Baseline Characteristics of the Study Population

Characteristics	SIRI			P value
	<1.6	1.6–3.8	>3.8	
Number of patients	817	816	817	
Age, years	67.6 ± 15.7	68.0 ± 16.1	68.9 ± 15.2	0.247
Sex, n (%)				<0.001
Female	440 (53.9)	375 (46.0)	354 (43.3)	
Male	377 (46.1)	441 (54.0)	463 (56.7)	
Ethnicity, n (%)				<0.001
Black	578 (70.7)	630 (77.2)	632 (77.4)	
White	100 (12.2)	49 (6.0)	40 (4.9)	
Other	139 (17.0)	137 (16.8)	145 (17.7)	
Vital signs				
Heart rate, beats/minute	78.4 ± 15.2	79.1 ± 14.5	84.2 ± 16.1	<0.001
SBP, mmHg	129.9 ± 17.6	130.5 ± 17.6	127.2 ± 18.3	<0.001
DBP, mmHg	63.3 ± 10.6	64.1 ± 11.7	62.8 ± 11.3	<0.001
MAP, mmHg	83.1 ± 11.1	83.6 ± 11.7	81.7 ± 11.9	<0.001
Respiratory rate, times/minute	18.0 ± 3.3	18.2 ± 3.6	19.4 ± 4.1	<0.001
Temperature, °C	36.8 ± 0.6	36.9 ± 0.6	37.0 ± 0.7	<0.001
SpO ₂ , %	97.6 ± 1.8	97.2 ± 3.1	97.4 ± 2.6	0.140
Laboratory parameters				
SIRI, 10 ⁹ /L	0.9 ± 0.4	2.6 ± 0.6	10.9 ± 14.2	<0.001
Neutrophil, %	67.9 ± 15.9	81.6 ± 8.0	85.9 ± 8.4	<0.001
Monocyte, %	4.0 ± 2.3	3.9 ± 2.0	4.6 ± 3.6	<0.001
Lymphocyte, %	23.8 ± 12.2	12.5 ± 4.9	7.1 ± 3.4	<0.001
White blood cell counts, 10 ⁹ /L	8.9 ± 11.1	11.0 ± 3.4	16.5 ± 13.9	<0.001
Platelet counts, 10 ⁹ /L	226.5 ± 103.7	243.9 ± 95.6	260.8 ± 123.1	<0.001
Glucose, mg/dL	138.7 ± 57.1	151.5 ± 65.6	163.8 ± 68.3	0.001
Blood urea nitrogen, mg/dl	22.1 ± 15.9	22.5 ± 16.0	27.3 ± 21.9	<0.001
Anion gap, mg/dl	15.0 ± 3.4	15.3 ± 3.3	16.3 ± 3.9	<0.001
Comorbidities, n (%)				
Atrial fibrillation	208 (25.5)	239 (29.3)	251 (30.7)	0.051
CAD	148 (18.1)	147 (18.0)	149 (18.2)	0.993
Liver disease [§]	21 (2.6)	16 (2.0)	26 (3.2)	0.296
Respiratory failure	168 (20.6)	219 (26.8)	297 (36.4)	<0.001
Pneumonia	123 (15.1)	177 (21.7)	253 (31.0)	<0.001
Scoring systems				
SOFA	3.4 ± 2.7	3.5 ± 2.6	4.4 ± 3.1	<0.001
SAPSII	34.8 ± 13.3	34.9 ± 13.0	41.0 ± 14.2	<0.001
GCS	12.9 ± 3.2	12.7 ± 3.3	12.3 ± 3.8	0.003
APSI	40.8 ± 19.7	40.2 ± 19.2	47.8 ± 22.6	
Clinical outcomes, n (%)				
30-day mortality	141 (17.3)	161 (19.7)	235 (28.8)	<0.001
90-day mortality	173 (21.2)	201 (24.6)	285 (34.9)	<0.001
One-year mortality	219 (26.8)	242 (29.7)	332 (40.6)	<0.001
In-hospital mortality	163 (20.0)	190 (23.3)	271 (33.2)	<0.001
Sepsis	193 (23.6)	232 (28.4)	330 (40.4)	<0.001

Notes: SIRI is calculated using the counts of peripheral venous blood neutrophils (N), monocytes (M), and lymphocytes (L) as follows: SIRI=N*M/L; Data were presented as the mean ± SD and n.

Abbreviations: SIRI, systemic inflammation response index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SpO₂, pulse oximetry-derived oxygen saturation; CAD, coronary artery disease; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; GCS, Glasgow Coma Scale; APSII, Antiphospholipid syndrome.

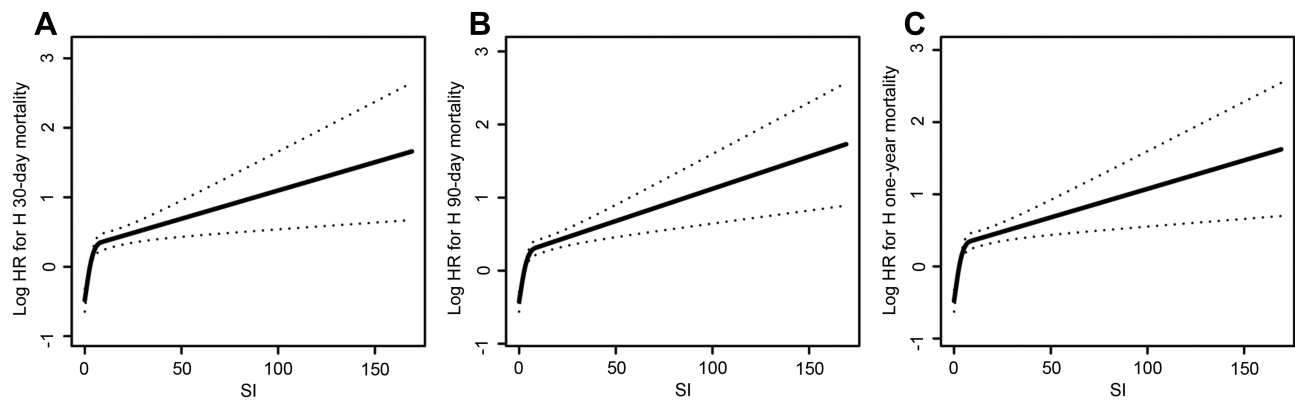


Figure 1 The relationship between systemic inflammatory response index (SIRI) and all-cause mortality. (A) 30-day mortality. (B) 90-day mortality. (C) one year mortality.

0.5349; 0.6216 vs 0.5628; 0.6216 vs 0.5579; 0.6216 vs 0.5865, respectively).

Association Between SIRI and NIHSS

The results of the Pearson correlation analysis in Figure 3 suggested that SIRI was significantly and positively correlated with NIHSS; the correlation coefficient was 0.3404 ($p < 0.001$).

Discussion

The results above indicate that high SIRI values were associated with all-cause mortality in stroke patients after adjusting for several confounding factors. As evidenced by the smooth curve fitting results. High SIRI values were also accompanied by significantly higher in-hospital mortality, 30-day, 90-day and one-year mortality in stroke patients. Considering that potential confounders, including comorbidities and clinical parameters, may also affect the main outcome, the subgroup analysis showed that our results were reliable. Simultaneously we observed that SIRI was strongly correlated with the occurrence of sepsis; the higher the SIRI, the more likely it was to occur. It is widely acknowledged that the higher the NIHSS score, the more severe the stroke. In our study, SIRI was positively correlated with NIHSS; it can be concluded that SIRI and stroke severity are positively correlated.

A growing number of studies have demonstrated the relevance of inflammation in the pathogenesis of stroke.^{22,23} Immune processes are usually activated by the ischemic cascade within minutes after stroke. Endovascular injury can trigger vascular occlusion and the chemotaxis of inflammatory cells into the brain parenchyma leading to tissue damage. Thus, inflammation plays a crucial role in stroke.²⁴ Inflammation in ischemic stroke involves releasing

cytokines, chemokines, and damage-associated molecular patterns that accentuate tissue destruction in the acute and repair stages of ischemic stroke. In addition, pro-inflammatory signals from immune mediators promptly activate permanent cells and affect the infiltration of various inflammatory cells (neutrophils, monocytes/macrophages, different subtypes of T cells and other inflammatory cells) into the ischemic zone intensifying the brain injury.²⁵ The above mechanisms explain why currently developed biological markers are based on various inflammatory parameters associated with stroke, such as neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR).²⁶ Studies have shown a positive correlation between NLR and the risk of death at three months in stroke patients;²⁷ an increase in PLR was predictive of the occurrence of post-stroke depression;²⁸ a low LMR was independently related to a higher risk of hemorrhagic transformation in stroke patients²⁹ and higher RDW could independently predict adverse outcomes in stroke patients.³⁰ Due to the simple structure, single indicators of inflammation are not sufficient to present the severity of inflammation. Consequently, new biomarkers have been designed by combining different subtypes of white blood cells.^{31,32}

In contrast, as a novel chronic low-grade inflammatory indicator, SIRI consists of more comprehensive, easily accessible and cheap parameters. SIRI has received much attention recently as its significant role in predicting patient outcomes has been documented in diseases such as cancer,³³ infectious diseases,³⁴ and cardiovascular disease.³⁵ However, to the best of our knowledge, no study has assessed the role of SIRI in predicting post-stroke mortality.

Studies have demonstrated that neutrophils are one of the first innate immune cells to respond to cerebral ischemia.⁴ Interestingly, neutrophils can aggravate inflammation in the

Table 2 Association Between SIRI and Clinical Outcomes of in Critically Ill Patients with Stroke

Clinical Outcomes	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Primary outcome						
90-day mortality ^a						
Continuous variable	1.01 (1.01, 1.02)	<0.0001	1.01 (1.01, 1.02)	<0.0001	1.01 (1.01, 1.02)	<0.0033
Tertile						
<1.6	1.0		1.0		1.0	
1.6–3.8	1.21 (0.99, 1.48)	0.0684	1.19 (0.97, 1.46)	0.0948	1.31 (1.04, 1.65)	0.0967
>3.8	1.80 (1.49, 2.18)	<0.0001	1.75 (1.45, 2.11)	<0.0001	1.42 (1.13, 1.78)	0.0128
P for trend		<0.0001		<0.0001		0.0238
Secondary outcomes						
30-day mortality						
Continuous variable	1.01 (1.01, 1.02)	<0.0001	1.01 (1.01, 1.02)	<0.0001	1.01 (1.01, 1.02)	<0.0033
Tertile						
<1.6	1.0		1.0		1.0	
1.6–3.8	1.19 (0.95, 1.49)	0.1368	1.17 (0.93, 1.47)	0.1721	1.16 (0.92, 1.47)	0.2162
>3.8	1.79 (1.46, 2.21)	<0.0001	1.73 (1.41, 2.14)	<0.0001	1.26 (1.00, 1.59)	0.0361
P for trend		<0.0001		<0.0001		0.0461
One-year mortality ^a						
Continuous variable	1.01 (1.01, 1.02)	<0.0001	1.01 (1.01, 1.02)	<0.0001	1.01 (1.00, 1.02)	0.0007
Tertile						
<1.6	1.0		1.0		1.0	
1.6–3.8	1.15 (0.96, 1.38)	0.1345	1.13 (0.94, 1.36)	0.0387	1.13 (0.93, 1.37)	0.2065
>3.8	1.69 (1.43, 2.01)	<0.0001	1.65 (1.39, 1.96)	<0.0001	1.28 (1.06, 1.54)	0.0108
P for trend		<0.0001		<0.0001		0.0128
In-hospital mortality						
Continuous variable	1.01 (1.01, 1.02)	<0.0001	1.01 (1.01, 1.02)	<0.0001	1.01 (1.00, 1.02)	0.0039
Tertile						
<1.6	1		1		1	
1.6–3.8	1.21 (0.98, 1.50)	0.0700	1.20 (0.97, 1.48)	0.0901	1.13 (0.90, 1.41)	0.0901
>3.8	1.86 (1.53, 2.26)	<0.0001	1.82 (1.50, 2.21)	<0.0001	1.26 (1.02, 1.57)	0.0330
P for trend		<0.0001		<0.0001		0.0379

Notes: ^aCox proportional hazards regression models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI). Model 1 covariates were adjusted for nothing. Model 2 covariates were adjusted for age, sex and ethnicity. Model 3 covariates were adjusted for age, sex, ethnicity, systolic blood pressure, diastolic blood pressure, heart rate, glucose, anion gap, temperature, platelet counts, atrial fibrillation, liver disease, respiratory failure, serum creatinine, hemoglobin GCS, SOFA.

Table 3 Association Between SIRI and Clinical Outcomes of Sepsis

Clinical Outcomes	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Continuous variable	1.04 (1.02, 1.05)	<0.0001	1.04 (1.02, 1.05)	<0.0001	1.02 (1.00, 1.03)	0.0085
Tertile						
<1.6	1.0		1.0		1.0	
1.6–3.8	1.28 (1.03, 1.60)	0.0270	1.32 (1.06, 1.65)	0.0145	1.20 (0.92, 1.57)	0.1822
>3.8	2.19 (1.77, 2.71)	<0.0001	2.26 (1.82, 2.81)	<0.0001	1.45 (1.10, 1.91)	0.0077
P for trend		<0.0001		<0.0001		0.0095

Notes: Logistic regression models were used to calculate odds ratios (OR) with 95% confidence intervals (CI). Model 1 covariates were adjusted for nothing. Model 2 covariates were adjusted for age, sex and ethnicity. Model 3 covariates were adjusted for systolic blood pressure, diastolic blood pressure, system inflammatory response syndrome, serum creatinine, hemoglobin, white blood cell count, platelet count, red cell volume distribution width, atrial fibrillation, coronary artery disease, chronic kidney disease, respiratory failure, pneumonia, GCS and SOFA.

Table 4 Subgroup Analysis of the Associations Between 90-Day All-Cause Mortality and the SIRI^a

	No. of Patients	HR (95% CI) ^b	P for Interaction
Age, years			0.2759
<70	1225	1.02 (1.01, 1.03)	
≥71	1225	1.01 (1.00, 1.02)	
Gender			0.8323
Male	1281	1.01 (1.01, 1.02)	
Female	1169	1.01 (1.01, 1.02)	
Ethnicity			0.7819
White	1840	1.01 (1.01, 1.02)	
Black	189	1.00 (0.95, 1.06)	
Other	421	1.02 (1.00, 1.03)	
MAP, mmHg			0.4585
<82	1222	1.01 (1.01, 1.02)	
≥83	1222	1.02 (1.01, 1.04)	
Heart rate, beats/minute			0.8849
<78	1222	1.02 (1.01, 1.02)	
≥79	1223	1.01 (1.00, 1.02)	
Respiratory rate, times/minute			0.8322
<18	1221	1.02 (1.01, 1.02)	
≥18	1222	1.01 (1.00, 1.02)	
Congestive hearts failure			0.2162
Yes	232	1.01 (0.98, 1.04)	
No	2218	1.01 (1.01, 1.02)	
Atrial fibrillation			0.2627
Yes	698	1.01 (1.00, 1.02)	
No	1752	1.02 (1.01, 1.02)	
Liver disease			0.7741
Yes	63	1.09 (1.05, 1.13)	
No	2387	1.01 (1.01, 1.02)	
Coronary artery disease			0.4418
Yes	444	1.01 (1.00, 1.02)	
No	2006	1.02 (1.01, 1.02)	
Pneumonia			0.1167
Yes	553	1.02 (1.01, 1.03)	
No	1897	1.01 (1.01, 1.02)	
Anion gap, mmol/l			0.0494
≤14	994	1.01 (1.01, 1.02)	
≥15	1447	1.02 (1.00, 1.03)	
Glucose, mg/dl			0.0952
≤133	1207	1.03 (1.02, 1.04)	
≥134	1241	1.01 (1.00, 1.02)	
Serum urea nitrogen, mg/dl			0.1809
≤18	1196	1.02 (1.01, 1.03)	
≥19	1253	1.01 (1.00, 1.02)	

(Continued)

Table 4 (Continued).

	No. of Patients	HR (95% CI) ^b	P for Interaction
Potassium, mmol/l			0.8999
≤3.9	1096	1.02 (1.01, 1.02)	
≥4.0	1354	1.01 (1.01, 1.02)	
Sodium, mmol/l			0.4633
≥138	1011	1.01 (1.01, 1.02)	
≥139	1438	1.02 (1.01, 1.02)	
APTT, second			0.8038
≤26.6	1193	1.02 (1.01, 1.03)	
>26.7	1217	1.01 (1.01, 1.02)	
INR			0.0214
≤1.0	578	1.02 (0.99, 1.05)	
≥1.1	1836	1.01 (1.01, 1.02)	
PT, second			0.6098
≤13.1	1140	1.02 (1.00, 1.04)	
≥13.2	1274	1.01 (1.01, 1.02)	
SAPSII			0.3413
≤34	1154	1.05 (1.02, 1.08)	
≥35	1296	1.01 (1.00, 1.01)	
APSI			0.1427
≤37	1189	1.03 (1.02, 1.05)	
≥38	1261	1.01 (1.00, 1.01)	

Notes: Cox proportional hazards regression models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI). ^aCox proportional hazards regression models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI). ^bcovariates were adjusted for age, sex and ethnicity.

brain parenchyma by liberating multiple pro-inflammatory mediators. The homeostasis of its damage is connected with

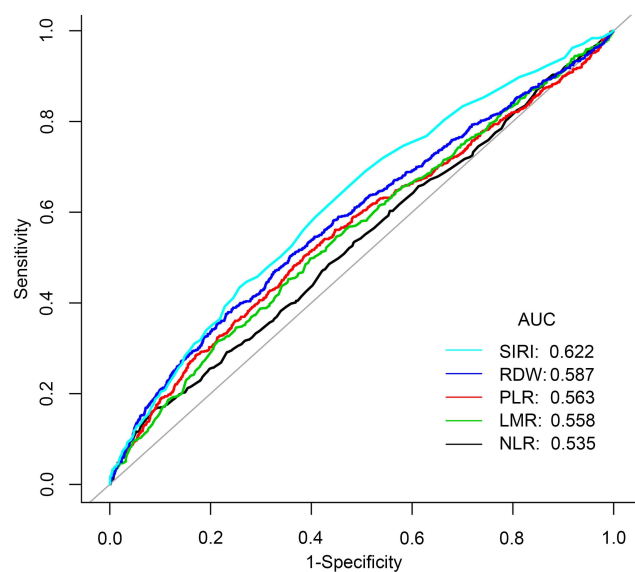


Figure 2 Receiver operating curve (ROC) for prediction in stroke patients using systemic inflammatory response index (SIRI). (AUC: SIRI: 0.622; RDW: 0.587; PLR: 0.563; LMR: 0.558; NLR: 0.535, separately).

stroke severity by influencing systemic inflammation and the blood-brain barrier (BBB).³⁶ Inflammatory reactions can cause secondary tissue injury in the brain,³⁷ and the adhesion of neutrophils to endothelial cells has been documented as the basis of inflammation.³⁸ Besides, other immune cells have been reported to play a significant role in ischemic stroke. For instance, cerebral ischemia and hypoxia can stimulate monocytes to generate inflammatory mediators, such as interleukins-6 (IL-6) and tumor necrosis factor (TNF), further worsening cerebral ischemia and hypoxia, leading to more extensive brain tissue destruction.³⁹ Alternatively, monocytes can activate platelets to become platelet-monocyte aggregates (PMA), facilitating the liberation of an inflammatory response, adhesion, and vasoactive substances. The PMA can also promote thrombosis and vascular occlusion, causing hemodynamic changes and exacerbating the cerebral ischemic injury.⁴⁰ Another study suggested that microglia exhaustion could intensify neuroinflammation in the brain after ischemia. Studies showed that microglia depletion enhanced leukocyte infiltration, neuronal death and inflammatory mediator release as well as enlarged

Table 5 Receiver Operating Curve (ROC) for Prediction in Stroke Patients

	ROC Area (AUC)	95% CI Low	95% CI Upp
NLR	0.5349	0.5102	0.5598
PLR	0.5628	0.5378	0.5879
LMR	0.5579	0.5332	0.5825
RDW	0.5865	0.5618	0.6113
SIRI	0.6216	0.5979	0.6453

Abbreviations: AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte to monocyte ratio; RDW, red blood cell distribution width; SIRI, systemic inflammation response index.

brain infarct size in stroke patients.⁴¹ Microglia are more likely to release cytotoxic factors in a severe ischemic environment compared to a mild ischemic environment.⁴² Apart from it, lymphocytes can coordinate the inflammatory response. However, explaining the role of lymphocytes in stroke is complicated due to the huge diversity of lymphocytes.⁴³ T lymphocytes have been found to play both beneficial and detrimental roles in stroke. Natural killer (NK) cells exacerbate brain damage by catalyzing neuronal death.⁴⁴ In contrast, T regulatory cells (Tregs) are generally involved in suppressing inflammation and regulating and maintaining homeostasis and immune tolerance in the periphery. Furthermore, Tregs secreting the cytokine IL-10 demonstrate protection from stroke. Studies indicated that animals with increased numbers of post-stroke Tregs exhibited better outcomes post-stroke.⁴⁵

In the present study, we found that SIRI was positively correlated with NIHSS. Since NIHSS is commonly used in clinical practice to assess the severity of a stroke, we can conclude that SIRI was closely related to stroke severity. To the best of our knowledge, no studies have previously

documented the role of SIRI in stroke prognosis. Accordingly, there is great potential to use SIRI as a predictor of stroke prognosis.

There were many limitations in this study. First, subjects in this study were from only one region, which may have caused selection bias or geographically biased results; the next step will be conducting a multi-center study. Moreover, the number of covariates related to stroke prognosis was extremely large and was inadequately collected in our study. More data on other parameters is essential to improve the robustness of our results. Finally, the sample size of our study was relatively small; greater sample sizes are necessary to substantiate our findings.

Conclusions

We delivered the first study demonstrating that SIRI is strongly correlated with stroke mortality and severity and the risk of sepsis. The higher the SIRI value, the worse the stroke prognosis. Furthermore, SIRI exhibited better ability in predicting stroke prognosis than NLR, PLR, LMR and RDW. Accordingly, SIRI may be a new promising low-grade inflammatory indicator for predicting the prognosis of stroke.

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Disclosure

The authors report no conflicts of interest in this work.

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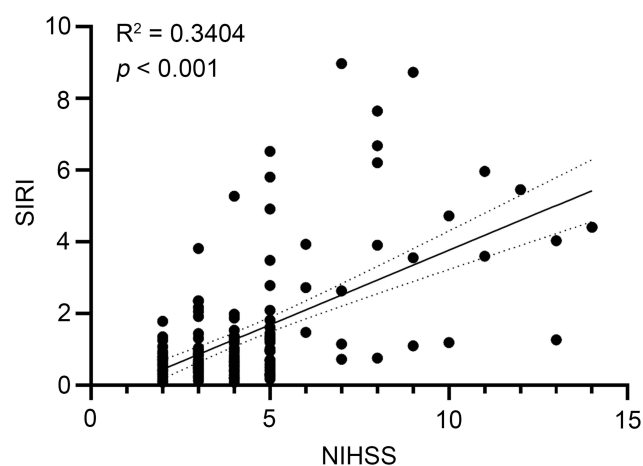


Figure 3 Pearson's correlation test to analyze the relationship between systemic inflammatory response index (SIRI) and National Institute of Health stroke scale (NIHSS). ($R^2 = 0.3404$, $p < 0.001$).

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