


Association of the Systemic Inflammation Response Index with Functional Outcome in Acute Large Vessel Occlusion Stroke Patients Receiving Mechanical Thrombectomy

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Purpose: The systemic inflammation response index (SIRI) has recently emerged as a novel inflammatory and prognostic marker across various diseases. However, there is limited research examining the relationship between SIRI and 90-day functional outcome in patients with acute large vessel occlusion stroke (ALVOS) undergoing mechanical thrombectomy (MT). This study aimed to investigate the potential of SIRI as an innovative, inflammation-based predictor of 90-day functional outcome.

Methods: This retrospective cohort study consecutively recruited 604 Chinese patients with diagnosed ALVOS who underwent MT at the First College of Clinical Medical Science of China Three Gorges University between July 2017 and April 2023. Comprehensive data, including baseline demographic and clinical characteristics, were systematically extracted from electronic medical records. Poor functional outcome at 90 days was defined as modified Rankin Scale (mRS) score ≥ 3 . We employed logistic regression models, curve fitting, sensitivity analyses, subgroup analyses, and receiver operating characteristic (ROC) curves to validate the association between SIRI and poor outcome, as well as to assess the predictive efficacy.

Results: Final analysis included 604 ALVOS subjects of whom 54.3% experienced poor functional outcome at 90 days. In the multivariate analysis, after adjusting for potential confounders, SIRI remained significantly associated with an elevated risk of poor outcomes (OR 1.18, 95% CI 1.08–1.28, $P < 0.001$). Nonlinear curve fitting revealed a reverse J-shaped association between SIRI and poor outcomes, with inflection points at 4.5. Subgroup analyses showed no significant interactions (all P for interaction > 0.05), However, atrial fibrillation demonstrated a significant interaction (all P for interaction = 0.001).

Conclusion: SIRI shows promise as a novel prognostic marker for 90-day functional outcome in patients with ALVOS undergoing MT. The identified nonlinear relationship and inflection point may provide valuable insights for risk stratification and clinical decision-making in this specific patient population.

Keywords: systemic inflammation response index (SIRI), acute large vessel occlusion stroke (ALVOS), functional outcome, mechanical thrombectomy (MT)

Introduction

Ischemic stroke, accounting for approximately 70% of all stroke cases, remains a leading cause of disability and mortality worldwide.¹ The standard treatment for acute ischemic stroke (AIS) patients with large vessel occlusion (LVO) has evolved to include endovascular thrombectomy (EVT), often preceded by intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA).^{1,2} Despite advancements in treatment modalities, studies indicate that nearly half of these patients experience futile recanalization, a frequent occurrence following mechanical thrombectomy (MT).^{3–6}

Futile recanalization is defined as poor functional independence (modified Rankin scale score of >2 at 3 months) or treatment failure despite successful angiographic recanalization after endovascular intervention.^{3,7} The etiology of this

phenomenon is multifactorial, potentially involving blood-brain barrier dysfunction, capillary damage, impaired cerebral autoregulation, inadequate collateral circulation, and the development of secondary brain injuries such as cerebral edema, subacute re-occlusion, infarct expansion, and hemorrhagic transformation.^{4,8} However, the precise mechanisms underlying these complications remain incompletely elucidated.

Accumulating evidence suggests that immune and inflammatory responses play pivotal roles in stroke pathobiology. Inflammatory signaling is involved throughout the ischemic cascade, from early damaging events triggered by arterial occlusion to late regenerative processes underlying post-ischemic remodeling and tissue repair.⁵ The immune system contributes to ischemia-induced brain damage, while the damaged brain, in turn, exerts an immunosuppressive effect that promotes potentially fatal infections, thereby threatening post-stroke survival.⁶

Recent investigations have identified novel biomarkers for predicting stroke severity and poor prognosis in both ischemic and hemorrhagic stroke, including the neutrophil-to-lymphocyte ratio (NLR)^{9,10} and the monocyte-to-lymphocyte ratio (MLR).^{11,12} The systemic inflammatory response index (SIRI), which incorporates both NLR and MLR using neutrophil, monocyte, and lymphocyte counts, has emerged as a readily available and cost-effective measure of inflammatory status and immune pathway activity. While SIRI has been extensively studied as a prognostic indicator in oncology, evidence regarding its relationship with functional outcome in stroke patients is limited. Recent studies have explored SIRI in various stroke subtypes, including aneurysmal subarachnoid hemorrhage,^{13,14} intracerebral hemorrhage,¹⁵ and ischemic stroke^{16,17} with recanalization therapy.¹⁸

However, the prognostic value of SIRI in acute large vessel occlusion stroke (ALVOS) patients undergoing successful mechanical thrombectomy remains understudied, particularly in Chinese populations. We hypothesized that SIRI could serve as a reliable predictor of functional outcome in these patients. This study aimed to investigate the association between admission SIRI and functional outcome in Chinese ALVOS patients following successful MT recanalization.

Materials and Methods

Study Design

In this observational, retrospective study, we recruited stroke patients consecutively treated with mechanical thrombectomy at the Comprehensive Stroke Center (CSC) in Yichang Central People's Hospital, between July 2017 and April 2023. The study protocol was reviewed and approved by the Hospital of Medicine Ethics Committee (ethical approval number: 2023–129-01) and conducted in accordance with the Declaration of Helsinki.

Inclusion and Exclusion Criteria

This retrospective analysis utilized data from a prospectively maintained database at our CSC, encompassing patients admitted between July 2017 and April 2023. We included consecutive patients who presented with acute neurological deficits and were diagnosed with acute ischemic stroke (AIS) using a “one-stop-shop” multimodal CT examination within 24 hours of symptom onset.

The inclusion criteria were as follows: (1) Acute intracranial large vessel occlusion (ALVO) confirmed by computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or digital subtraction angiography within 24 hours of symptom onset; (2) Treatment with acute recanalization therapy, either EVT alone or in combination with IVT; (3) Achievement of complete or near-complete recanalization following reperfusion therapy.

Exclusion criteria: (1) without obvious LVO at baseline CTA; (2) Severe hepatic or renal disease; (3) Active malignancy, hematologic disorders, or immunosuppressed status; (4) Presence of infectious disease at admission; (5) Incomplete admission laboratory data; (6) Pre-stroke modified Rankin scale (mRS) score ≥ 2 and (7) Loss to follow-up at 90 days post-intervention. [Figure 1](#) illustrates the patient selection process and study flow diagram.

EVT consisted of mechanical thrombectomy with aspiration catheters alone, stent-retrievers alone, or both, depending on occlusion type/location and neuro-interventionist's choice. Revascularization was assessed by applying the modified thrombolysis in cerebral infarction (mTICI) classification.¹⁹ Successful recanalization was defined as grade 2b, 2c, or 3 of reperfusion. According to the 2018/2019 American Guidelines for Early Management of AIS,²⁰ patients were treated using IVT or/and MT or stent implantation, while patients with thrombolysis contraindication or unsuitable for EVT were treated using general supportive treatment.

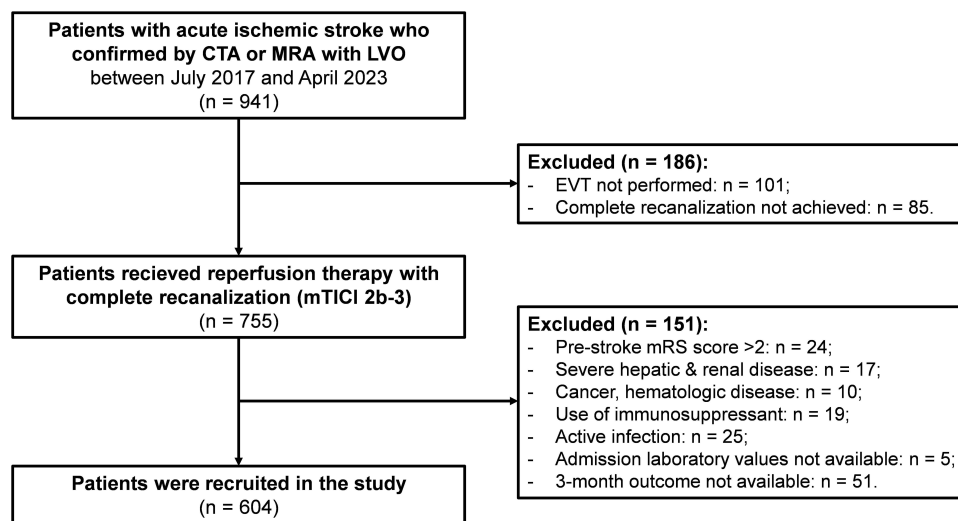


Figure 1 Flowchart of patient selection.

Abbreviations: CTA, computed tomographic angiography; MRA, magnetic resonance angiography; LVO, large vessel occlusion; EVT, endovascular thrombectomy; mTICI, modified thrombolysis in cerebral infarction; mRS, modified Rankin scale.

Baseline Characteristics and Data Collection

We extracted baseline demographic, clinical characteristics and pre-admission treatments, from our prospectively maintained stroke registry database. The following data were collected: (1) Demographics (age and sex); (2) Medical history of current stroke risk factors (smoking status, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, coronary artery disease); (3) Clinical and Imaging Parameters (Time from last known well (TFLKW) to CT examination, baseline the National Institutes of Health Stroke Scale (NIHSS) score on admission,²¹ Pre-stroke modified Rankin Scale (mRS) score and Alberta Stroke Program Early CT Score (ASPECTS) to determine the extent of initial core infarct on pre-therapeutic CT.²² (4) Laboratory Parameters (hemoglobin, white blood cell count, neutrophil count, monocyte count, platelet count, lymphocyte count, serum creatinine and blood pressure). All blood samples were collected upon arrival at neurocritical care unit after thrombectomy. Laboratory tests were performed using standardized methods in our hospital's central laboratory. The inflammatory indices were calculated as follows: NLR = neutrophil count / Absolute lymphocyte count; MLR = monocyte count / lymphocyte count; PLR = platelet count / lymphocyte count; Systemic Immune Inflammation Index (SII) = NLR × platelet count; System Inflammation Response Index (SIRI) = (Neutrophil count × Monocyte count) / Lymphocyte count.

Outcome Parameters

The primary outcome was neurological functional status at 90 days post-intervention, assessed using the modified Rankin Scale (mRS). Functional independence was evaluated through either telemedicine consultation or in-person assessment at our CSC. All assessments were conducted by trained neurologists who were blinded to the patients' SIRI values and other clinical data not essential for mRS scoring. Outcomes were categorized as follows: Poor functional outcome: mRS score ≥ 3 ; good functional outcome: mRS score 0–2.

The secondary outcome was the occurrence of early neurological deterioration (END),^{23,24} within the first week of admission. END was defined as any new neurologic symptoms/signs or neurologic worsening meeting one or more of the following criteria: (1) an increase of ≥ 2 points in total NIHSS score, (2) an increase of ≥ 1 point in the motor NIHSS score, and/or (3) an increase of ≥ 1 point in the consciousness score.^{25,26}

Statistical Analysis

The continuous variables were presented as mean \pm standard deviation (SD) for normally distributed data or median with interquartile range (IQR) for non-normally distributed data. Categorical variables were summarized as frequencies and percentages. Shapiro–Wilk and Kolmogorov–Smirnov tests were used to assess normality of continuous variables. Levene's test was employed to evaluate variance homogeneity. The Chi-square test (categorical variables), the one-way ANOVA

(normal distributed variables), or the Kruskal–Wallis *H*-test (skewed distributed variables) was used to test the differences between SIRI groups. The relationship between SIRI and poor functional outcome was examined using univariate and multivariable logistic regression analyses. Results are reported as odds ratios (OR) with 95% confidence intervals (CI).

Four progressive models were employed: Non-adjusted Model, without adjust any variables. Model 1 was adjusted for age, sex; Model 2 was adjusted for model 1 plus smoking status, hypertension, diabetes mellitus, coronary artery disease, hyperlipemia, atrial fibrillation, temperature, systolic BP and diastolic BP on admission; Model 3 was adjusted for variables in model 2 as well as time from last known well to reperfusion, baseline NIHSS score, ASPECTS, AIS location, Stroke subtypes, TOAST classification, CRP, albumin and recanalization therapy.

In addition, Smooth curve fitting, adjusted for Model 3 covariates, was used to visualize the relationship between SIRI and poor outcome. A two-piecewise binary logistic regression model further explored observed nonlinearity.

Furthermore, to identify modifications and interactions, we used a stratified linear regression model and likelihood ratio test (LRT) in subgroups of age (<65 and ≥65 years), sex (female and male), diabetes, atrial fibrillation, acute ischemic stroke location (anterior and posterior circulation), stroke subtypes (non-cardioembolic and cardioembolic), recanalization therapy (MT alone and MT combined with IVT), CRP (<5 mg/L and ≥5 mg/L), and NIHSS (<16 score and ≥16 score). Multiple imputation was used to handle missing data.²⁷

All the analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation) and Free Statistics software versions 1.9. A two-tailed test was performed and $P < 0.05$ was considered statistically significant.

Results

Baseline Clinical Characteristics

A total of 604 patients with MT for ALVOS achieved successful recanalization were enrolled in this study. Among them, 328 patients (54.3%) experienced poor functional outcome, defined as mRS ≥ 3 at 3 months. Baseline characteristics based on functional outcome are summarized in Table 1. There were no statistically significant differences between the good and poor outcome groups regarding in age, sex, current smoking status, history of hypertension, diabetes mellitus, atrial fibrillation, admission temperature, systolic BP, diastolic BP, CRP, albumin, ASPECTS, AIS location, stroke subtypes, time from last known well to reperfusion, or white blood cells (all $P > 0.05$). Conversely, significant differences were observed between the groups in terms of coronary artery disease, hyperlipemia, baseline NIHSS, location of intracranial vessel occlusion, recanalization therapy, lymphocytes, neutrophils, monocytes, NLR, MLR, PLR, SII, as well as SIRI ($P < 0.05$). Baseline demographic characteristics and clinical data of the included patients according to SIRI tertiles are presented in Table 2. Patients in the highest SIRI tertile (T3) exhibited higher baseline NIHSS, elevated white blood cells, neutrophils, and monocytes, increased NLR, PLR, SII, and a greater prevalence of early neurological deterioration (END) and posterior

Table 1 Baseline Characteristics and Comparison of Clinical Variables Stratified by Functional Outcome

Characteristics	Total (n = 604)	Good Outcome mRS < 3 (n = 276)	Poor Outcome mRS ≥ 3 (n = 328)	p-value
Demographics				
Age (year)	69.0 (61.8, 78.0)	69.0 (61.8, 77.0)	70.0 (61.8, 78.2)	0.214
Male	330 (54.6)	142 (51.4)	188 (57.3)	0.149
Vascular risk factors				
Smoking				0.938
Never	467 (77.3)	213 (77.2)	254 (77.4)	
Former and Current	137 (22.7)	63 (22.8)	74 (22.6)	

(Continued)

Table 1 (Continued).

Characteristics	Total (n = 604)	Good Outcome mRS < 3 (n = 276)	Poor Outcome mRS ≥ 3 (n = 328)	p-value
Hypertension	224 (37.1)	104 (37.7)	120 (36.6)	0.781
Diabetes mellitus	93 (15.4)	36 (13)	57 (17.4)	0.141
Coronary artery disease	138 (22.8)	52 (18.8)	86 (26.2)	0.031
Hyperlipemia	130 (21.5)	41 (14.9)	89 (27.1)	< 0.001
Atrial fibrillation	281 (46.5)	120 (43.5)	161 (49.1)	0.169
Clinical features				
Time of Last known well to reperfusion				0.813
≤6h	564 (93.4)	257 (93.1)	307 (93.6)	
>6h	40 (6.6)	19 (6.9)	21 (6.4)	
Baseline NIHSS (score)	15.0 (12.0, 18.0)	14.0 (10.0, 17.0)	16.0 (13.0, 20.0)	< 0.001
Temperature (degree C)	36.6 (36.4, 36.8)	36.5 (36.4, 36.8)	36.6 (36.5, 36.8)	0.379
Systolic BP (mmHg)	136.0 (114.8, 157.0)	134.0 (114.0, 156.2)	137.5 (115.0, 157.0)	0.557
Diastolic BP (mmHg)	70.0 (59.0, 80.0)	71.0 (59.8, 80.0)	69.5 (59.0, 79.0)	0.518
Imaging features				
ASPECTS (score)	8.0 (8.0, 9.0)	8.0 (8.0, 9.0)	8.0 (7.0, 9.0)	0.079
AIS Location				0.833
Anterior circulation	499 (82.6)	229 (83)	270 (82.3)	
Posterior circulation	105 (17.4)	47 (17)	58 (17.7)	
Location of intracranial vessel occlusion				0.043
Internal carotid artery	128 (21.2)	46 (16.7)	82 (25)	
Middle cerebral artery	323 (53.5)	152 (55.1)	171 (52.1)	
Anterior cerebral artery	48 (7.9)	31 (11.2)	17 (5.2)	
VA and/or BA	105 (17.4)	47 (17)	58 (17.7)	
Stroke subtypes				0.071
Cardioembolic	337 (55.8)	143 (51.8)	194 (59.1)	
Non-Cardioembolic	267 (44.2)	133 (48.2)	134 (40.9)	
Recanalization therapy				0.008
MT	172 (28.5)	64 (23.2)	108 (32.9)	
IVT+MT	432 (71.5)	212 (76.8)	220 (67.1)	

(Continued)

Table 1 (Continued).

Characteristics	Total (n = 604)	Good Outcome mRS < 3 (n = 276)	Poor Outcome mRS ≥ 3 (n = 328)	p-value
Laboratory findings				
CRP (mg/L)	4.2 (1.5, 9.5)	3.7 (1.5, 8.3)	5.0 (1.3, 10.1)	0.429
Albumin (g/L)	37.8 (33.3, 41.0)	37.8 (34.0, 41.0)	37.8 (32.7, 41.0)	0.165
White blood cells (×10 ⁹ /L)	9.2 (6.8, 13.3)	9.1 (6.5, 12.7)	9.2 (7.1, 13.9)	0.298
Lymphocytes (×10 ⁹ /L)	1.4 (0.9, 1.9)	1.5 (0.9, 2.2)	1.2 (0.8, 1.8)	< 0.001
Neutrophils (×10 ⁹ /L)	6.9 (5.1, 11.0)	6.7 (4.7, 10.2)	7.1 (5.4, 11.7)	0.025
Platelets (×10 ⁹ /L)	207.0 (185.8, 250.0)	203.0 (184.0, 241.2)	210.5 (188.0, 254.0)	0.051
Monocytes (×10 ⁹ /L)	0.6 (0.4, 0.8)	0.5 (0.4, 0.8)	0.6 (0.5, 0.9)	0.002
NLR	6.0 (4.0, 9.1)	5.1 (3.3, 8.4)	6.6 (4.7, 9.7)	< 0.001
MLR	0.4 (0.3, 0.8)	0.4 (0.2, 0.7)	0.5 (0.4, 0.8)	< 0.001
PLR	161.6 (103.2, 269.5)	135.9 (84.5, 240.2)	177.6 (120.6, 288.9)	< 0.001
SII (×10 ⁹ /L)	1291.0 (849.1, 1982.6)	1062.4 (649.2, 1730.8)	1451.6 (1000.8, 2094.2)	< 0.001
SIRI (×10 ⁹ /L)	3.6 (2.5, 5.0)	2.9 (2.0, 4.3)	4.1 (3.0, 5.4)	< 0.001
Clinical outcomes				
mRS (score)	3.0 (2.0, 4.0)	2.0 (1.0, 2.0)	4.0 (3.0, 5.0)	< 0.001
END	190 (31.5)	47 (17)	143 (43.6)	< 0.001

Notes: Values are expressed as mean ± SD or median (IQR) for continuous variables and percentage for categorical variables.

Abbreviations: AIS, acute ischemia stroke; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; BA, basilar artery; BP, blood pressure; END, early neurological deterioration; MT, mechanical thrombectomy; CRP, C reactive protein; IQR, interquartile range; IVT, intravenous thrombolysis; MLR, monocyte-to-lymphocyte ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NLR, Neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SD, standard deviation; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; VA, vertebral artery.

Table 2 Baseline Characteristics and Comparison of Clinical Variables Stratified by the SIRI Tertile

Characteristics	(n = 604) Total	T1 (n = 201) SIRI: <2.78	T2 (n = 201) SIRI: 2.79–4.46	T3 (n = 202) SIRI: >4.47	p-value
Demographics					
Age (year)	68.0 (61.0, 76.0)	66.0 (59.0, 72.0)	67.0 (61.0, 74.0)	70.0 (64.0, 78.0)	< 0.001
Male	330 (54.6)	104 (51.7)	106 (52.7)	120 (59.4)	0.243
Vascular risk factors					
Smoking					0.141
Never	467 (77.3)	151 (75.1)	165 (82.1)	151 (74.8)	
Former and Current	137 (22.7)	50 (24.9)	36 (17.9)	51 (25.2)	

(Continued)

Table 2 (Continued).

Characteristics	(n = 604) Total	T1 (n = 201) SIRI: <2.78	T2 (n = 201) SIRI: 2.79–4.46	T3 (n = 202) SIRI: >4.47	p-value
Hypertension	224 (37.1)	70 (34.8)	82 (40.8)	72 (35.6)	0.405
Diabetes mellitus	93 (15.4)	23 (11.4)	31 (15.4)	39 (19.3)	0.091
Coronary artery disease	138 (22.8)	44 (21.9)	55 (27.4)	39 (19.3)	0.145
Hyperlipemia	130 (21.5)	33 (16.4)	46 (22.9)	51 (25.2)	0.083
Atrial fibrillation	281 (46.5)	99 (49.3)	98 (48.8)	84 (41.6)	0.225
Clinical features					
Time of Last known well to reperfusion					0.088
≤6h	564 (93.4)	194 (96.5)	184 (91.5)	186 (92.1)	
>6h	40 (6.6)	7 (3.5)	17 (8.5)	16 (7.9)	
Baseline NIHSS (score)	15.0 (12.0, 18.0)	13.0 (10.0, 16.0)	15.0 (12.0, 18.0)	16.0 (13.0, 21.0)	< 0.001
Temperature (degree C)	36.7 ± 0.5	36.7 ± 0.5	36.7 ± 0.5	36.7 ± 0.5	0.345
Systolic BP (mmHg)	135.2 ± 25.8	134.9 ± 25.8	134.7 ± 25.3	136.0 ± 26.3	0.848
Diastolic BP (mmHg)	69.3 ± 11.8	69.0 ± 12.3	69.8 ± 11.9	69.1 ± 11.3	0.776
Imaging features					
ASPECTS (score)	8.0 (8.0, 9.0)	9.0 (8.0, 9.0)	8.0 (7.0, 9.0)	8.0 (7.0, 9.0)	< 0.001
AIS Location					0.044
Anterior circulation	499 (82.6)	177 (88.1)	161 (80.1)	161 (79.7)	
Posterior circulation	105 (17.4)	24 (11.9)	40 (19.9)	41 (20.3)	
Location of intracranial vessel occlusion					< 0.001
Internal carotid artery	128 (21.2)	27 (13.4)	49 (24.4)	52 (25.7)	
Middle cerebral artery	323 (53.5)	127 (63.2)	97 (48.3)	99 (49)	
Anterior cerebral artery	48 (7.9)	23 (11.4)	15 (7.5)	10 (5)	
VA and/or BA	105 (17.4)	24 (11.9)	40 (19.9)	41 (20.3)	
Stroke subtypes					0.063
Cardioembolic	337 (55.8)	99 (49.3)	116 (57.7)	122 (60.4)	
Non-Cardioembolic	267 (44.2)	102 (50.7)	85 (42.3)	80 (39.6)	
Recanalization therapy					0.034
MT	172 (28.5)	49 (24.4)	52 (25.9)	71 (35.1)	
IVT+MT	432 (71.5)	152 (75.6)	149 (74.1)	131 (64.9)	
Laboratory findings					
CRP (mg/L)	4.2 (1.5, 9.5)	3.4 (1.5, 7.8)	5.3 (1.5, 10.3)	5.0 (1.2, 10.2)	0.331
Albumin (g/L)	37.8 (33.3, 41.0)	37.8 (33.3, 41.6)	37.8 (33.3, 38.8)	37.8 (33.1, 41.1)	0.173
White blood cells (×10 ⁹ /L)	9.2 (6.8, 13.3)	9.1 (6.4, 11.3)	9.8 (7.6, 14.5)	8.9 (6.9, 15.4)	0.031
Lymphocytes (×10 ⁹ /L)	1.4 (0.9, 1.9)	1.8 (1.4, 2.4)	1.4 (0.9, 1.9)	0.9 (0.6, 1.4)	< 0.001

(Continued)

Table 2 (Continued).

Characteristics	(n = 604) Total	T1 (n = 201) SIRI: <2.78	T2 (n = 201) SIRI: 2.79–4.46	T3 (n = 202) SIRI: >4.47	p-value
Neutrophils ($\times 10^9/L$)	6.9 (5.1, 11.0)	6.3 (4.3, 8.3)	7.4 (5.6, 11.4)	7.0 (5.5, 13.0)	< 0.001
Platelets ($\times 10^9/L$)	207.0 (185.8, 250.0)	202.0 (184.0, 235.0)	220.0 (194.0, 257.0)	203.5 (179.2, 245.0)	0.003
Monocyte ($\times 10^9/L$)	0.6 (0.4, 0.8)	0.5 (0.4, 0.7)	0.6 (0.4, 0.8)	0.7 (0.5, 1.0)	< 0.001
NLR	6.0 (4.0, 9.1)	3.6 (2.7, 5.0)	6.3 (4.5, 8.6)	9.5 (6.9, 12.5)	< 0.001
MLR	0.4 (0.3, 0.8)	0.3 (0.2, 0.4)	0.5 (0.3, 0.6)	0.8 (0.5, 1.3)	< 0.001
PLR	161.6 (103.2, 269.5)	117.6 (79.4, 176.4)	163.6 (105.9, 261.4)	224.3 (141.8, 347.6)	< 0.001
SII	1291.0 (849.1, 1982.6)	767.4 (527.2, 1091.4)	1395.0 (990.2, 1965.5)	1955.7 (1424.4, 2508.2)	< 0.001
SIRI	3.6 (2.5, 5.0)	2.0 (1.6, 2.4)	3.6 (3.2, 4.0)	5.7 (5.0, 8.3)	< 0.001
Clinical outcomes					
mRS (score)	3.0 (2.0, 4.0)	2.0 (1.0, 3.0)	3.0 (2.0, 4.0)	4.0 (2.0, 5.0)	< 0.001
mRS					< 0.001
<3 good outcome	276 (45.7)	134 (66.7)	78 (38.8)	64 (31.7)	
≥ 3 poor outcome	328 (54.3)	67 (33.3)	123 (61.2)	138 (68.3)	
END	190 (31.5)	37 (18.4)	56 (27.9)	97 (48)	< 0.001

Notes: Values are expressed as mean \pm SD or median (IQR) for continuous variables and percentage for categorical variables.

Abbreviations: AIS, acute ischemia stroke; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; BA, basilar artery; BP, blood pressure; END, early neurological deterioration; MT, mechanical thrombectomy; CRP, C reactive protein; IQR, interquartile range; IVT, intravenous thrombolysis; MLR, monocyte-to-lymphocyte ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NLR, Neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SD, standard deviation; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; VA, vertebral artery.

circulation stroke compared to lower tertiles. Conversely, they had lower lymphocyte counts, ASPECTS scores, and a lower proportion of combined intravenous thrombolysis and mechanical thrombectomy (IVT + MT) for recanalization therapy. No significant differences were found among SIRI tertiles for age, sex, current smoking status, history of hypertension, diabetes mellitus, history of stroke, coronary artery disease, hyperlipemia, atrial fibrillation, admission temperature, systolic BP, diastolic BP, CRP, albumin, and time from last known well to reperfusion (all $P > 0.05$).

Univariate and Multivariate Logistic Regression Analyses of SIRI and Poor Functional Outcome

According to univariate analysis, baseline NIHSS score, monocytes, END, history of coronary artery disease, diabetes mellitus, hyperlipemia, lymphocytes, non-cardioembolic stroke, and elevated SIRI were correlated with poor outcome ($P < 0.1$; details in [Table S1](#)).

We constructed multivariate logistic regression analysis with models to evaluate the independent effects of SIRI on the presence of 90-day poor functional outcome ([Table 3](#)). When SIRI was evaluated as a continuous variable, in the full variables adjusted model (model 3), the adjusted OR was 1.18 (95% CI: 1.08–1.28) for 90-day poor outcome. When SIRI was analyzed as tertiles, also in model 3, the adjusted OR for 90-day poor functional outcome in T2 and T3 were 2.35 (95% CI: 1.49–3.70, $P < 0.001$) and 2.58 (95% CI: 1.59–4.2, $P < 0.001$), respectively, with T1 as reference. Moreover, it was statistically significant in all models (P for trend < 0.001), indicating that the risk of 90-day poor outcome increased stepwise across SIRI tertiles.

The Nonlinear Relationship Between SIRI and Poor Functional Outcome

[Figure 2](#) demonstrates a reverse J-shaped curve (P for non-linearity < 0.01) in restricted cubic spline model.

Table 3 Multivariate Logistic Regression Analyses of SIRI on the Risk of Poor Outcome

Variable	Non-Adjusted Model		Adjusted Model 1		Adjusted Model 2		Adjusted Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
SIRI	1.25 (1.16~1.35)	<0.001	1.23 (1.14~1.33)	<0.001	1.24 (1.14~1.34)	<0.001	1.18 (1.08~1.28)	<0.001
SIRI, tertile								
T1	Reference		Reference		Reference		Reference	
T2	3.15 (2.1~4.74)	<0.001	3.09 (2.04~4.66)	<0.001	2.98 (1.96~4.54)	<0.001	2.35 (1.49~3.7)	<0.001
T3	4.31 (2.84~6.54)	<0.001	3.94 (2.58~6.01)	<0.001	3.91 (2.54~6.04)	<0.001	2.58 (1.59~4.2)	<0.001
p for trend	<0.001		<0.001		<0.001		<0.001	

Notes: Results for each model are presented as OR (95% CI), P value. Non-adjusted model: no other covariates were adjusted. Model 1: adjusted for age, sex; Model 2: adjusted as for the Model 1, additionally adjusted for smoking status, hypertension, diabetes mellitus, coronary artery disease, hyperlipemia, atrial fibrillation, temperature, systolic BP and diastolic BP; Model 3: adjusted as for the Model 2, additionally adjusted for time of last known well to reperfusion, baseline NIHSS, ASPECTS, AIS location, stroke subtypes, recanalization therapy, CRP and Albumin.

Abbreviations: AIS, acute ischemia stroke; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, Odds ratio; 95% CI, 95% confidence interval.

In the threshold analysis, the data were fitted to a piecewise multiple logistic regression model with two different slopes (Table 4). There was dose-responsive relationship between increasing SIRI levels and elevated adjusted odds ratios for 90-day poor outcomes in patients with SIRI < 4.5. While, there was no association between SIRI and 90-day poor outcome when SIRI was ≥ 4.5 . This means that the risk of poor outcomes no longer elevates with increasing SIRI.

ROC Curves for Comparison of Biomarkers to Predict Poor Outcome

From Figure 3, we compared the predictive value of various inflammation-related indicators for poor outcome in patients with ALVOS. Among these, the area under the ROC curve (AUC) for the SIRI was 68.20% (95% CI: 63.91–72.49%), which was higher than NLR, MLR, PLR, and SII, but lower than the NIHSS score. The details were seen in Table S2.

Subgroup Analysis

Subgroup analyses explored possible associations of the SIRI (treated as a continuous variable) with 90-day poor outcome among different stratification variables (Figure 4).

The associations between the SIRI (treated as a continuous variable) with 90-day unfavorable outcome were similar among the following subgroups: age (<65 years vs ≥ 65 years), sex, diabetes mellitus, atrial fibrillation, hyperlipemia, AIS location (anterior vs posterior circulation), time from last known well to reperfusion (≤ 6 h vs > 6 h), stroke subtypes (Cardioembolic vs Non-cardioembolic), NIHSS (<16 vs ≥ 16), CRP (<5 mg/L vs ≥ 5 mg/L) and recanalization therapy (MT alone vs MT with IVT) (all P interaction > 0.05). Noticeably, the SIRI interacted significantly with atrial fibrillation (OR 1.43, 95% CI 1.18–1.74 for subjects without atrial fibrillation vs OR 1.11, 95% CI 1.01–1.21 for subjects with atrial fibrillation, P interaction = 0.001).

Discussion

In this study, we examined 604 patients with acute large vessel occlusion stroke (ALVOS) who underwent mechanical thrombectomy in China to investigate the association between the SIRI and poor functional outcome at 90 days post-intervention. Our findings indicate that SIRI is an independent risk factor for poor 90-day functional outcome in MT patients, exhibiting a dose-response relationship with adverse outcomes. Furthermore, our analysis revealed that SIRI outperformed other inflammatory and clinical markers, including SII, NLR, MLR, PLR, and WBC in predicting functional outcome. Consequently, SIRI emerges as a viable non-invasive predictive tool for assessing the risk of unfavorable 90-day functional outcome in the Chinese population undergoing endovascular thrombectomy for ALVOS.

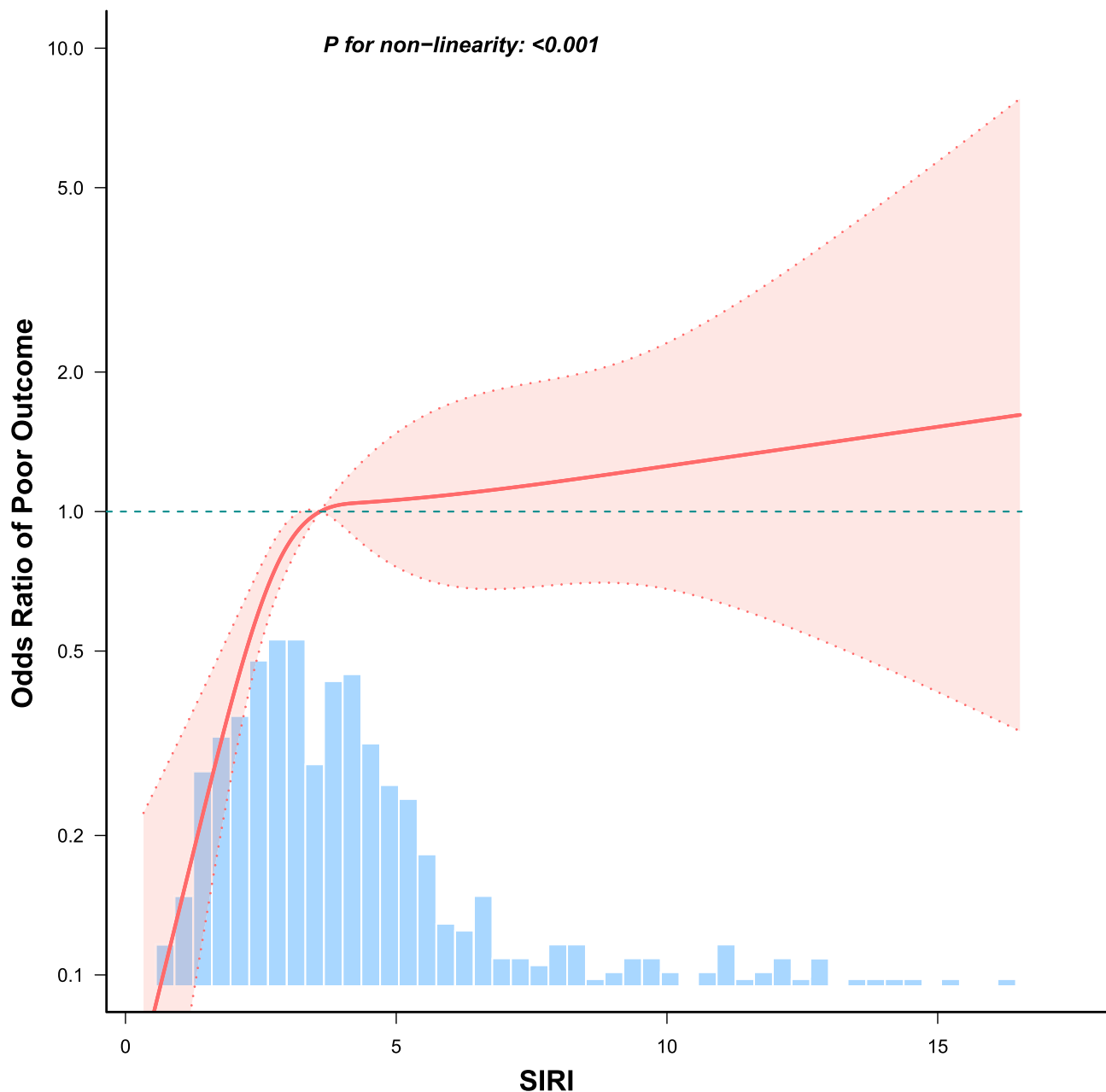


Figure 2 Multivariate adjusted restricted cubic spline for association between SIRI and 90-day functional outcome. Odds ratio were adjusted for variates with model 3. The red line represents the best-fit line, and the red dot lines are 95% confidence intervals.

Abbreviation: SIRI, systemic inflammation response index.

While various pathophysiological mechanisms contribute to post-stroke injury at the site of cerebral ischemia, mounting evidence indicates that inflammatory responses are closely associated with injury repair, regeneration, systemic inflammation, immunosuppression, and patient functional prognosis.^{6,28,29} Inflammation contributes to progress of acute ischemia stroke, and leukocytes, with different leukocyte subsets playing distinct roles in the inflammatory reaction.^{9–11,30} Neutrophils activate inflammatory reaction and induce brain damage by releasing inflammatory mediators and induce damage to the blood-brain barrier,³¹ whereas monocytes contribute to inflammatory and prothrombotic pathways by interacting with platelets and endothelial cells. They also differentiate into brain-resident macrophages as part of the initial inflammatory cascade.^{11,12,32} In contrast, lymphocytes have a downregulation effect on inflammation.^{9,10,12,33} Various subsets of lymphocytes and specific T-cell lymphocytes secrete anti-inflammatory factors, regulate the activation of glial

Table 4 Threshold Effect Analyses of SIRI on the Risk of Poor Outcome Using Two-Piecewise Regression Models

SIRI	Non-Adjusted Model		Adjusted Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value
< 4.5	1.89 (1.52–2.34)	<0.001	1.74 (1.36–2.22)	<0.001
≥ 4.5	1.06 (0.96–1.16)	0.265	1.09 (0.95–1.26)	0.212
Non-linear test		<0.001		0.012
Log-likelihood ratio test		0.001		<0.001

Notes: The data was adjusted for all the covariates of model 3.

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval.

cells, and reduce the body's immune response to cerebral ischemia. In addition, lymphocytes play an important role in anti-inflammatory response functions and confer endothelial protection.³⁴

The systemic inflammation response index (SIRI) was described as a novel inflammatory marker by Qi et al.³⁵ SIRI, which combines neutrophil, monocyte, and lymphocyte count, has been established as a prognostic indicator in patients with malignancies.^{35–37} Given the complex interplay of immune-inflammatory processes in stroke, utilizing indices or ratios that incorporate multiple cellular lines may provide a more reliable reflection of the balance between innate and adaptive immunity, compared to single blood parameters alone. It offers a comprehensive evaluation of inflammation, immunity, hemostasis, and thrombosis. Our study showed that SIRI has the ability to effectively predict 90-day functional outcome with an AUC of 0.682 (0.639–0.725), and the optimal cut-off point of SIRI for predicting 90-day functional outcome was 3.31, with a sensitivity of 69.51% and a specificity of 62.68%. Moreover, SIRI showed superior prognostic predictivity compared to NLR, LMR, PLR, and SII.

These findings suggest that SIRI could be a valuable addition to existing clinical predictors such as age, baseline stroke severity, and success of brain reperfusion in patients undergoing mechanical thrombectomy for acute large vessel occlusion stroke.^{38,39} Recent studies have confirmed that SIRI is linked to poor functional outcomes, post-stroke pneumonia, and the incidence of sICH in patients undergoing thrombectomy.^{40–44}

Our study consistently demonstrated that patients with poor prognoses had higher neutrophil and monocyte counts and lower lymphocyte counts than those with favorable prognoses.^{16,17,42}

In addition, our study found a non-linear relationship between SIRI and 90-day functional outcome. Moreover, subgroup analysis revealed that the predictive value of SIRI for unfavorable functional outcome was prominent in patients with atrial fibrillation (OR 1.69, 95% CI: 1.41–2.03) compared to those without atrial fibrillation (OR 1.14, 95% CI: 1.06–1.24), indicating that this atrial fibrillation subgroup may be more vulnerable to poor functional outcome. It is possible to believe that atrial fibrillation could increase the risk of acute heart failure, pulmonary infections, and recurrent thromboembolic events, potentially worsening overall outcomes. Notably, patients admitted to our hospital showed low compliance with standard anticoagulation therapy before admission, which is essential for long-term outcomes and reducing stroke mortality.⁴⁵

While the exact biological mechanisms underlying the association between the SIRI and adverse functional outcome are not fully elucidated, several rational pathways have been proposed based on current evidence. Following cerebral infarction, the activating of microglia, macrophages, and mast cells leads to the release of pro-inflammatory cytokines. This inflammatory cascade triggers the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increased secretion of stress hormones, which ultimately contribute to neutrophil leucocytosis and lymphopenia.⁴⁶ Lymphocytes depletion may compromise pathogen resistance and heighten susceptibility to infections, which are common complications after cerebral infarction can adversely affect the clinical trajectory.⁴⁷ Moreover, specific regulatory lymphocyte subpopulations are essential for maintaining immune homeostasis and offer neuroprotective effects by modulating the immune response. These cells counteract pro-inflammatory mediator production,

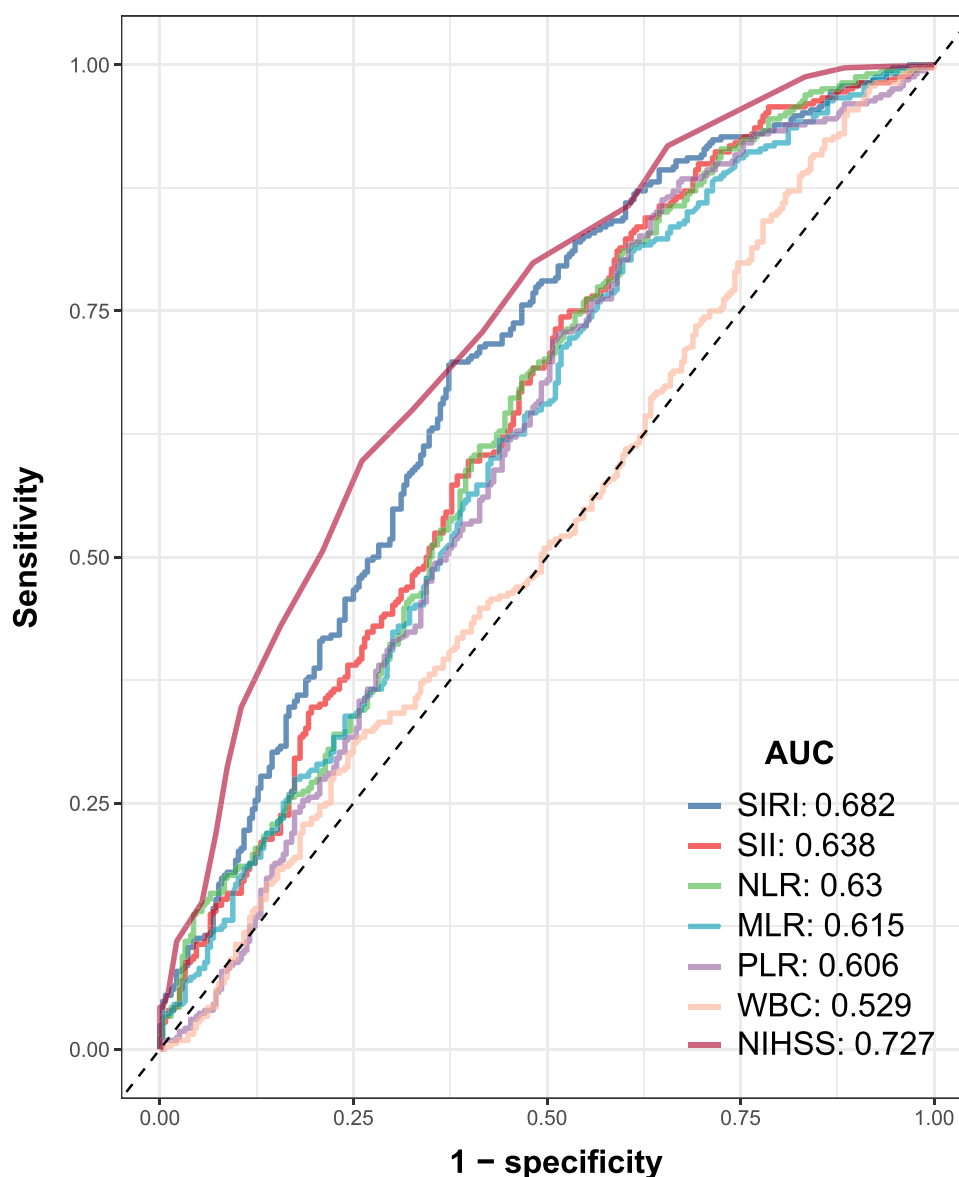


Figure 3 ROC curves for comparison of biomarkers to predict functional outcome.

Abbreviations: SRI, systemic inflammation response index; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; NIHSS, National Institutes of Health Stroke Scale.

regulate microglial activation, suppress autoreactive cellular responses, and promote neurogenesis and tissue repair processes within the ischemic region.^{48,49}

In summary, our analysis indicates that the SRI provides a comprehensive evaluation of an individual's inflammatory and immune status and holds promise as a prognostic biomarker for functional outcome in patients with ALVOS undergoing mechanical thrombectomy. Furthermore, incorporating the SRI into routine clinical practice may enhance risk stratification and improve predictions related to clinical outcomes.

However, our study also had several limitations. First of all, the retrospective nature of this investigation precludes the establishment of definitive causal relationships. Although we employed multivariate adjustments and subgroup analyses to mitigate confounding factors, the potential influence of residual confounders on clinical outcomes cannot be entirely excluded. Secondly, this study exclusively analyzed baseline SRI values. Future research should evaluate the dynamic changes in SRI over time to better understand its predictive power and potential fluctuations during the clinical course. Consequently, further studies with larger sample sizes and prospective designs are essential to validate these findings.

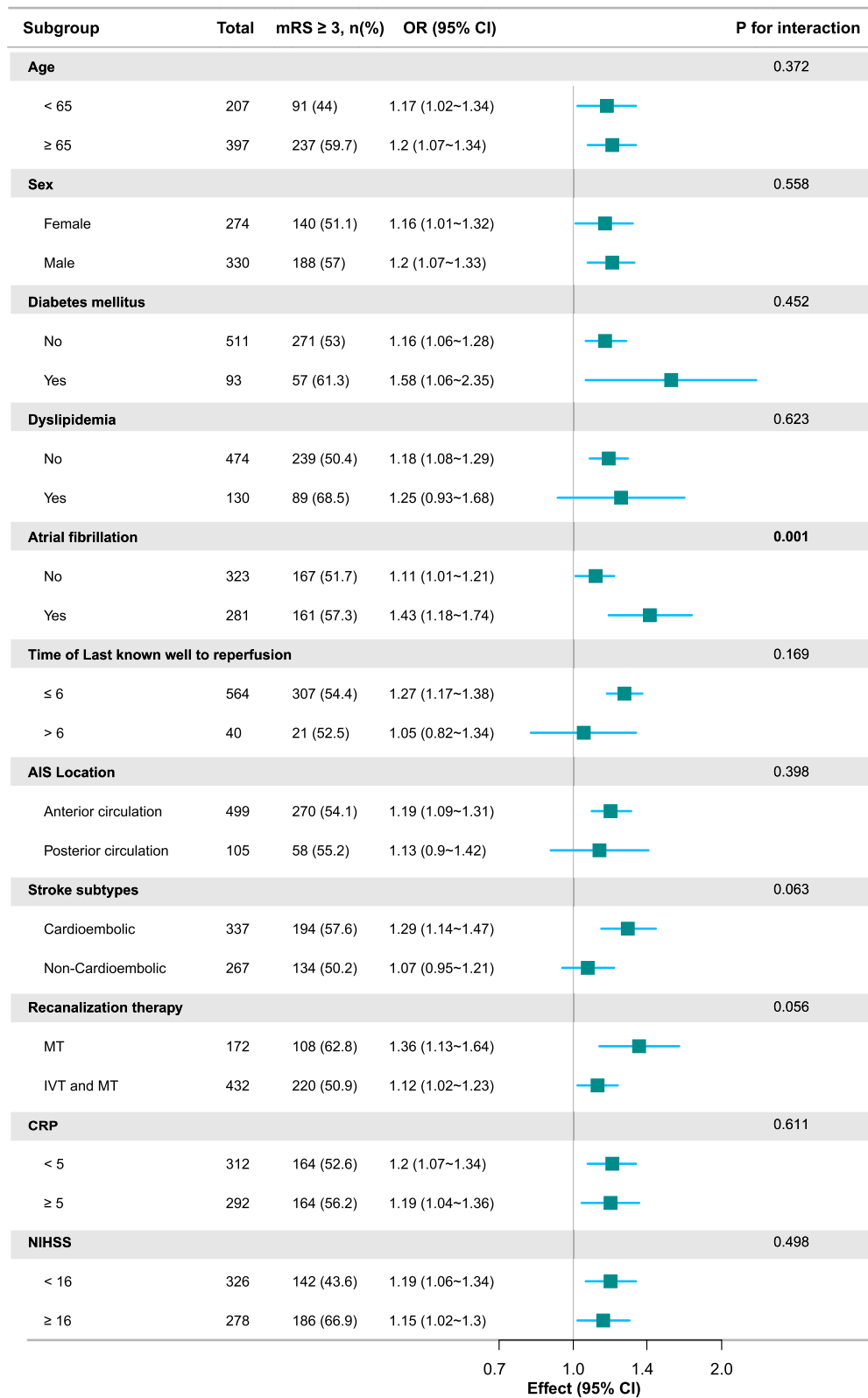


Figure 4 Stratified logistic regression analysis to identify variables that modify the correlation between SIRI and poor outcome. Covariates were adjusted for model 3. In each stratification, the model was not adjusted for the stratification variable.

Abbreviations: CI, confidence interval; MT, mechanical thrombectomy; CRP, C reactive protein; IVT, intravenous thrombolysis; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, Odds ratio.

Conclusion

This study revealed that SIRI, an affordable and readily available biomarker, exhibits an independent association with an elevated risk of poor functional outcome in a cohort of Chinese patients due to ALVOS with endovascular reperfusion. However, the intricate mechanisms underlying inflammation in AIS remain incompletely elucidated, necessitating further exploration of the complex interplay between inflammatory markers and clinical outcomes.

Data Sharing Statement

Data is available from the corresponding author on reasonable request.

Ethical Statement

The current retrospective study was approved by the Ethics Committee of the First College of Clinical Medical Science of China Three Gorges University (ethical approval number: 2023-129-01), which waived consent from study participants as it was not required due to the retrospective nature of the study. All patient data was anonymized during processing. This study was performed following the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors have declared that they have no conflicts of interest in this work.

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