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ORIGINAL RESEARCH

A Mediation Analysis of the Association Between Systemic Inflammation Response Index, in-Hospital Complications, and Poor Long-Term Functional Outcomes in Patients with Aneurysmal Subarachnoid Hemorrhage: Insights from a Large Prospective Cohort Study

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Purpose: Early systemic inflammatory changes are increasingly recognized as factors influencing outcomes after aneurysmal subarachnoid hemorrhage (aSAH). Systemic inflammation response index (SIRI), an inflammation biomarker, was thought to be associated with adverse outcomes in many other diseases. However, in aSAH, research on SIRI remains limited. Thus, our objective was to investigate the association between SIRI and poor long-term functional outcomes while evaluating the mediating role of in-hospital complications in this association.

Patients and Methods: SIRI was defined as neutrophil count × monocyte count/lymphocyte count. Patients were categorized according to SIRI quartiles. Stabilized inverse probability of treatment weighting (sIPTW) was utilized to minimize group differences. The association between SIRI and in-hospital complications as well as poor 90-day functional outcomes (mRS 3–6) was estimated by multivariable logistic regression analyses. Mediation analysis was performed to investigate the relationship between SIRI and poor functional outcomes mediated by in-hospital complications.

Results: A total of 650 patients were prospectively included. After sIPTW, compared to the lowest quartile, an elevated SIRI was associated with delayed cerebral ischemia (DCI) (OR 2.12, 95% CI 1.20–3.74), post-operative pneumonia (POP) (OR 2.16, 95% CI 1.29–3.62) and poor 90-day functional outcomes (OR 3.03, 95% CI 1.55–5.91). In-hospital complications including DCI (mediation proportion, 18.18% before sIPTW and 20.0% after sIPTW) and POP (mediation proportion, 18.18% before sIPTW and 26.7% after sIPTW) partially mediated the association between SIRI and poor 90-day functional outcomes. Mediation analysis yielded comparable results in subgroups stratified by age and sex.

Conclusion: In this study, SIRI was associated with poor long-term functional outcomes in aSAH, which was partially mediated by DCI and POP with a mediation proportion exceeding 18%. Our findings might underscore the potential utility of SIRI in prompting physicians to address systemic inflammatory status timely to prevent in-hospital complications, including DCI and POP, and ultimately improve long-term functional outcomes.

Keywords: aneurysmal subarachnoid hemorrhage, systemic inflammation response index, complications, functional outcomes, mediation analysis

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Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a neurosurgical disease characterized by substantial morbidity and mortality.[1] The initial 72 hours period following the ictus is of paramount importance in aSAH, as it associated significantly with future adverse prognosis.[2–4] During this critical phase, early systemic inflammatory responses have been identified as a significant contributor hospitalization-related complications and unfavorable long-term functional outcomes.[5]

Among various biomarkers, the systemic inflammatory response index (SIRI) has gained widespread utility in assessing the systemic inflammatory status of patients affected by conditions such as stroke, myocardial infarction, and cancer.[6–10] Computed as neutrophil count * monocyte count/lymphocyte count, SIRI remains relatively underexplored in the context of aSAH.[11] Prior studies have focused solely on the correlation between SIRI and poor functional outcomes, with limited insights into the involvement of in-hospital complications in the causal relationship.[12–14] In the case of aSAH patients, multiple complications, such as delayed cerebral ischemia (DCI), postoperative pneumonia (POP), deep vein thrombosis (DVT), and major cardiovascular adverse events (MACE) often arise during hospitalization.[15,16] These complications exhibit varying degrees of association with systemic inflammatory responses and impact functional outcomes differently.[17–20] Consequently, a more comprehensive examination of the relationship between SIRI, in-hospital complications, and 90-day functional outcomes is essential. Such an investigation may contribute to targeted prevention of complications and reduction of long-term disability rates through early anti-inflammatory treatment according to SIRI level.

In this study, we employed SIRI as an indicator to assess early systemic inflammatory changes in aSAH, aiming to 1) investigate the association between SIRI, in-hospital complications, and poor 90-day functional outcomes within our study cohort; and 2) uncover the causal relationship between SIRI and poor 90-day functional outcomes, while exploring the potential mediating role of in-hospital complications in this relationship.

Material and Methods

Study Design and Participants

All patients' data were derived from the Long-term Prognosis of Emergency Aneurysmal Subarachnoid Hemorrhage (LongTEAM) Registry study (Clinicaltrials.gov, NCT 04785976). This study prospectively recorded information from December 2016 to December 2022.

The study applied specific inclusion and exclusion criteria. The inclusion criteria were as follows: 1) age ≥ 18 years; 2) presence of a single aneurysm without a history of previous SAH. Conversely, the exclusion criteria encompassed: 1) admission to the emergency department beyond 48 hours after rupture; 2) serious medical history or existing comorbidities; 3) previous treatment, including external ventricular drainage, lumbar puncture, angiography, intubation, and/or mechanical ventilation before admission to our hospital; 4) incomplete 90-day follow-up. Detailed information was presented in Figure 1.

Furthermore, this study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline for cohort studies.[21]

Ethic Approval

This study received approval from the Institutional Review Board of Beijing Tiantan Hospital on 2021–02-01 (KY 2021–008-01), and all patients (unconscious patients' data were recorded under the consensus of the relatives) provided written informed consent. Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975.

Data Collection and Outcomes Assessment

SIRI was calculated as neutrophil count × monocyte count/lymphocyte count.[6] Blood samples were collected within 24 hours of admission. Plasma specimens were extracted, aliquoted and transported through cold chain to the central laboratory in our hospital and stored at 80°C until tests were performed centrally and blindly.) When multiple blood samples were taken from the patient, the analyzation process relied on the results obtained from the first blood sample. Patient demographics (age and sex), medical history (hypertension, hyperlipidemia, diabetes mellitus, current smoking), clinical grade on admission utilizing World Federation of Neurological Surgeons (WFNS) grading scale,[22] were collected

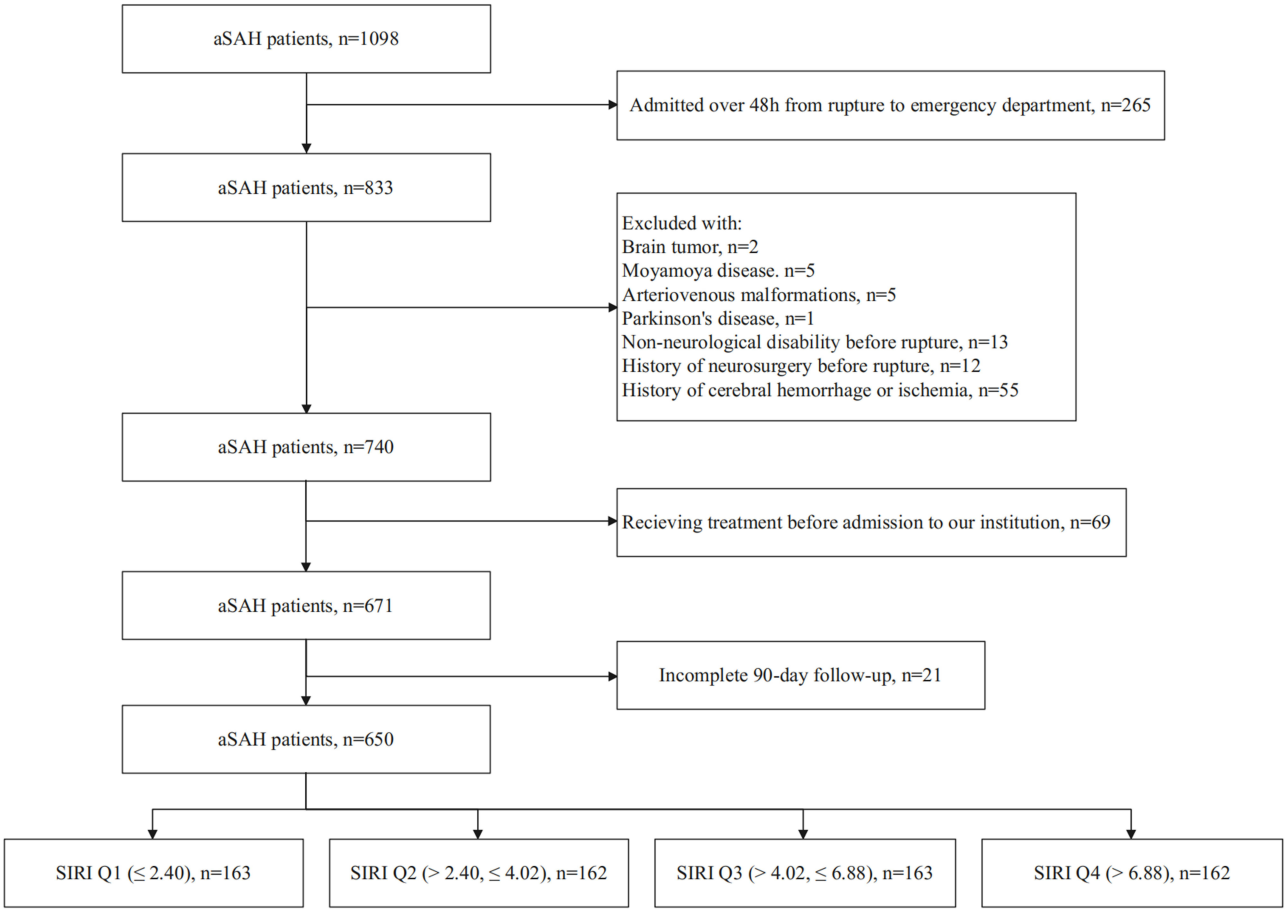

Figure 1 Flow chart of inclusion/exclusion of patients.
Notes: aUnit of measurement: *109/L.
Abbreviations: aSAH, Aneurysmal subarachnoid hemorrhage; SIRI, systemic inflammatory response index; Q, quartiles.

through face-to-face interviews on admission by trained physicians from our center (unconscious patients' data were recorded with relatives). The initial CT/CTA/DSA scan results including location of aneurysms, presence of acute hydrocephalus,[23] the Subarachnoid Hemorrhage Early Brain Edema Score[24] (SEBES) and modified Fisher Scale[25] (mFS) were recorded by trained physicians on our standard imaging reading platform. The occurrence of in-hospital complications including stress related gastrointestinal bleeding (SRGB), Liver dysfunction, MACEs, DVT, DCI and POP were diagnosed and recorded in our medical records by standard process. The above important complications were selected in this study according to the latest aSAH guidelines and the detailed diagnostic criteria of in-hospital complications were shown in Table S1.[26] Poor functional outcomes were defined as modified Rankin Scale (mRS) score of 3 or higher, indicating significant disability or dependency in daily activities. Patients were followed up through telephonic consultations or outpatient appointments 90 days after discharge by physicians who underwent standardized training.

Statistical Analysis

Analyses were performed using R statistical program (version 4.2.0). All p-values were two-tailed, with $p < 0.05$ considered statistically significant.

In the main analyses, patients were categorized according to quartiles of SIRI [Quartiles 1: ≤2.40; Quartiles 2: >2.40, ≤4.02; Quartiles 3: >4.02, ≤6.88; Quartiles 4: >6.88 (Unit of measurement: *109/L)]. There were no missing data in this study. To mitigate baseline imbalances, we applied stabilized inverse probability of treatment weighting (sIPTW) with twang R package.[27,28] All available covariates were considered, and 3000 iterations were utilized for the boosting model.

We assessed balance diagnostic using standardized mean differences (SMD) before and after weighting, where an SMD of 0.2 or less was deemed satisfactory.[29]

Baseline characteristics with SMD before and after sIPTW were tabulated for each group segmented by SIRI quartiles. Descriptive variables were represented as frequencies (percentage) for categorical variables and mean ± standard deviation for continuous variables. Univariate analysis was used for preliminary screening of in-hospital complications. To investigate the association of SIRI with significant in-hospital complications and poor 90-day functional outcomes, we utilized unadjusted, multivariable adjusted (Confounders included clinically important and SIRI-related variables in Table 1), and sIPTW adjusted binary logistic regression models. The group with the lowest SIRI quartile was defined as the reference, and the association was expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). Furthermore, we ascertained the p for trend by incorporating SIRI as a continuous variable into the models.[30]

Subsequently, to investigate the mediating role of significant in-hospital complications (identified through univariate and multivariate analysis) in the association of SIRI with poor functional outcomes, a hypothesized model was examined by lavaan R package (version 0.6–12) both before and after sIPTW.[31] According to previous studies, the sample size and the data nature of our study was qualified for performing mediation analyses.[32] Among various mediation models, we chose parallel mediation analysis, suitable for research involving multiple mediators. This approach enabled us to investigate the specific mediating effect of each variable separately.[33] SIRI served as the predictor, in-hospital complications as mediators, and poor 90-day functional outcomes as the outcome variable. The total effect could be decomposed into direct effect and multiple indirect effects [Total effect = direct effect (C) + multiple indirect effects (∑AnBn)]. The direct effect represented the independent effect of SIRI on poor functional outcomes, unaffected by the included in-hospital complications. Each indirect effect represented the impact of SIRI on poor functional outcomes mediated by a specific in-hospital complication. We presented the estimates (95% CI), standard error, and p value for all the paths. Mediation proportion was computed as indirect effect/total effect *100%, denoting the percentage of the total effect mediated by the mediator. To ensure model stability, we repeated the results in 1000 bootstrap resamples. Finally, we conducted subgroup analyses of mediation analyses stratified by age (≥60 and <60 years) and gender (female and male) to assess the comparability of results.

Results

Baseline Characteristics

A total of 650 patients were included in this study, the mean (SD) age was 55.3 (10.5) years, and 371 (57.1%) were female. The patients were categorized into four groups according to the quartiles of SIRI. Table 1 displayed the distribution of patient characteristics before implementing sIPTW. The data revealed that patients with higher SIRI were prone to being of advanced age, having a history of diabetes mellitus and presenting a higher proportion of acute hydrocephalus. Moreover, their admission records exhibited a higher prevalence of WFNS grade 4–5, SEBES grade 3–4, and mFS grade 3–4.

Subsequently, after the application of sIPTW, baseline characteristics among the four groups demonstrated a satisfactory balance (Table 2). Furthermore, in univariate analyses, patients with elevated SIRI levels displayed a higher likelihood of experiencing DCI, POP, and poor 90-day functional outcomes both before and after sIPTW. Graphical assessments of balance were visually depicted in Figure S1 and Figure S2.

Association of Elevated SIRI with DCI, POP, and Poor 90-Day Functional Outcomes

Elevated SIRI demonstrated a significant association with DCI, POP, and poor 90-day functional outcomes, as evident across different models. In the unadjusted model, the ORs for DCI, POP, and poor 90-day functional outcomes comparing quartiles 4 to quartiles 1, were 2.69 (95% CI 1.60–4.52), 3.82 (95% CI 2.31–6.32), and 4.62 (95% CI 2.43–8.77). After adjusting for confounding factors in the multivariable model, the ORs remained significant at 1.97 (95% CI 1.11–3.52) for DCI, 2.45 (95% CI 1.38–4.43) for POP, and 3.41 (95% CI 1.62–7.19) for poor functional outcomes. (Confounding factors for adjustment were listed in Table 3).

These associations were also observed in the sIPTW model, with ORs of 2.12 (95% CI 1.20–3.74) for DCI, 2.16 (95% CI 1.29–3.62) for POP and 3.03 (95% CI 1.55–5.91) for poor functional outcomes. The significant p-value for

Table 1 Distribution of Patient Characteristics According to Quartiles of Systemic Inflammation Response Index Before Stabilized Inverse Probability of Treatment Weighting

Patient Characteristics	Quartiles 1	Quartiles 2	Quartiles 3	Quartiles 4	p^a	SMD
No. of patients	163	162	163	162		
Age, mean ± SD	55.83 ± 10.1	53.03 ± 10.5	51.72 ± 10.6	52.57 ± 11.9	0.004	0.201
Female, n (%)	103 (63.2)	81 (50.0)	97 (59.5)	90 (55.6)	0.096	0.147
Hypertension, n (%)	90 (55.2)	90 (55.6)	98 (60.1)	97 (59.9)	0.700	0.064
Hyperlipidemia, n (%)	20 (12.3)	15 (9.3)	14 (8.6)	9 (5.6)	0.208	0.123
Diabetes mellitus, n (%)	24 (14.7)	15 (9.3)	6 (3.7)	15 (9.3)	0.008	0.197
Currently smoking, n (%)	40 (24.5)	59 (36.4)	46 (28.2)	45 (27.8)	0.110	0.132
Posterior circulation, n (%)	15 (9.2)	18 (11.1)	16 (9.8)	15 (9.3)	0.934	0.035
Acute hydrocephalus, n (%)	51 (31.3)	58 (35.8)	63 (38.7)	89 (54.9)	<0.001	0.254
WFNS grade of 4–5, n (%)	17 (10.4)	16 (9.9)	30 (18.4)	59 (36.4)	<0.001	0.369
SEBES score of 3–4, n (%)	53 (32.5)	68 (42.0)	91 (55.8)	114 (70.4)	<0.001	0.447
mFS grade of 3–4, n (%)	105 (64.4)	115 (71.0)	136 (83.4)	147 (90.7)	<0.001	0.381
Treatment modalities, n *(%)*					0.897	0.045
Microsurgical	77 (47.2)	81 (50.0)	79 (48.5)	83 (51.2)		
Endovascular	86 (52.8)	81 (50.0)	84 (51.5)	79 (48.8)		
Outcomes, n *(%)*						
SRGB	28 (17.2)	23 (14.2)	40 (24.5)	40 (24.7)	0.055	0.164
Liver dysfunction	34 (20.9)	44 (27.2)	47 (28.8)	56 (34.6)	0.065	0.161
MACEs	61 (37.4)	58 (35.8)	65 (39.9)	66 (40.7)	0.789	0.059
DVT	11 (6.7)	9 (5.6)	12 (7.4)	20 (12.3)	0.116	0.124
DCI	28 (17.2)	33 (20.4)	48 (29.4)	58 (35.8)	0.001	0.250
POP	30 (18.4)	27 (16.7)	56 (34.4)	75 (46.3)	<0.001	0.395
Poor 90-day functional outcomes	14 (8.6)	12 (7.4)	31 (19.0)	49 (30.2)	< 0.001	0.357

Notes: Levels: Level 1: ≤ 2.40; Level 2: > 2.40, ≤ 4.02; Level 3: > 4.02, ≤ 6.88; Level 4: > 6.88 (Unit of measurement: $*10^9$/L). p^a was calculated by One-way ANOVA, Chi-square test.

Abbreviations: SMD, standardized mean differences; SD, standard error; WFNS, World Federation of Neurological Societies; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; mFS, modified Fisher Scale; SRGB, Stress related gastrointestinal bleeding; MACEs, Major adverse cardiac events; DVT, Deep vein thrombosis; DCI, Delayed cerebral ischemia; POP, Postoperative pneumonia.

Table 2 Distribution of Patient Characteristics According to Quartiles of Systemic Inflammation Response Index After Stabilized Inverse Probability of Treatment Weighting

Patient Characteristics	Quartiles 1	Quartiles 2	Quartiles 3	Quartiles 4	p^a	SMD
No. of patients	143	144	134	141		
Age, mean ± SD	54.1 ± 10.2	53.51 ± 10.78	53.53 ± 10.48	53.10 ± 10.60	0.945	0.038
Female, n (%)	90 (62.9)	73 (50.7)	82 (60.7)	81 (57.4)	0.230	0.132
Hypertension, n (%)	81 (57.0)	80 (55.9)	81 (60.4)	81 (57.0)	0.886	0.047
Hyperlipidemia, n (%)	16 (11.2)	13 (9.1)	11 (8.1)	8 (5.6)	0.430	0.107
Diabetes mellitus, n (%)	14 (9.8)	12 (8.4)	7 (5.2)	12 (8.5)	0.616	0.081
Currently smoking, n (%)	35 (24.5)	51 (35.4)	39 (29.1)	39 (27.7)	0.276	0.128
Posterior circulation, n (%)	15 (10.5)	15 (10.5)	13 (9.7)	14 (9.9)	0.989	0.022
Acute hydrocephalus, n (%)	57 (40.1)	57 (39.6)	54 (40.3)	60 (42.6)	0.969	0.029
WFNS grade of 4–5, n (%)	27 (18.9)	23 (16.1)	25 (18.7)	30 (21.3)	0.782	0.065
SEBES score of 3–4, n (%)	70 (49.0)	71 (49.3)	70 (51.9)	78 (55.3)	0.759	0.071
mFS grade of 3–4, n (%)	112 (78.3)	111 (77.1)	105 (78.4)	120 (85.1)	0.457	0.101
Treatment modalities, n *(%)*					0.873	0.054
Microsurgical	72 (50.3)	69 (48.3)	62 (45.9)	72 (51.1)		
Endovascular	71 (49.7)	74 (51.7)	73 (54.1)	69 (48.9)		

(*Continued*)

Table 2 (Continued).

Patient Characteristics	Quartiles 1	Quartiles 2	Quartiles 3	Quartiles 4	p^a	SMD
Outcomes, n *(%)*						
SRGB	31 (21.7)	22 (15.4)	34 (25.2)	32 (22.5)	0.266	0.123
Liver dysfunction	39 (27.3)	41 (28.5)	41 (30.6)	45 (31.7)	0.908	0.050
MACEs	55 (38.5)	55 (38.2)	55 (40.7)	60 (42.3)	0.903	0.123
DVT	10 (7.0)	10 (6.9)	9 (6.7)	18 (12.8)	0.339	0.106
DCI	24 (16.8)	32 (22.2)	41 (30.4)	42 (29.8)	0.022	0.215
POP	33 (23.1)	27 (18.8)	46 (34.3)	56 (39.4)	0.001	0.276
Poor 90-day functional outcomes	14 (9.8)	15 (10.4)	24 (17.9)	35 (24.8)	0.006	0.238

Notes: Levels: Level 1: ≤ 2.40; Level 2: > 2.40, ≤ 4.02; Level 3: > 4.02, ≤ 6.88; Level 4: > 6.88 (Unit of measurement: $*10^9$/L). p^a was calculated by One-way ANOVA, Chi-square test.

Abbreviations: SMD, standardized mean differences; SD, standard error; WFNS, World Federation of Neurological Societies; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; mFS, modified Fisher Scale; SRGB, Stress related gastrointestinal bleeding; MACEs, Major adverse cardiac events; DVT, Deep vein thrombosis; DCI, Delayed cerebral ischemia; POP, Postoperative pneumonia.

trend in the models suggested a clear association between increasing SIRI and a heightened risk of patients experiencing DCI, POP, and poor outcomes at 90 days. Refer to Table 3 for detailed information.

Mediation Analysis

The standardized regression coefficients of the hypothesized model were depicted in Figure 2. DCI (mediation proportion, 18.18% before sIPTW and 20.0% after sIPTW) and POP (mediation proportion, 18.18% before sIPTW and 26.7% after sIPTW) partially mediated the association between SIRI and poor 90-day functional outcomes. Generally, the indirect effects of DCI and POP exhibited similarities, yet the indirect effects of POP slightly surpassed those of DCI. Notably, both before and after sIPTW, path A1 showed smaller coefficients (0.008 before sIPTW and 0.012 after sIPTW) compared to path A2 (0.015 before sIPTW and 0.018 after sIPTW), while path B1 (0.208 before sIPTW and 0.246 after sIPTW) demonstrated larger coefficients in contrast to path B2 (0.148 before sIPTW and 0.219 after sIPTW).

Additionally, we performed mediation analyses in subgroups stratified by age and sex, and the result were consistent (Table 4).

Discussion

In this study, SIRI was applied to assess early systemic inflammatory changes. Our findings unveiled a significant association between elevated SIRI and the occurrence of DCI, POP, and poor 90-day functional outcomes. Notably, DCI and POP partially mediated the relationship between SIRI and 90-day functional outcomes, accounting for more than 18% of the mediation proportion.

Previous studies have emphasized early systemic inflammation response within the first 24 hours of the aSAH onset, closely associated with the poor prognosis of patients.[34,35] Investigating changes in early systemic inflammation requires consideration of various inflammatory biomarkers, such as white blood cells, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammatory index (SII).[36,37] However, the clinical application of SIRI, which combines multiple inflammatory parameters and has been validated as a reliable inflammatory indicator in other domains, remains relatively unexplored in aSAH.[38] Furthermore, the correlation between SIRI and long-term functional outcomes has been examined, but its relationship with multiple in-hospital complications in aSAH, let alone the causal connection between SIRI, in-hospital complications, and poor functional outcomes, has been scarcely investigated.[13,14] Therefore, our cohort study not only reaffirmed the association between SIRI and long-term poor outcomes but also further delved into its relationship with various in-hospital complications. Subsequently, we probed into mediating role of significant in-hospital complications in the link between SIRI and poor functional outcomes.

Regarding the association between SIRI and poor 90-day functional outcomes, akin to the findings in the studies conducted by Yuyang Hou et al and Seonyong Yun et al, we observed that elevated SIRI levels are indeed linked to a 90-day poor

Table 3 Association of Systemic Inflammation Response Index with Delayed Cerebral Ischemia, Postoperative Pneumonia, and Poor 90-Day Functional Outcomes

Outcomes	Models	Level 1		Level 2		Level 3		Level 4		Continuous	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*p for trend*
DCI	Unadjusted	Reference	–	1.23 (0.71–2.16)	0.462	2.01 (1.19–3.41)	0.009	2.69 (1.60–4.52)	< 0.001	1.08 (1.04–1.12)	< 0.001
	Multivariable adjusted[a]	Reference	–	1.24 (0.69–2.23)	0.464	2.00 (1.13–3.54)	0.018	1.97 (1.11–3.52)	0.021	1.05 (1.01–1.09)	0.034
	sIPTW adjusted	Reference	–	1.41 (0.78–2.53)	0.258	2.15 (1.22–3.81)	0.009	2.12 (1.20–3.74)	0.009	1.06 (1.02–1.10)	0.006
POP	Unadjusted	Reference	–	0.89 (0.50–1.57)	0.680	2.32 (1.39–3.87)	0.001	3.82 (2.31–6.32)	< 0.001	1.14 (1.10–1.19)	< 0.001
	Multivariable adjusted[a]	Reference	–	0.80 (0.43–1.50)	0.491	2.16 (1.21–3.86)	0.009	2.45 (1.38–4.43)	0.002	1.09 (1.05–1.15)	< 0.001
	sIPTW adjusted	Reference	–	0.76 (0.43–1.34)	0.341	1.74 (1.03–3.62)	0.039	2.16 (1.29–3.62)	0.003	1.09 (1.04–1.14)	0.001
mRS 3–6 (90-day)	Unadjusted	Reference	-	0.85 (0.38–1.90)	0.695	2.50 (1.28–4.90)	0.008	4.62 (2.43–8.77)	< 0.001	1.13 (1.08–1.17)	< 0.001
	Multivariable adjusted[a]	Reference	-	0.88 (0.37–2.10)	0.766	2.86 (1.34–6.14)	0.007	3.41 (1.62–7.19)	0.001	1.08 (1.02–1.13)	0.002
	sIPTW adjusted	Reference	-	1.07 (0.50–2.29)	0.869	1.99 (1.20–5.91)	0.042	3.03 (1.55–5.91)	0.001	1.09 (1.05–1.15)	0.001

Notes: [a]: adjusted for age, female, hypertension, diabetes mellitus, currently smoking, posterior circulation, acute hydrocephalus, WFNS grade of 4–5, SEBES score of 3–4, mFS grade of 3–4, and treatment modalities.

Abbreviations: OR, odds ratio; CI, confidence interval; DCI, delayed cerebral ischemia; POP, Postoperative pneumonia; mRS, modified Rankin Scale; sIPTW, stabilized inverse probability of treatment weighting; WFNS, World Federation of Neurological Societies; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; mFS, modified Fisher Scale.

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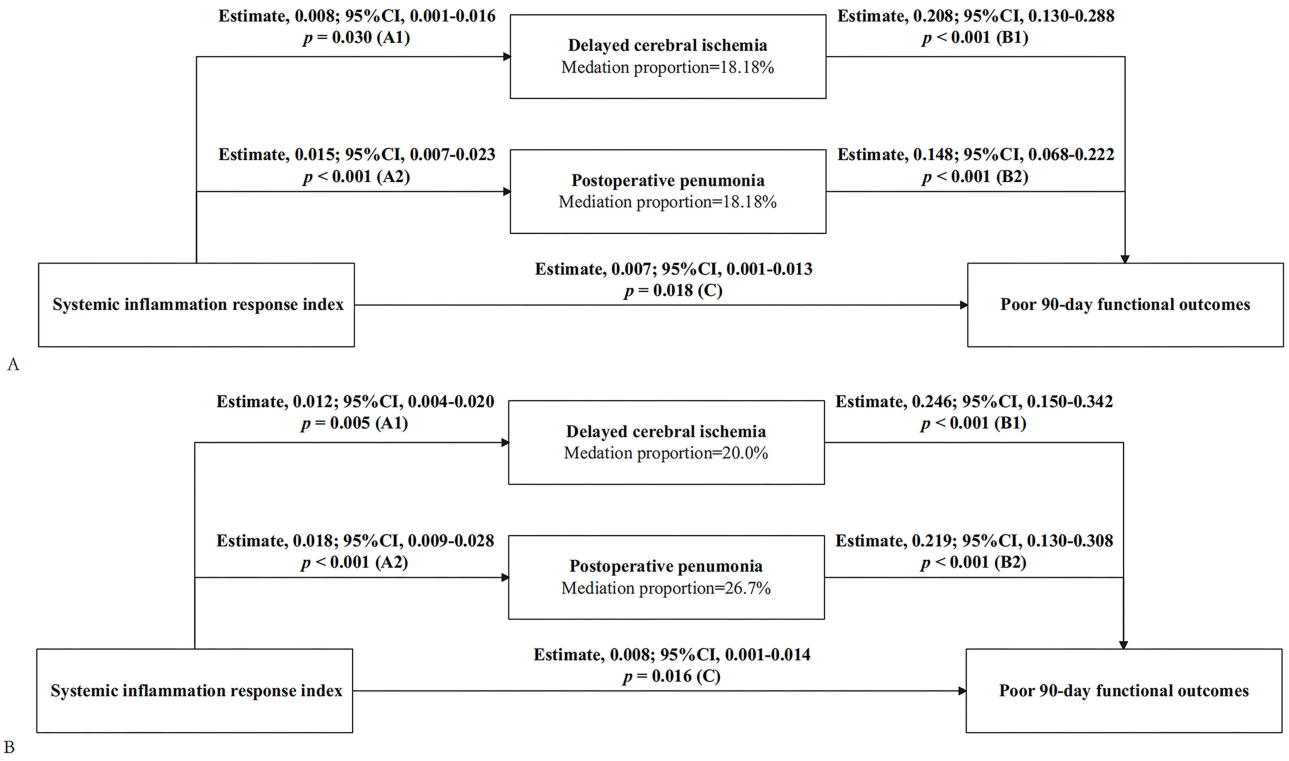

Figure 2 Mediation analysis depicting the mediating role of in-hospital complications in the association of systemic inflammatory response index with poor functional outcomes.

Notes: Total effect = direct effect (**C**) + indirect effect (∑AnBn). (**A**) mediation analysis adjusted by multivariable including age, female, hypertension, diabetes mellitus, currently smoking, posterior circulation, acute hydrocephalus, WFNS grade of 4–5, SEBES score of 3–4, mFS grade of 3–4, and treatment modalities. (**B**) mediation analysis adjusted by stabilized inverse probability of treatment weighting.

Abbreviations: CI, confidence interval; WFNS, World Federation of Neurological Societies; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; mFS, modified Fisher Scale.

prognosis.[13,14] However, in comparison to their studies, our research exhibits several noteworthy distinctions: Firstly, we employed more stringent inclusion and exclusion criteria, diligently excluding all patients with underlying conditions that could potentially influence long-term disability assessment; Secondly, our study incorporated trend analysis and a more meticulous process to correct for confounding factors.; Thirdly, while the optimal cutoff value for SIRI in their studies was 5.36×109/L and 3.2×109/L respectively, our results indicate that SIRI levels above Q3 (>4.02×109/L) hold conspicuous predictive value in comparison to Q1. Fourthly, our study encompasses prospective data and features a sample size similar to that of Seonyong Yun's, but larger than Yuyang Hou's. Following our confirmation of the association between SIRI and poor 90-day prognosis, we aspired to delve deeper and explore the underlying mechanisms.

Subsequently, we embarked on an investigation into the link between SIRI, a systemic inflammatory marker, and multiple in-hospital complications. Existing studies have established that patients with aSAH are prone to experiencing multisystem complications during their hospitalization. Notably, the latest guidelines emphasize the significance of complications such as DCI, POP, deep vein thrombosis (DVT), major adverse cardiac events (MACEs), among others.[26] It has been reported that patients with aSAH who encounter medical complications tend to have worse outcomes compared to those without complications.[39] Moreover, systemic inflammation is believed to play a pivotal role in the pathogenesis of multiple complications, making it imperative to scrutinize the relationship between SIRI and in-hospital complications.[40] In our study, we have observed a correlation between SIRI and DCI as well as POP, but not with DVT, MACEs, stress related gastrointestinal bleeding (SRGB), and liver dysfunction. Although the exact connection between systemic inflammation and DCI remains somewhat elusive, numerous studies have suggested the influence of early systemic inflammation changes on DCI, triggered by early brain injury.[41,42] Furthermore, in the context of pneumonia, widely considered an infectious disease, the impact of systemic inflammation is deemed substantial, a confirmation that our study further validates. Regarding the

Table 4 Parallel Mediation Analyses Stratified by Age and Sex

Subgroups	Variables	Model	Indirect effect (DCI = A1B1)		Indirect effect (POP = A2B2)		Direct effect (C)		Total effect	
			Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Age	≥ 60	Multivariable[a]	0.004 (0.001–0.009)	0.002	0.004 (0.001–0.009)	0.002	0.011 (0.003–0.025)	0.032	0.019 (0.010–0.035)	0.007
		SIPTW	0.005 (0.001–0.009)	0.031	0.005 (0.001–0.011)	0.034	0.012 (0.002–0.022)	0.024	0.022 (0.009–0.035)	0.001
	< 60	Multivariable[a]	0.002 (−0.001–0.005)	0.347	0.002 (0.001–0.003)	0.048	0.004 (0.001–0.012)	0.042	0.006 (0.001–0.015)	0.046
		SIPTW	0.002 (0.001–0.005)	0.041	0.003 (0.001–0.006)	0.019	0.006 (0.001–0.014)	0.045	0.011 (0.002–0.020)	0.014
Sex	Female	Multivariable[a]	0.001 (0.001–0.003)	0.048	0.002 (0.001–0.004)	0.047	0.012 (0.006–0.020)	0.001	0.014 (0.006–0.023)	0.001
		SIPTW	0.001 (0.001–0.003)	0.048	0.002 (0.001–0.005)	0.046	0.011 (0.003–0.018)	0.003	0.014 (0.004–0.024)	0.007
	Male	Multivariable[a]	0.003 (0.001–0.006)	0.050	0.003 (0.001–0.007)	0.041	0.003 (−0.009–0.013)	0.557	0.009 (−0.002–0.019)	0.107
		sIPTW	0.007 (0.003–0.012)	0.002	0.006 (0.001–0.010)	0.008	0.003 (−0.009–0.016)	0.570	0.016 (0.005–0.027)	0.004

Notes: [a]: adjusted for age, female, hypertension, diabetes mellitus, currently smoking, posterior circulation, acute hydrocephalus, WFNS grade of 4–5, SEBES score of 3–4, mFS grade of 3–4, and treatment modalities.

Abbreviations: DCI, Delayed cerebral ischemia; POP, Postoperative pneumonia; CI, confidence interval; sIPTW, stabilized inverse probability of treatment weighting; WFNS, World Federation of Neurological Societies; SEBES, Subarachnoid Hemorrhage Early Brain Edema Score; mFS, modified Fisher Scale.

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lack of a significant effect of systemic inflammation on other in-hospital complications, it is possible that other pathophysiological changes, such as hypercoagulability, may emerge as more pivotal factors.[43,44] And in the future, it is recommended to conduct continuous collection of laboratory examinations during the early stage, as this will help further validate the association between SIRI and different complications, thus enhancing its reliability.

Currently, with the advancements in the survival rate of aSAH, greater attention is being devoted to enhancing the long-term prognosis.[45] Therefore, gaining a more lucid comprehension of the mediating role played by in-hospital complications between systemic inflammatory markers and long-term functional outcomes will aid in identifying clinically significant inflammatory biomarkers and may guide early anti-inflammatory interventions to improve long-term outcomes. Interestingly, our study found that the impact of SIRI on DCI was weaker compared to its effect on pneumonia (A1). Conversely, DCI's effect on 90-day poor prognosis was stronger than pneumonia's effect on the same outcome (B1>B2). Overall, our study revealed that the indirect effects of DCI and POP were comparable, though slightly higher for POP, after sIPTW. The precise extent and pathway of systemic inflammation on DCI remain unclear, as some studies suggest uncertainty regarding the directly exacerbate of the proinflammatory response in brain tissue by systemic inflammatory mediators.[5] In contrast, pneumonia, being an infectious disease, is widely regarded as a systemic condition heavily associated with systemic inflammation.[46] This likely explains the stronger association between SIRI and pneumonia compared to SIRI and DCI. It is understandable that DCI is more closely related to poor 90-day functional outcomes than pneumonia, as numerous studies have confirmed DCI to be the primary cause of poor functional outcomes in aSAH.[24] Therefore, while systemic inflammation may not exert the same impact on DCI as it does on pneumonia, both DCI and pneumonia played comparable roles in the process of systemic inflammation affecting poor long-term functional outcomes, mainly due to the generally worse prognosis associated with DCI. Our study also suggests that by proactively managing systemic inflammatory responses, such as the application of non-steroidal anti-inflammatory drugs, corticosteroids, albumin supplement, extracorporeal cooling approaches and cytokine-targeted therapy, physicians may have the potential to optimize and potentially improve nearly 40% of poor long-term functional outcomes under optimal circumstances.[47]

Our study, however, had several limitations. Firstly, this study was conducted as a single-center cohort study with a limited sample size and involved numerous statistical assumptions, which may have contributed to a higher Type I error rate. Therefore, our next step is to validate the clinical significance of SIRI through multicenter collaborations. Secondly, this was an observational study. Future research on early interventions based on early SIRI levels will be needed. Thirdly, it is necessary to continuously collect laboratory examinations during the patient's hospitalization to further investigate cumulative inflammatory burdens. This will enable a more accurate assessment of the patient's inflammatory status and help validate the association between SIRI and various complications, particularly infectious complications such as pneumonia. Fourthly, the heterogeneity of the devices used to detect inflammatory cells and the subjectivity of doctors in evaluating complications in different centers might have slightly affected the results. Fifthly, potential bias might still exist in the study, as certain crucial confounders might not have been fully adjusted for. Sixthly, future studies are encouraged to explore more in-hospital complications, such as delayed hydrocephalus, epilepsy, septicemia, etc. Seventhly, further research is needed to investigate the clinical significance of SIRI at different time periods during the early stages of the disease. Meanwhile, it is important to note that mediation analysis primarily explores statistical causal relationships. To confirm the clinical value of the results obtained from mediation analysis, additional clinical studies and intervention trials are necessary. Furthermore, the data used for analysis was limited to patients with single aneurysms. Finally, longer follow-up periods will be necessary to assess the durability of the observed associations in future studies.

Conclusion

In summary, our study revealed that heightened SIRI exhibited associations with DCI, POP, and poor 90-day functional outcomes. DCI and POP acted as partial mediators in the relationship between SIRI and 90-day functional outcomes, with each accounting for a mediation proportion exceeding 18%. Our findings might emphasize the potential significance of SIRI as a dependable marker for early systemic inflammation responses, prompting physicians to address early systemic inflammatory states diligently to prevent in-hospital complications, including DCI and POP, ultimately leading to enhanced long-term functional outcomes.

Data Sharing Statement

Patient data was not available for this study.

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Disclosure

The authors report no conflicts of interest in this work.

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