

# 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

Tu Li<sup>1</sup>, Runting Li<sup>1</sup>, Fa Lin<sup>1</sup>, Xiaolin Chen<sup>1-3</sup>

<sup>1</sup>Department of Neurosurgery, Beijing Tiantan Hospital, Beijing, People's Republic of China; <sup>2</sup>Stroke Center, Beijing Institute for Brain Disorders, Beijing, People's Republic of China; <sup>3</sup>Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Capital Medical University, Beijing, People's Republic of China

Correspondence: Xiaolin Chen, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, No. 119 South Fourth Ring West Road, Beijing, Fengtai District, 100070, People's Republic of China, Email [chenxiaolin@bjtth.org](mailto:chenxiaolin@bjtth.org)

**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

## Introduction

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

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.<sup>6–10</sup> Computed as neutrophil count \* monocyte count/lymphocyte count, SIRI remains relatively underexplored in the context of aSAH.<sup>11</sup> 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.<sup>12–14</sup> 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.<sup>15,16</sup> These complications exhibit varying degrees of association with systemic inflammatory responses and impact functional outcomes differently.<sup>17–20</sup> 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  $\geq$  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](#).

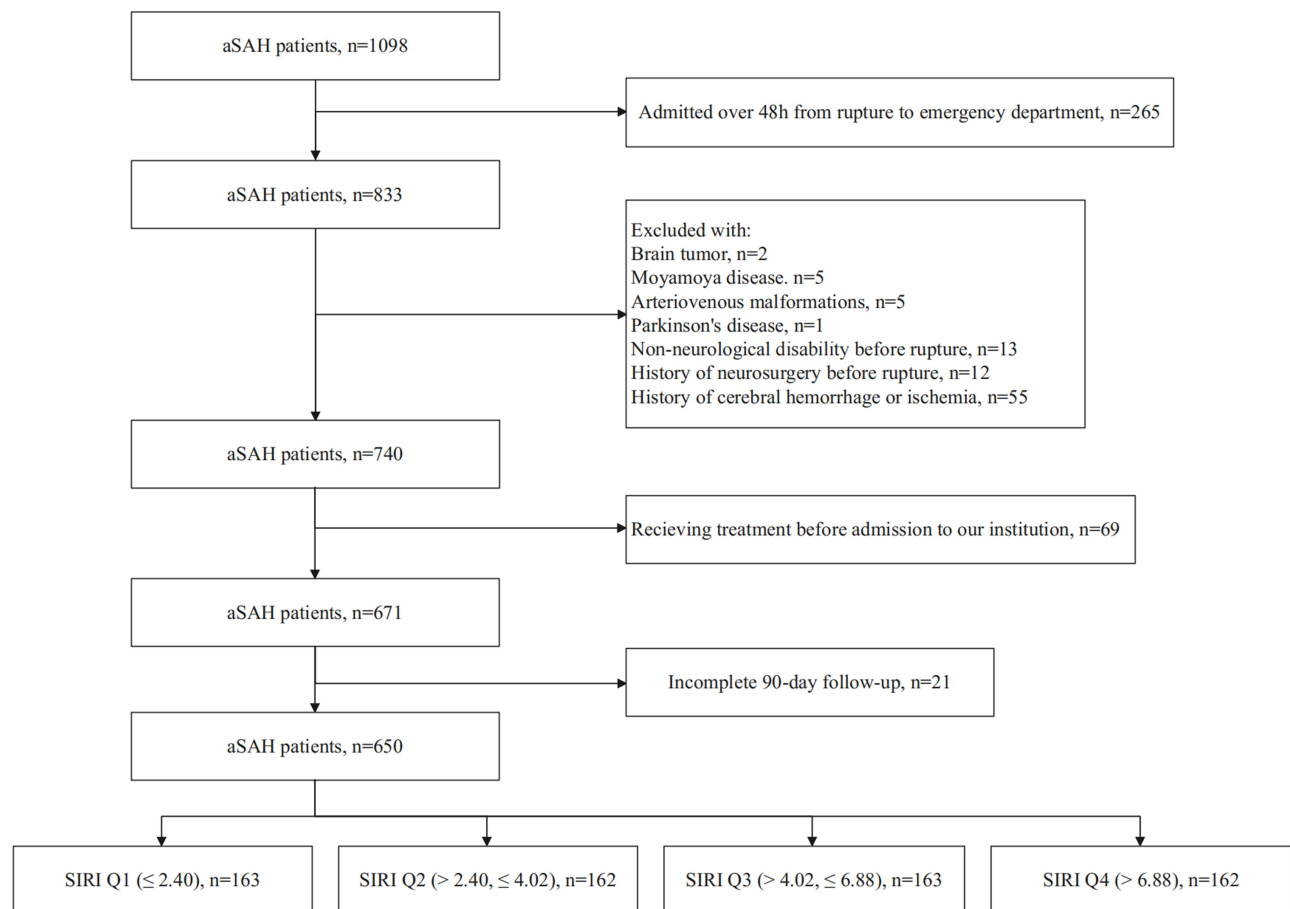
Furthermore, this study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline for cohort studies.<sup>21</sup>

### 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  $\times$  monocyte count/lymphocyte count.<sup>6</sup> 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,<sup>22</sup> 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,<sup>23</sup> the Subarachnoid Hemorrhage Early Brain Edema Score<sup>24</sup> (SEBES) and modified Fisher Scale<sup>25</sup> (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](#).<sup>26</sup> 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:  $\leq 2.40$ ; Quartiles 2:  $>2.40, \leq 4.02$ ; Quartiles 3:  $>4.02, \leq 6.88$ ; 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.<sup>27,28</sup> 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.<sup>29</sup>

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  $\pm$  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.<sup>30</sup>

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.<sup>31</sup> According to previous studies, the sample size and the data nature of our study was qualified for performing mediation analyses.<sup>32</sup> 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.<sup>33</sup> 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 ( $\sum A_n B_n$ )]. 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 ( $\geq 60$  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 <sup>a</sup>	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<sup>9</sup>/L). p<sup>a</sup> 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 <sup>a</sup>	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:  $\leq 2.40$ ; Level 2:  $> 2.40, \leq 4.02$ ; Level 3:  $> 4.02, \leq 6.88$ ; Level 4:  $> 6.88$  (Unit of measurement:  $\times 10^9/L$ ).  $p^a$  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.<sup>34,35</sup> 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).<sup>36,37</sup> 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.<sup>38</sup> 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.<sup>13,14</sup> 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.

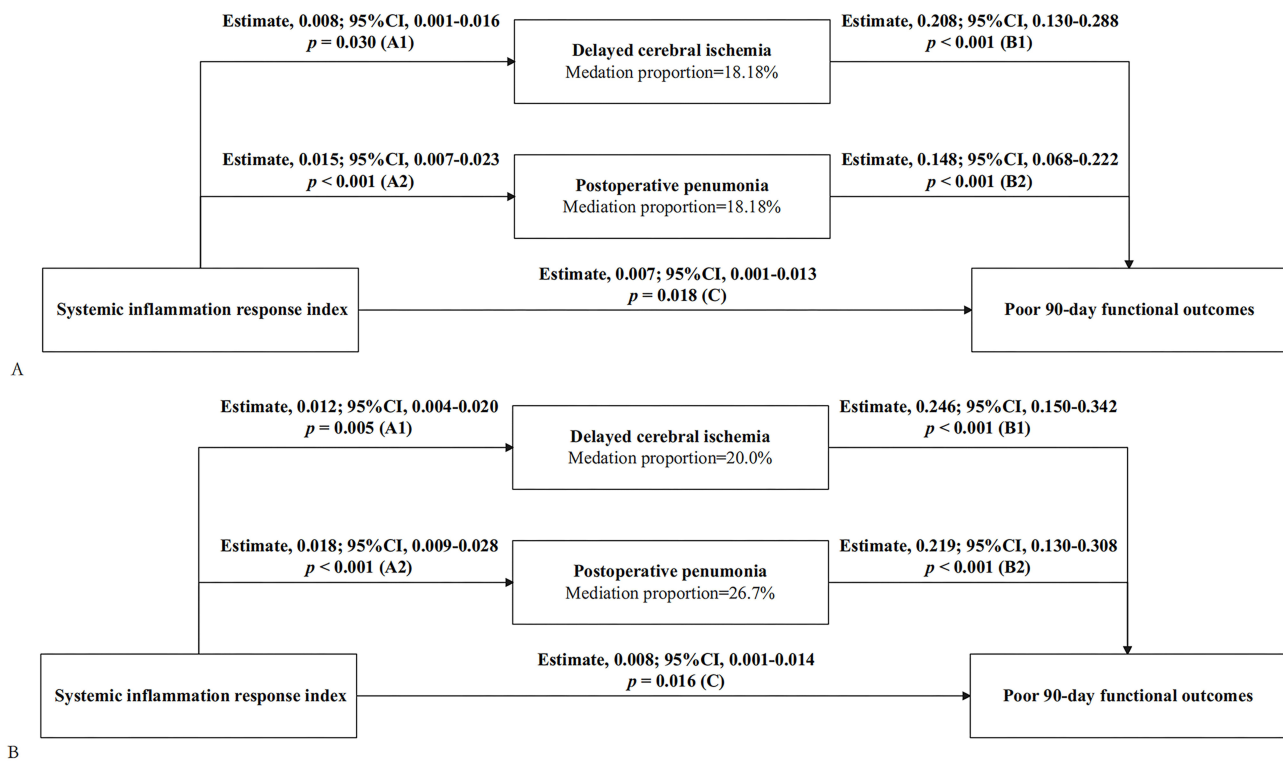
Regarding the association between SIRI and poor 90-day functional outcomes, akin to the findings in the studies conducted by Yuyang Hou et al and Seonyong Yun et al, we observed that elevated SIRI levels are indeed linked to a 90-day poor

**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 <sup>a</sup>	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 <sup>a</sup>	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 <sup>a</sup>	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:** <sup>a</sup>: 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.



**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 ( $\sum AnBn$ ). (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.<sup>13,14</sup> 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  $5.36 \times 10^9/L$  and  $3.2 \times 10^9/L$  respectively, our results indicate that SIRI levels above Q3 ( $>4.02 \times 10^9/L$ ) 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.<sup>26</sup> It has been reported that patients with aSAH who encounter medical complications tend to have worse outcomes compared to those without complications.<sup>39</sup> 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.<sup>40</sup> 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.<sup>41,42</sup> 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 <sup>a</sup> SIPTW	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
			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 <sup>a</sup> SIPTW	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
			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 <sup>a</sup> SIPTW	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
			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 <sup>a</sup> SIPTW	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
			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:** <sup>a</sup>: 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.

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.<sup>43,44</sup> 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.<sup>45</sup> 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.<sup>5</sup> In contrast, pneumonia, being an infectious disease, is widely regarded as a systemic condition heavily associated with systemic inflammation.<sup>46</sup> 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.<sup>24</sup> 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.<sup>47</sup>

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.

## Acknowledgments

We thank all the staff and participants for their contribution to this study.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Lawton MT, Vates GE, Solomon CG. Subarachnoid Hemorrhage. *N Engl J Med.* 2017;377:257–266. doi:10.1056/NEJMcpl605827
2. Cahill J, Calvert JW, Zhang JH. Mechanisms of early brain injury after subarachnoid hemorrhage. *J Cereb Blood Flow Metab.* 2006;26:1341–1353. doi:10.1038/sj.jcbfm.9600283
3. de Oliveira Manoel AL, Goffi A, Marotta TR, et al. The critical care management of poor-grade subarachnoid haemorrhage. *Crit Care.* 2016;20:21. doi:10.1186/s13054-016-1193-9
4. Kusaka G, Ishikawa M, Nanda A, et al. Signaling pathways for early brain injury after subarachnoid hemorrhage. *J Cereb Blood Flow Metab.* 2004;24:916–925. doi:10.1097/01.WCB.0000125886.48838.7E
5. Rass V, Gaasch M, Kofler M, et al. Systemic inflammatory response syndrome as predictor of poor outcome in nontraumatic subarachnoid hemorrhage patients. *Crit Care Med.* 2018;46:e1152–e1159. doi:10.1097/CCM.0000000000003429
6. Jin Z, Wu Q, Chen S, et al. The associations of two novel inflammation indexes, sii and siri with the risks for cardiovascular diseases and all-cause mortality: A ten-year follow-up study in 85,154 Individuals. *J Inflamm Res.* 2021;14:131–140. doi:10.2147/JIR.S283835
7. Chao B, Ju X, Zhang L, et al. A novel prognostic marker systemic inflammation response index (SIRI) for operable cervical cancer patients. *Front Oncol.* 2020;10:766. doi:10.3389/fonc.2020.00766
8. Hu M, Xu Q, Yang S, et al. Pretreatment systemic inflammation response index (SIRI) is an independent predictor of survival in unresectable stage III non-small cell lung cancer treated with chemoradiotherapy: a two-center retrospective study. *Ann Transl Med.* 2020;8:1310. doi:10.21037/atm-20-6484
9. Urbanowicz T, Michalak M, Ołasińska-Wiśniewska A, et al. Neutrophil counts, neutrophil-to-lymphocyte ratio, and Systemic Inflammatory Response Index (SIRI) predict mortality after off-pump coronary artery bypass surgery. *Cells.* 2022;11. doi:10.3390/cells11071124
10. Wang RH, Wen WX, Jiang ZP, et al. The clinical value of neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR) and systemic inflammation response index (SIRI) for predicting the occurrence and severity of pneumonia in patients with intracerebral hemorrhage. *Front Immunol.* 2023;14:1115031. doi:10.3389/fimmu.2023.1115031
11. Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer.* 2016;122:2158–2167. doi:10.1002/encr.30057
12. Bacigaluppi S, Bragazzi NL, Ivaldi F, et al. systemic inflammatory response in spontaneous subarachnoid hemorrhage from aneurysmal rupture versus subarachnoid hemorrhage of unknown origin. *J Inflamm Res.* 2022;15:6329–6342. doi:10.2147/JIR.S380101
13. Yun S, Yi HJ, Lee DH, et al. Systemic Inflammation response index and systemic immune-inflammation index for predicting the prognosis of patients with aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis.* 2021;30:105861. doi:10.1016/j.jstrokecerebrovasdis.2021.105861
14. Hou Y, Fan J, Yuan H, et al. Prognostic capacity of the systemic inflammation response index for functional outcome in patients with aneurysmal subarachnoid hemorrhage. *Front Neurol.* 2023;14:1054315. doi:10.3389/fneur.2023.1054315
15. Connolly E, Rabinstein A, Carhuapoma J, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2012;43:1711–1737. doi:10.1161/STR.0b013e3182587839
16. Charalambous L, Adil S, Rajkumar S, et al. A nationwide analysis of aneurysmal subarachnoid hemorrhage mortality, complications, and health economics in the USA. *Trans Stroke Res.* 2023;14:347–356. doi:10.1007/s12975-022-01065-w
17. Bender M, Stein M, Uhl E, et al. Troponin I as an early biomarker of cardiopulmonary parameters within the first 24 hours after nontraumatic subarachnoid hemorrhage in intensive care unit patients. *J Intensive Care Med.* 2020;35:1368–1373. doi:10.1177/0885066618824568
18. Yuan K, Li R, Zhao Y, et al. Pre-Operative predictors for post-operative pneumonia in aneurysmal subarachnoid hemorrhage after surgical clipping and endovascular coiling: a single-center retrospective study. *Front Neurol.* 2022;13:893516. doi:10.3389/fneur.2022.893516
19. Liang CW, Su K, Liu JJ, et al. Timing of deep vein thrombosis formation after aneurysmal subarachnoid hemorrhage. *J Neurosurg.* 2015;123:891–896. doi:10.3171/2014.12.JNS141288
20. Hammer A, Ranaie G, Erbguth F, et al. Impact of complications and comorbidities on the intensive care length of stay after aneurysmal subarachnoid haemorrhage. *Sci Rep.* 2020;10:6228. doi:10.1038/s41598-020-63298-9
21. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007;370:1453–1457. doi:10.1016/S0140-6736(07)61602-X
22. Oshiro EM, Walter KA, Piantadosi S, et al. A new subarachnoid hemorrhage grading system based on the Glasgow coma scale: A comparison with the hunt and hess and world federation of neurological surgeons scales in a clinical series. *Neurosurg.* 1997;41:140–147. doi:10.1097/00006123-199707000-00029
23. Hostettler IC, Sebök M, Ambler G, et al. Validation and optimization of barrow neurological institute score in prediction of adverse events and functional outcome after subarachnoid hemorrhage-creation of the hatch (hemorrhage, age, treatment, clinical state, hydrocephalus) score. *Neurosurg.* 2020;88:96–105. doi:10.1093/neuros/nyaa316
24. Ahn SH, Savarraj JP, Pervez M, et al. The subarachnoid hemorrhage early brain edema score predicts delayed cerebral ischemia and clinical outcomes. *Neurosurg.* 2018;83:137–145. doi:10.1093/neuros/nyx364
25. Frontera JA, Claassen J, Schmidt JM, et al. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurg.* 2006;59:21–27. doi:10.1227/01.neu.0000243277.86222.6c

26. Hoh BL, Ko NU, Amin-Hanjani S, et al. Guideline for the management of patients with aneurysmal subarachnoid hemorrhage: a guideline from the American heart association/American stroke association. *Stroke*. 2023;54:e314–e370. doi:10.1161/STR.0000000000000436
27. Rajan P, Sooriakumaran P, Nyberg T, et al. Effect of comorbidity on prostate cancer-specific mortality: a prospective observational study. *J clin oncol*. 2017;35:3566–3574. doi:10.1200/JCO.2016.70.7794
28. McCaffrey DF, Griffin BA, Almirall D, et al. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med*. 2013;32:3388–3414. doi:10.1002/sim.5753
29. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107. doi:10.1002/sim.3697
30. Fang F, Wang P, Yao W, et al. Association between D-dimer levels and long-term mortality in patients with aneurysmal subarachnoid hemorrhage. *Neurosurg Focus*. 2022;52:E8. doi:10.3171/2021.12.FOCUS21512
31. Rosseel Y. lavaan: An R package for structural equation modeling. *J Statist Soft*. 2012;48:1–36. doi:10.18637/jss.v048.i02
32. Fritz MS, Mackinnon DP. Required sample size to detect the mediated effect. *Psychol Sci*. 2007;18:233–239. doi:10.1111/j.1467-9280.2007.01882.x
33. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods*. 2008;40:879–891. doi:10.3758/BRM.40.3.879
34. Yoshimoto Y, Tanaka Y, Hoya K. Acute systemic inflammatory response syndrome in subarachnoid hemorrhage. *Stroke*. 2001;32:1989–1993. doi:10.1161/hs0901.095646
35. Geraghty JR, Lung TJ, Hirsch Y, et al. Systemic immune-inflammation index predicts delayed cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Neurosurg*. 2021;89:1071–1079. doi:10.1093/neuros/nyab354
36. Giede-Jeppe A, Reichl J, Sprügel MI, et al. Neutrophil-to-lymphocyte ratio as an independent predictor for unfavorable functional outcome in aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2019;132:400–407. doi:10.3171/2018.9.JNS181975
37. Qin Y, Zhang B, Zhao S, et al. Association between higher systemic immune inflammation index (SII) and deep vein thrombosis (DVT) in patients with aneurysmal subarachnoid hemorrhage (aSAH) after endovascular treatment. *Neurosurg Rev*. 2023;46:142. doi:10.1007/s10143-023-02048-7
38. Zhang Y, Xing Z, Zhou K, et al. The Predictive role of systemic inflammation response index (SIRI) in the prognosis of stroke patients. *Clin Interv Aging*. 2021;16:1997–2007. doi:10.2147/CIA.S339221
39. Asehnoune K, Mrozek S, Perrigault PF, et al. A multi-faceted strategy to reduce ventilation-associated mortality in brain-injured patients. The BI-VILI project: a nationwide quality improvement project. *Intensive Care Med*. 2017;43:957–970. doi:10.1007/s00134-017-4764-6
40. Wang Z, Pu Q, Huang C, et al. Crosstalk Between Lung and Extrapulmonary Organs in Infection and Inflammation. *Adv Exp Med Biol*. 2021;1303:333–350.
41. Budohoski KP, Guilfoyle M, Helmy A, et al. The pathophysiology and treatment of delayed cerebral ischaemia following subarachnoid haemorrhage. *J Neurol Neurosurg Psych*. 2014;85:1343–1353. doi:10.1136/jnnp-2014-307711
42. Miller BA, Turan N, Chau M, et al. Inflammation, vasospasm, and brain injury after subarachnoid hemorrhage. *Biomed Res Int*. 2014;2014:384342. doi:10.1155/2014/384342
43. Goshgarian C, Gorelick PB. DVT prevention in stroke. *Curr Neurol Neurosci Rep*. 2017;17:81. doi:10.1007/s11910-017-0782-6
44. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. *Nat Rev Cardiol*. 2021;18:666–682. doi:10.1038/s41569-021-00552-1
45. Nussbaum ES, Mikoff N, Paranjape GS. Cognitive deficits among patients surviving aneurysmal subarachnoid hemorrhage. A contemporary systematic review. *Br J Neurosurg*. 2021;35:384–401. doi:10.1080/02688697.2020.1859462
46. Ji R, Wang D, Shen H, et al. Interrelationship among common medical complications after acute stroke: pneumonia plays an important role. *Stroke*. 2013;44:3436–3444. doi:10.1161/STROKEAHA.113.001931
47. CZ C, UC H, LT K. Systemic inflammation after aneurysmal subarachnoid hemorrhage. *Int J Mol Sci*. 2023;24. doi:10.3390/ijms241310943

## Publish your work in this journal

The Journal of Inflammation Research is an international, peer-reviewed open-access journal that welcomes laboratory and clinical findings on the molecular basis, cell biology and pharmacology of inflammation including original research, reviews, symposium reports, hypothesis formation and commentaries on: acute/chronic inflammation; mediators of inflammation; cellular processes; molecular mechanisms; pharmacology and novel anti-inflammatory drugs; clinical conditions involving inflammation. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-inflammation-research-journal>