Article

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Correlation Analysis between Systemic Immune Inflammation Index and Adverse Outcomes in Aneurysmal Subarachnoid Hemorrhage

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Background: The prognosis of patients with cerebral hemorrhage is strongly linked to systemic inflammatory responses. This study aimed to investigate the correlation between the systemic immune inflammation index (SII) and adverse outcomes in patients diagnosed with aneurysmal subarachnoid hemorrhage (aSAH).
Method: Between February 2020 and September 2022, we conducted a retrospective cohort analysis involving 102 aSAH patients who visited our hospital. We collected baseline and clinical data to assess the relationship between SII and prognosis. Patients were categorized into either the good or poor prognosis group based on the modified Rankin Scale (mRS) score three months post-discharge. Comparative analysis of baseline and clinical data at admission and three months post-discharge was conducted between the two groups.
Result: The study included 51 patients in the good prognosis group and 51 patients in the poor prognosis group. Statistically significant differences were observed between the groups in terms of age, the number of patients undergoing craniotomy clipping surgery, the number of patients receiving endovascular embolization treatment, main grade of Fisher at admission, and postoperative complications ($p < 0.05$). The Area Under Curve (AUC) for predicting adverse outcomes in aSAH using SII was 0.812 (95% confidence interval (CI): 0.730–0.894, $p < 0.001$), with a sensitivity of 0.863, specificity of 0.627, and an optimal cut-off value of 2214.5. Furthermore, the odds ratio (OR) of SII as an independent influencing factor was 10.586 (95% CI: 3.977–28.177, $p < 0.001$).
Conclusion: The prognosis of aSAH patients at three months post-discharge is associated with their SII at admission. An elevated SII indicates a higher incidence of adverse outcomes in aSAH patients.

Keywords: systemic immune inflammation index; aneurysmal subarachnoid hemorrhage; prognosis; inflammation

Introduction

Subarachnoid hemorrhage (SAH) is a form of stroke characterized by blood flow into the subarachnoid space following the rupture of blood vessels at the base or surface of the brain, leading to distinctive clinical manifestations [1]. Intracranial aneurysm is currently the predominant etiological factor for SAH, known as aneurysmal subarachnoid hemorrhage (aSAH) [2]. Epidemiological data show a notable global incidence and mortality rate associated with aSAH, with a crude global incidence rate of 6.67 cases per 100000 individuals, displaying significant regional variations per WHO classifications [2,3]. Annually, nearly 500000 individuals worldwide experience aSAH, resulting in a mortality rate of 35% [2]. Timely prognostic evaluation of aSAH patients is significant for guiding clinical interventions and predicting outcomes.

Presently, clinical assessments of aSAH prognosis rely on the World Federation of Neurosurgical Societies Grading System of Subarachnoid Hemorrhage (WFNS-SAH) classification, Fisher classification, and Hunt-Hess classification. However, these evaluations predominantly hinge on subjective clinical performance rather than objective laboratory data. Consequently, there is a pressing need to identify more precise indicators to enhance the accuracy of prognostic predictions.

The systemic immune inflammatory index (SII), a novel biomarker reflecting systemic inflammatory response, is defined as SII = neutrophil count ($\times$ 10^9/L) $\times$ Platelet count ($\times$ 10^9/L)/lymphocyte count ($\times$ 10^9/L) [4]. Previous studies have proposed a close association between systemic inflammatory response and the prognosis of patients with cerebral hemorrhage. Notably, early SII has been postulated as a novel independent prognostic indicator for the initial stages of the disease [5–7]. Building upon this foundation, our study investigated the correlation between the prognosis of aSAH patients three months post-discharge and SII levels at admission. Additionally, the research aimed to elucidate the predictive value of SII at admission in determining the short-term prognosis of aSAH.

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Objects and Methods

Research Subjects

The research methodology outlined by Geraghty JR *et al*. [8] served as the foundational framework for this study. The Department of Neurology of our hospital (Henan Vocational College of Nursing Internal) designed a retrospective cohort study focusing on the prognosis of SAH. Subsequently, we conducted an observational retrospective cohort study, selecting 102 patients with aSAH who sought medical attention at our hospital (Henan Vocational College of Nursing Internal) between February 2020 and September 2022. The study received approval from the Ethics Committee of Henan Vocational College of Nursing Internal (S202001018), and informed consent was obtained from all participants.

Sample size calculation: Using the area under the Receiver Operating Characteristic (ROC) curve of SII as the primary indicator, assuming an area of at least 0.5 based on previous literature [8], where the area was identified as 0.767, we set the number of cases with good or bad prognosis as equal. With a power of 0.09, a first class error of 0.05, and a dropout rate of 20%, PASS software calculated that 28 cases were required in each group.

Inclusion criteria: (1) Conforming to the diagnostic criteria of aSAH, confirmed through head CT and lumbar puncture examinations; (2) Onset to admission time less than 24 hours, and onset to surgical treatment time more than 48 hours; (3) First onset of aSAH; (4) Clinical manifestations include headache, accompanied by nausea, vomiting, limb twitching, or varying degrees of consciousness disorders, with a positive meningeal stimulation sign.

Exclusion criteria: (1) Absence of intracranial aneurysm; (2) Presence of other cerebrovascular diseases, such as arteriovenous malformations, arteriovenous fistulas, moyamoya disease, etc.; (3) Severe organ dysfunction involving the heart, lung, liver, and kidney; (4) Presence of mental disorders and poor treatment compliance; (5) Incomplete clinical data.

Baseline information collected from patients includes age, gender, time from onset to admission, time from onset to surgical treatment, surgical method, accompanying symptoms and complications, World Federation of Neurosurgical Societies Grading System of Subarachnoid Hemorrhage (WFNS-SAH) grading at admission, Fisher grading, Hunt-Hess grading, etc. At admission, 5 mL of fasting peripheral venous blood was drawn in the morning, allowed to stand at room temperature for 30–60 minutes, centrifuged at 3000 r/min for 10 minutes, and the serum was separated and stored at –20 °C for testing. The KS-480 fully automatic biochemical analyzer (Shandong Kelisen Biological Co., Ltd., Shangdong, China) was used to assess blood routine indicators (neutrophil count, lymphocyte count, platelet count). The operation process was conducted following the manufacturer's instructions for calculating SII.

Prognostic Evaluation and Grouping Methods

Clinical data were collected from patients three months after discharge, and their prognosis was evaluated based on the modified Rankin Scale (mRS) score, categorizing the patients into a good prognosis group and a poor prognosis group. The specific scoring criteria were as follows: 0 point indicates complete asymptomatic status; 1 point signifies symptomatic classification without apparent functional impairment, retaining the ability to perform all daily activities; 2 points denote mild disabilities, where individuals cannot complete all pre-illness activities but can manage personal affairs independently; 3 points represent moderate disabilities, requiring some mild assistance, yet independent in walking; 4 points indicate severe disability, involving the inability to walk independently and meet personal needs without assistance; 5 points denote severe disability, with the patient bedridden, experiencing incontinence, and requiring continuous care and attention; and a score of 6 signifies death [9]. A score of 0–2 points implies a good prognosis, while a score of 3–6 points indicates a poor prognosis. Based on the mRS score, 102 patients were divided into a good prognosis group (51 cases) and a poor prognosis group (51 cases).

Evaluation Criteria

WFNS-SAH Grading

The WFNS-SAH scale is a simple and commonly used clinical scale. WFNS-SAH grade I denotes a Glasgow Coma Scale (GCS) score of 15 points without motor deficits, grade II indicates a GCS score of 13–14 points with no motor defects, grade III signifies a GCS score of 13–14 points with motor disorders, grade IV indicates a GCS score of 7–12 points with or without motor disorders, grade V denotes a GCS score of 3–6 points with or without motor disorders [10].

Fisher Grading

The Fisher scale is an essential index for evaluating the risk of vasospasm in patients with aSAH. Fisher grade I corresponds to CT findings without bleeding, grade II refers to CT findings of diffuse bleeding without the blood clot formation, grade III indicates a thick arachnoid membrane with a thickness of $>$1 mm in the vertical plane or a length $\times$ width exceeding 5 mm $\times$ 3 mm in the horizontal plane, and grade IV signifies intracerebral hematoma or intraventricular hemorrhage, with little or no diffuse bleeding in the basal cistern [11].

Hunt-Hess Grading

The Hunt-Hess grading system is clinically used to assess the severity of SAH [12]. Hunt-Hess grade I indicates asymptomatic or mild headache with mild neck stiffness, grade II signifies moderate to severe headache with neck stiffness without neurological deficits other than cra-

Table 1. Baseline data.

Influence factor		Good prognosis group (n = 51)	Poor prognosis group (n = 51)	$t/\chi^2/z$ value	p
Age (years)		51.47 ± 4.02	61.47 ± 3.97	12.640	<0.001*
Male [n (%)]		32 (62.75)	36 (70.59)	0.706	0.401
Time from onset to surgical treatment <24 h [n (%)]		38 (74.51)	45 (88.24)	3.169	0.075
Patients undergoing craniotomy clipping surgery [n (%)]		5 (9.80)	17 (33.33)	8.345	0.004*
Receiving endovascular embolization treatment [n (%)]		46 (90.20)	34 (66.67)	8.345	0.004*
Main grade of WFNS-SAH at admission [n (%)]		Grade II: 19 (37.25)	Grade III: 19 (37.25)	0.031	0.860
Main grade of Fisher at admission [n (%)]		Grade IV: 27 (52.94)	Grade IV: 19 (37.25)	4.741	0.029*
Main grade of Hunt-Hess at admission [n (%)]		Grade II: 19 (37.25)	Grade II: 18 (35.29)	0.623	0.430
	Diabetes	8 (15.69)	10 (19.61)		
Underlying disease [n (%)]	Hypertension	15 (29.41)	12 (23.53)	1.596	0.450
	Hyperlipidemia	10 (19.61)	16 (31.37)		
Postoperative complications [n (%)]		37 (72.55)	48 (94.12)	8.541	0.004*
Lymphocyte count (10^9/L)		1.11 ± 0.36	1.00 ± 0.36	1.514	0.133
Neutrophil count (10^9/L)		6.74 ± 1.85	7.63 ± 2.70	–1.939	0.056
Platelet count (10^9/L)		346.51 ± 93.14	406.02 ± 116.75	–2.846	0.005*
SII [M (P_{25}–P_{75})]		2086.96 (1836.03–2489.02)	2680.41 (2371.42–3878.51)	–5.431	0.000*

$^*p < 0.05$.

nial nerve paralysis, grade III refers to drowsiness, blurred consciousness, or mild disorientation, grade IV indicates coma with moderate to severe hemiplegia, and grade V describes deep coma, brain loss, ankylosis, and near-death status.

Statistical Methods

Statistical analysis was conducted using SPSS software (version 20.0; SPSS, Chicago, IL, USA). Categorical variable data were expressed as n%, and group comparisons were made using the χ^2 test. Disordered categorical variable data were assessed using the chi-square test, one-way ordered classification data were compared using the rank sum test, and continuous variable data conforming to normal distribution were expressed as mean ± standard deviation (SD). The independent sample t-test was employed for comparisons between the two groups. For variables not adhering to the normal distribution, the median (interquartile range) (M (P_{25}–P_{75})) was used, and differences between groups were assessed using the Mann-Whitney U test.

The diagnostic accuracy of each parameter was evaluated through the area under the Receiver Operating Characteristic (ROC) curve. Area Under Curve (AUC) values ranging from 0.5–0.7 indicated low accuracy, while AUC >0.7 indicated good accuracy. The odds ratio (OR) was used to test the correlation between SII and aSAH adverse outcomes in aneurysmal subarachnoid hemorrhage (aSAH), with the significance determined using the Chi-square test. A significance level of $p < 0.05$ was considered statistically significant.

Table 2. The predictive SII value for adverse outcomes in aneurysmal subarachnoid hemorrhage (aSAH).

Indicator	SII
AUC	0.812
95% CI	0.730–0.894
Sensitivity	0.863
Specificity	0.627
Youden index	0.490
Optimum cut-off values	2214.50

AUC, Area Under Curve; CI, confidence interval; SII, systemic immune inflammation index.

Results

Baseline Data

In the good prognosis group, comprising 51 patients, 32 were male (62.75%), with an age range of 44 to 61 years (51.47 ± 4.02). Furthermore, 38 patients (74.51%) underwent surgical treatment within <24 hours of onset, 5 patients (9.80%) underwent craniotomy clipping surgery, and 46 patients (90.20%) received intravascular embolization treatment. Upon admission, the WFNS-SAH grading predominantly fell into grade II (37.25%), Fisher grading into grade IV (52.94%), and Hunt-Hess grading into grade II (37.25%). Additionally, 33 patients (64.71%) had underlying diseases, and 37 patients (72.55%) experienced postoperative complications. The SII value in the good prognosis group was 2086.96 (1836.03–2489.02).

In the poor prognosis group, consisting of 51 patients aged 50–70 years (61.47 ± 3.97), 36 cases (70.59%) were male. Among these patients, 45 (88.24%) received surgical treatment within <24 hours and 17 (33.33%) underwent craniotomy. Moreover, 34 patients (66.67%) received en-

Table 3. The distribution of SII numbers and aSAH outcomes.

SII	Prognosis status		Total	p	95% CI	χ^2
	Poor prognosis group (n = 51)	Good prognosis group (n = 51)				
High SII group	44	19	63	$p < 0.001$	3.977–28.177	25.946
Low SII group	7	32	39			
Total	51	51	102			

SII, systemic immune inflammation index.

dovascular embolization treatment. At admission, WFNS-SAH grading was predominantly grade III (37.25%), Fisher grading was mainly grade IV (37.25%), and Hunt-Hess grading was primarily grade II (35.29%). Additionally, 38 patients (74.51%) had underlying diseases, and 48 patients (94.12%) experienced postoperative complications. The SII value in the poor prognosis group was 2680.41 (2371.42–3878.51).

Significant differences were observed between the two groups in terms of age, patients undergoing craniotomy clipping surgery, receiving endovascular embolization treatment, main Fisher grade at admission, postoperative complications, lymphocyte count, and SII ($p < 0.05$). Specific baseline data are presented in Table 1.

Predictive Value of SII for Adverse Outcomes in aSAH

In the analysis of the Receiver Operating Characteristic (ROC) curve, the Area Under Curve (AUC) for predicting adverse outcomes in aSAH was 0.812 (95% confidence interval (CI): 0.730–0.894, $p < 0.001$). The sensitivity and specificity were determined to be 0.863 and 0.627, respectively, with an optimal cut-off value of 2214.5, as shown in Table 2 and Fig. 1.

Correlation between SII and Adverse Outcomes in aSAH

A potential correlation between the SII and adverse outcomes in aSAH at admission was explored. Patients were grouped into High SII and Low SII groups using the optimal cot-off value of SII (Table 3). The odds ratio (OR) was calculated as (44/19)/(7/32) = 10.586 (95% CI: 3.977–28.177, $p < 0.001$), indicating a significant association between SII and adverse outcome in aSAH.

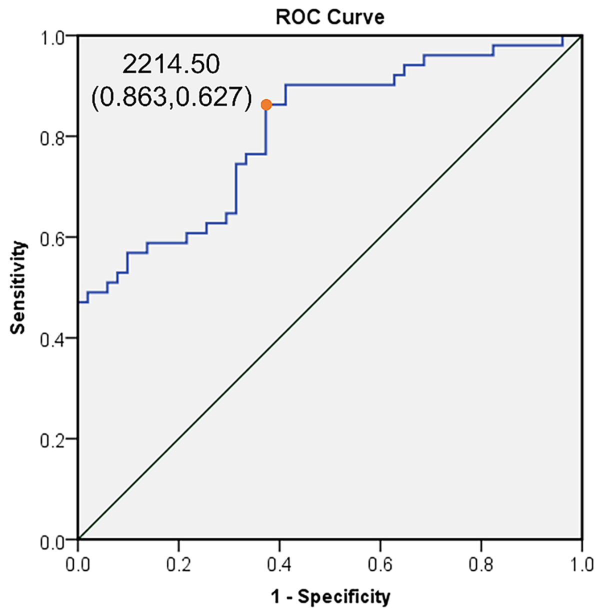

Fig. 1. ROC curve for SII value. ROC, Receiver Operating Characteristic.

Discussion

The hallmark clinical symptom of aSAH is an abrupt, severe headache, often accompanied by loss of consciousness, nausea, vomiting, photophobia, and neck pain. Moreover, a significant number of patients exhibit systemic inflammation following aSAH [13]. Upon the rapture of an intracranial aneurysm, blood infiltrates the subarachnoid space, leading to the degradation of red blood cells and the production of hemoglobin, methemoglobin, and heme. These degradation products activate Toll-like receptor 4 (TLR4), triggering an intense inflammatory reaction. The extent of inflammatory response is intricately linked to cerebral vasospasm and subsequent brain tissue damage [14]. Current treatment modalities for aSAH involve surgical interventions or vascular therapy. The choice of different treatment options has varying impacts on patient prognosis. However, a reliable and objective method for predicting prognosis in clinical practice remains elusive.

A growing body of evidence suggests that the SII is associated with clinical outcomes in aSAH patients. An elevated SII index independently predicts poor prognosis in aSAH patients [15,16]. In light of this, the present study investigated the relationship between SII at admission and the prognosis of aSAH patients three months post-discharge. Additionally, the study explored the predictive value of SII at admission for the short-term prognosis of aSAH patients.

SII, a novel biomarker encompassing neutrophil count, lymphocyte count, and platelet count, closely mirrors the inflammatory response and reflects the delicate equilibrium between host inflammation and immune response. An elevated SII signifies a pre-thrombotic state (high platelet count) and immune dysfunction (high neutrophil count and low lymphocyte count) [17]. Within three days of aSAH occurrence, the white blood cells significantly increase in the patient's peripheral blood. Subarachnoid hemorrhage induces an increase in neutrophils and macrophages, prompting platelet aggregation. Subsequent immune suppression exacerbates the inflammatory response, elevating the incidence of infectious complications and contributing to a poor prognosis in aSAH patients. In addition, studies have confirmed the potential of SII to predict the adverse reactions related to inflammation, immunosuppression, and thrombosis post-aSAH [18–20]. Importantly, SII stands out from conventional clinical evaluation scales, relying on serological indicators measured by instruments, rendering its results objective.

In this study, 102 patients were divided into a good prognosis group and a poor prognosis group based on the mRS score. The comparison of baseline data revealed statistically significant differences in age, the number of patients undergoing craniotomy clipping surgery, the number of patients receiving endovascular embolization treatment, the main Fisher grade at admission, and postoperative complications. Subsequently, the ROC curve was used to analyze the predictive value of the SII at admission for adverse outcomes in aSAH, yielding an optimal cut-off value of 2214.5. Upon calculating the OR, a potential correlation was identified between SII at admission and adverse outcomes three months post-discharge.

Utilizing the optimal cut-off value from ROC analysis, SII was divided into high SII and low SII groups. Comparison between these groups revealed that patients in the high SII group were generally older, with a higher number of patients undergoing craniotomy clipping surgery and endovascular embolization treatment, a higher Fisher grade at admission, and a higher prevalence of adverse outcomes. Conversely, the low SII group exhibited more favorable outcomes. These findings suggest that an elevated SII may be inversely correlated with a poor prognosis in patients with aSAH, indicating that a higher SII is associated with a worse prognosis. However, it is essential to note that clinical data were collected three months post-hospital discharge. Further investigation is warranted to explore whether long-term monitoring results align with the three-month monitoring outcomes.

Conclusion

In conclusion, the SII at admission exhibits predictive value for the short-term prognosis of aSAH. These findings suggest a potential correlation between SII at admission and the prognosis of aSAH patients at three months post-discharge, with an elevated SII indicating a higher incidence of adverse outcomes in aSAH patients.

Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Author Contributions

Substantial contributions to conception and design: QZ, ZL. Data acquisition, data analysis and interpretation: QZ, ZL. Drafting the article or critically revising it for important intellectual content: QZ, ZL. Final approval of the version to be published: QZ, ZL. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved: QZ, ZL.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Henan Vocational College of Nursing Internal (S202001018). The informed consent was signed by all participants.

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Conflict of Interest

The authors declare no conflict of interest.

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