Systemic Immune-Inflammation Index Predicts the Outcome After Aneurysmal Subarachnoid Hemorrhage

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Abstract

Objectives: Systemic inflammatory response is closely related to the pathogenesis and prognosis in critical patients. Recently, systemic immune-inflammation index (SII), an indicator of systemic inflammatory response, was proved to predict the outcome in cancerous and non-cancerous diseases. The aim of this study is to evaluate the relationship between SII on admission and 6-month outcome in patients with aneurysmal subarachnoid hemorrhage (aSAH).

Methods: The clinical data and prognosis of 76 patients with aSAH was analyzed. Patients were divided into high SII group and low SII group. The 6-month outcome was assessed by the modified Rankin scale (mRS). The unfavorable outcome was defined as mRS score ≥ 3 . Receiver operating characteristics (ROC), area under the curve (AUC) and logistic regression were used to examine the relations between SII levels and 6-month clinical outcomes.

Results: Thirty-six patients (47.4%) in our study had a unfavorable outcome (mRS ≥ 3) at 6 months, and twenty-four (66.7%) of them had high SII. Spearman correlation analysis showed that the SII was correlated with mRS ($r=0.418$, $P=0.05$). Binary logistic regression showed that there was an independent association between SII on admission and 6-month clinical outcome (OR=4.271, 95%CI: 1.047-17.422, $P=0.05$). The AUC of the SII for predicting unfavorable outcome was 0.692(95% CI:0.571–0.814, $P=0.05$).

Conclusion: Systemic immune-inflammation index (SII) could be a novel independent prognostic factor for aSAH patients at the early stage of the disease.

Introduction

Aneurysmal Subarachnoid Hemorrhage (aSAH), which has a high fatality rate (8.3% ~ 66.7%) and high disability rate (10%-20%), accounts for 5% of all strokes[3, 8, 9, 22, 31]. Thirty to 50% of SAH survivors develop delayed neurological dysfunction(DND)and has unfavorable outcomes leading to decreased quality of life and increased societal monetary burden[6, 14]. Because of complex pathophysiology in early and delayed brain damage, inflammation after bleeding is an important factor affecting the prognosis of aneurysms[2, 22, 25].At present, indicators such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutrition index (PNI), MMP-9, TNF- α , IL-6 have shown associations with clinical complications and outcomes in aSAH[4, 5, 7, 10]. However, prediction effects of these indicators on aSAH prognosis were not satisfactory and contradictory findings existed in current studies. Based on this, it is well worth exploring more suitable serum biomarkers to assess the severity of aSAH and predict the outcome of aSAH.

Systemic immune-inflammation index (SII), which includes peripheral lymphocytes, neutrophils and platelets, is increasingly recognized as a readily available biomarker for systemic inflammation and plays an important role in predicting the prognosis and survival rate of patients with some diseases such as visceral tumors,brain malignant tumor, spontaneous cerebral hemorrhage, cerebral infarction, and dementia[11, 16, 17, 32, 33, 35]. However, it is unclear whether SII could be used as viable biomarkers for

predicting outcomes in patients with aSAH. This retrospective study aimed to investigate the relationship between SII and the 6-month outcome of aSAH.

Material And Methods

Patients

We retrospectively analyzed the clinical data of patients with aSAH who were hospitalized in the department of neurosurgery or intensive care unit of the Second Affiliated Hospital of Chongqing Medical University from March 2018 to July 2020. The inclusion criteria were as follows:

1. Sudden burst headache, vomiting with or without disturbance of consciousness and focal neurological impairment
2. Spontaneous SAH was confirmed by cranial Computerized Tomography (CT) or lumbar puncture
3. Patients with a definite diagnosis of Intracranial aneurysm (IA) by craniocerebral Computerized Tomography Angiography (CTA), Digital Subtraction Angiography (DSA), or surgery, and this IA is the cause of SAH
4. Age: From 18 to 80
5. Admitted within 72 h after aSAH

In addition, the exclusion criteria were as follows:

1. Other intracranial vascular diseases
2. Age less than 18 or more than 80
3. Acute and chronic infectious inflammation before admission (pneumonia supported by imaging examination, urinary tract infection by urine examination, chronic active viral hepatitis, etc.)
4. Systemic immune diseases
5. Epilepsy and acute obstructive hydrocephalus
6. Previous history of severe trauma, stroke, etc.
7. Diseases of the blood system other than anemia
8. Malignant tumor
9. Lost to follow-up

This study has been approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University.

Methods

Demographic data and the medical history of patients, including age and gender, hypertension, diabetes, and history of anticoagulation therapy, were collected from the hospital database. In addition, lifestyle risk factors such as smoking habits and drinking status were also recorded, as well as treatment during

hospitalization. Medical complications including infection, delayed cerebral ischemia, and cerebral vasospasm, were also recorded. The number of White Blood Cells [WBC], Platelet [PLT], Absolute Neutrophil [ANC] and Absolute Lymphocyte Counts [ALC] were obtained by automated test system systems Hitachi 7600 and BM2000 on admission. The severity of aSAH was assessed by Glasgow Coma Scale (GCS) on admission and the scores were divided into three levels: severe (13-15), moderate (9-12), and mild (3-8). The SII ($10^9/L$) was calculated as following formula: $PLT (10^9/L) \times ANC (10^9/L) / ALC (10^9/L)$ [12]. The receiver operating characteristic (ROC) curve for 6-month survival revealed that the best cut-off value of SII was 2344.65. The patients were divided into two groups according to prior cut-off value: high SII group (The SII >2344.65) and low SII group (The SII ≤ 2344.65). Follow-up was undertaken by telephone after 6 months of aSAH, and the 6-months neurological function was evaluated with modified Rankin scale (mRS). Patients were divided into a favorable outcome group with a low mRS (<3) and an unfavorable outcome group with a high mRS (≥ 3).

Statistical analysis

The analysis was performed with SPSS V.22. Continuous data were expressed as mean $\pm$ standard deviation (SD) or median (quartile range), and categorical data were presented as frequency and percentage (%). Comparisons of categorical variables were performed using the chi-square test or fisher's exact test, while the Mann-Whitney U test or unpaired t-test was applied for continuous variables. The ROC curves were plotted for predictors, and the area under the curve (AUC) was used to evaluate the predictive value. The correlations between the SII and mRS were assessed by Spearman correlation. The independent predictors of aSAH were determined by univariate analysis and binary logistic regression; odds ratios (OR) and 95% confidence interval (CI) were calculated. All P values were on the 2 sides and significance was set at $P < 0.05$.

Results

Patient characteristics

The patient characteristics were summarized in Table 1. Seventy-six patients with a mean age of 57.3 years (range from 18 to 80 years) met the criteria for inclusion in this study. The average length of hospital stay was 18.4 days. Forty-five patients (59.2%) in this study were female. Sixty-eight patients (89.5%) were admitted to the Intensive Care Unit (ICU). Forty-eight patients (63.2%) had one aneurysm and 19 patients (25%) had two. And 62 patients (81.6%) underwent surgery after admission. Thirty-six patients (47%) had a unfavorable outcome (mRS ≥ 3) at 6 months.

Differences between high SII and low SII groups

In Table 2, there was no significant difference between high SII and low SII in baseline data such as age, sex, length of hospital stays, etc. But lower GCS score, higher Hunt and Hess (H-H) grade and higher Fisher grade were detected in high SII groups. Spearman correlation analysis showed that SII was

correlated with GCS score, Hunt and Hess (H-H) grade and Fisher grade (GCS: $r = -0.521$, $P = 0.05$; H-H: $r = 0.436$, $P = 0.05$; Fisher: $r = 0.252$, $P = 0.05$).

Association of the SII with functional outcome

Thirty-six patients (47.4%) in our study had a unfavorable outcome ($mRS \geq 3$) at 6 months, and twenty-four (66.7%) of them had high SII (>2344.65) on admission (Table 3). Spearman correlation analysis showed that the SII was correlated with mRS ($r = 0.418$, $P = 0.05$). The univariate analysis demonstrated that patients in the unfavorable outcome group had significantly older age, lower GCS, Higher PAASH scores, higher Hunt and Hess (H-H) grade, higher infection rate, and higher SII than the favorable outcome group ($P < 0.05$). Multivariate analysis indicated that the SII might be an independent predictors for the unfavorable outcome (Table 4), and the adjusted odds ratio was 4.271 (95%CI: 1.047-17.422, $P = 0.05$). Furthermore, the ROC curve for unfavorable outcome also manifested the predictive value of the SII (Fig 1). The AUC of the SII for predicting unfavorable outcome was 0.692 (95% CI: 0.571–0.814, $P = 0.05$). The sensitivity and specificity of the expected performance of SII were 66.7% and 75.0%.

Comparison of white blood cell, platelets, neutrophils, lymphocytes and SII

Compared with those in favorable outcome group, significantly higher white blood cell count, higher neutrophil count, lower lymphocyte count and more patients with higher SII were found in the unfavorable outcome group ($P < 0.05$; Table 3). The average platelet number of the poor prognosis group was greater than that of the good prognosis group. According to the receiver operating characteristic (ROC) curve, however, the SII stood a distinctly predictive advantage over WBC, neutrophils, lymphocytes and platelets, which indicated that SII was the relatively better prognostic factor for aSAH compared with other indicators.

Discussion

In this retrospective study, our findings indicated that higher SII on admission was associated with poor prognosis. Thus, the SII on admission might be important independent predictors of functional outcomes at 6 months in patients with aSAH.

Neuroinflammation has been the subject of intense scholarly research in neurological disorders in the past few years, especially in cerebrovascular diseases. After acute vascular brain injuries, central nervous system (CNS)-specific antigen such as microtubule-associated protein-2, N-methyl D-aspartate receptor subunit NR-2A and MBP might directly activate the peripheral immune system and potentiate secondary brain injury [18, 19, 26]. Recent evidence implicates peripheral immune cells are both recruited and activated in damaged brain parenchyma and released inflammatory cytokines [13]. Therefore, immune system activation in the CNS might be critical to the development of DND and ultimately lead to a poor prognosis [20].

In our study, the SII showed associations with clinical complications and outcomes in aSAH, the underlying pathophysiological mechanism could be explained as follows. *Firstly*, the number of neutrophils is increased after aSAH. Pre-clinical data suggested that aSAH was associated with the attraction and subsequent deposition of neutrophils and macrophages in response to free hemoglobin and hemin[21, 24]. Evidence from human beings also consistently demonstrated that increased blood leukocyte count was associated with higher disease severity and worse outcomes in strokes[1, 5, 23]. Besides, the elevation of neutrophils within 0–14 days after SAH was relevant to higher risk for subsequent vasospasm and poor long-term outcome[5]. In our study, higher level of WBC and neutrophils were also detected in aSAH patients compared with those in healthy individuals. In addition, the neutrophil count was even higher in patients with poor prognosis than those with favorable prognosis, which was consistent with previous research[1, 5]. *Secondly*, the risk for immunosuppression and infection was increased after aSAH. Previous study showed that immunosuppression after stroke, characterized by lymphocytopenia, was closely associated with increased susceptibility to infection[34]. Recent studies manifested that the spleen gradually shrank after stroke, then expanded again and returned to normal size 7 to 10 days after stroke[28]. Post-stroke spleen contraction was associated with peripheral immune activation characterized by lymphocyte and NK-cell count decrease[28]. Similar with the case in stroke, previous study consistently recognized great decrease in circulating T lymphocytes during acute phase SAH[30]. Decreased T lymphocyte count may be associated with higher risk for pneumonia and 3-month mortality[15]. Our research also noticed a lower lymphocyte count in aSAH patients. The level of lymphocyte was even lower in poor prognosis group compared with those in favorable prognosis group, which confirmed previous studies. Unfortunately, we have no evidence that the patient's spleen volume changes during the course of the disease. *Thirdly*, the platelet-derived factors might have effect on secondary brain injury after SAH. Lauren H's study showed that platelet-derived factors interacted with brain tissue surrounding the hemorrhage and lead to the development of edema [29]. Meanwhile, activated platelets might interact with the coagulation cascade and thrombin, ultimately lead to further cerebral edema[29]. what's more, additional cytokine accumulation, which takes place during storage time of platelet products, could give rise to increased pro-inflammatory effects and indicate a more complex inflammatory pathophysiology in these aSAH patients[27]. It is surprising that use of an antiplatelet agent had no effect on edema and platelet transfusion was associated with more complications during admission, higher in-hospital mortality, and poor clinical outcome after six months[27, 29]. In our study, the higher average number of platelets was also found in the poor prognosis group in comparison with those in good prognosis group. Thus, the SII which combined ANC, ALC, and PLT together, may be a comprehensive biomarker for assessing aSAH severity and predicting 6-month outcome.

It's easy to obtain specific serological indicators for calculating SII in clinic. What's more, our research proved a relatively greater predictive value of SII than WBC, neutrophils, lymphocytes and platelets. Based on the results of this study, it is reasonable to believe that the SII could be used to guide the stratification of the risk of aSAH with poor prognosis and provide personalized treatment in the early stage of aSAH,

which might improve the patient's prognosis. It is important to combine the SII with clinical guidelines for aSAH patients and develop standardized personal protocols performed by nurses.

Limitation

There are potential limitations to our study. Firstly, the study lacks prospective and multicenter design, and the threshold value obtained from the total sample size may be biased, so it is necessary to increase the sample size for further verification. Secondly, the level of peripheral blood inflammatory indicators varies greatly during the acute attack and progression of aSAH, and inflammation is often observed to be biphasic in nature, with elements that are both protective as well as deleterious. We only collected blood samples from patients at the time of admission, and there was a lack of blood samples during hospitalization.

Conclusion

In conclusion, this study suggests that SII was more accurate than WBC, neutrophils, lymphocytes, etc. and high SII was related with poor outcome after SAH. As a rapidly accessible clinical indicator, SII has important guiding value for identifying aSAH patients with unfavorable outcome. Further prospective studies about SII need to be evaluated in the future.

Abbreviations

aSAH: aneurysmal subarachnoid hemorrhage; AUC: area under the curve; ANC: absolute neutrophil counts; ALC: absolute lymphocyte counts; CT: computerized tomography; CTA: computerized tomography angiography; CNS: central nervous system; CI: confidence interval; DND: delayed neurological dysfunction; DSA: digital subtraction angiography; GCS: Glasgow Coma Scale; H-H: Hunt and Hess grade; IA: intracranial aneurysm; mRS: modified Rankin scale; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratios; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutrition index; PLT: platelet; PLC: platelet counts; ROC: receiver operating characteristics; SII: systemic immune-inflammation index; SD: standard deviation; WBC: white blood cells.

Declarations

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Author contributions Author contributions to the study and manuscript preparation include the following. Conception and design: Fushu Luo, Yuanyou Li, Zongyi Xie. Acquisition of data: Yuanyou Li, Mingjiang Sun. Analysis and interpretation of data: Fushu Luo, Yuanyou Li, Yuantong Zhao. Drafting the article: Fushu Luo, Yuanyou Li. Critically revising the article: all authors. Reviewed submitted version of

manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Zongyi Xie.
Study supervision: Zongyi Xie.

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Availability of data and material The data used and/or analyzed during the current study are available from the corresponding author upon reasonable request

Code availability Not applicable

Conflicts of interest No potential conflict of interest was reported by the authors

Ethics approval This study has been approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (No.34)

Consent to participate Not applicable

Consent for publication Not applicable

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Tables

Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Receiver operating characteristic analysis of ANC, ALC, PLT and SII in predicting functional outcome of aSAH Abbreviations: ANC: absolute neutrophil counts; ALC: absolute lymphocyte counts; PLT: platelets; SII: systemic immune-inflammation index.

Supplementary Files

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