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Prognostic value of albumin-fibrinogen ratio in subarachnoid hemorrhage patients

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Abstract

Inflammation plays an important role in the pathophysiology of subarachnoid hemorrhage (SAH). Recent studies have indicated that the albumin to fibrinogen ratio (AFR) is a useful biomarker of inflammation.

This research aimed to determine the ability of AFR to predict the prognosis of patients with SAH.

A total of 440 patients with SAH who had been diagnosed within 72 hours of symptom onset were retrospectively reviewed. Clinical findings and laboratory data were retrieved from the hospital database. Functional outcome was measured according to the modified Rankin scale at 30 days. Logistic regression analysis was used to evaluate the correlation between AFR and the prognosis of patients with SAH. Receiver operating characteristic (ROC) analysis was performed to determine the prognostic ability of AFR at admission to predict the 30-day outcomes.

The average age of all 440 patients with SAH was 56.75 ± 11.19 years and 31.4% (138) were male. Of these patients, 161 exhibited unfavorable outcomes at 30 days. According to the multivariate logistic regression analysis, the AFR was positively correlated with the outcome of patients with SAH (odds ratio 0.939, 95% confidence interval 0.885–0.996, $P = .038$). The ROC analysis revealed an area under the curve of 0.713 for AFR's ability to predict the 30-day outcomes.

AFR is independently associated with the outcome of SAH patients. As a parameter that can be easily assessed at admission, AFR could be used to help the decision-making of clinical treatment.

Abbreviations: AFR = albumin to fibrinogen ratio, DAMP = damage-associated molecular pattern, IL = interleukin, mRS = modified Rankin scale, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, RBC = red blood cell, ROC = receiver operating characteristic, SAH = subarachnoid hemorrhage, WBC = white blood cell count, WFNS = World Federation of Neurosurgical Societies.

Keywords: albumin, biomarker, fibrinogen, prognosis, subarachnoid hemorrhage

1. Introduction

Subarachnoid hemorrhage (SAH), which accounts for 5% of all strokes, is a serious, life-threatening disease associated with both high mortality and morbidity.[1,2] Studies have revealed that the prognosis of patients with SAH is greatly affected by early brain injury, which is defined as injury within 72 hours after disease onset.[3–5] Therefore, finding a parameter that allows us to understand the patients' status at admission, perform proper treatments, and prevent poor outcomes is an urgent need.[6–8]

Epidemiological studies have indicated that the majority of SAHs are caused by the rupture of intracranial aneurysms in combination with high-pressure bleeding.[9] These severe pathological changes not only cause mass lesions in the subarachnoid space, but also initiate robust innate immune responses via the damage-associated molecular patterns (DAMPs) signaling pathway.[10] Hence, in addition to mass effects caused by bleeding, inflammation also plays a well-recognized role in inducing secondary damage and poor outcomes in patients with SAH.[11] Several inflammatory parameters, including white blood cell (WBC) count, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR), have been applied to predict the prognosis of SAH patients.[12–14] As a novel inflammatory biomarker, the albumin to fibrinogen ratio (AFR) was found to have major predictive ability in several forms of disease, such as cancer and myocardial infarction.[15–18] In patients after acute ischemic stroke, low AFR was found to be independently associated with an increased risk of hemorrhagic transformation.[19] However, whether AFR could predict the prognosis of SAH patients, and the predictive value of AFR compared to other inflammatory biomarkers, remains unknown.

Fibrinogen is originally synthesized in the liver and participates in multiple physiological processes after bleeding, and is also a marker of pathological inflammation.[20] According to previous studies, elevated serum levels of fibrinogen after SAH are associated with poor outcomes at 14 days and 3 months,

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request. The data belongs to our hospital's data center and is not available due to hospital policy.

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respectively.[21–23] Additionally, fibrinogen levels in plasma are also considered as powerful and independent predictors of myocardial infarction, stroke, and atherothrombotic events.[24] On the other hand, as a well-recognized nutritional and antiinflammatory marker, albumin was found to be closely related to the prognosis of patients with SAH in several studies. A lower level of albumin in patients with SAH is usually considered to be a marker of poor prognosis.[25] Results from both animal models and clinical studies revealed that transfusion of albumin could significantly improve SAH prognosis by increasing nutritional supplements, antioxidative stress, and microcirculation.[26–28]

The aim of this study was to discover the prognostic value of AFR in patients with SAH. Therefore, a total of 440 SAH patients were retrospectively reviewed. The pathological factors, clinical features, blood test results, and functional outcome of these patients were investigated. By using logistic regression analysis and ROC analysis, the prognostic ability of AFR in SAH patients was explored.

Table 1

Baseline clinical characteristics of 440 subarachnoid hemorrhage patients.

	MRS $\leq$ 2 (n=279)	MRS $\geq$ 3 (n=161)	*P*
Age (years)	54.63 ± 10.57	60.42 ± 11.31	<.001*
Male sex	86	52	.748
Smoking	46	24	.662
Alcohol abuse	22	15	.602
Hypertension	108	71	.268
Diabetes	11	7	.836
SBP (mm Hg)	148.33 ± 23.53	153.14 ± 28.68	.072
DBP (mm Hg)	85.96 ± 13.76	87.83 ± 16.45	.223
MBP (mm Hg)	106.71 ± 15.53	109.60 ± 18.41	.094
Temperature (°C)	36.63 ± 0.31	36.68 ± 0.39	.158
WFNS grade	1.59 ± 1.01	3.54 ± 1.70	<.001*
Modified Fisher Scale	1.70 ± 0.79	2.48 ± 1.15	<.001*

MRS = modified Rankin scale, SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure, WFNS = World Federation of Neurosurgical Societies.
* $P < .05$.

2. Methods

2.1. Patients with SAH

All patients with SAH had been treated at the Department of Neurosurgery, West China Hospital, Sichuan University from December 2018 to November 2019. The SAH patients were retrospectively identified and were included if they met the following criteria:

1. age > 18 years;
2. digital subtraction angiography or computed tomography angiography were employed to verify the rupture of intracranial aneurysm;
3. SAH was diagnosed by computed tomography at admission; and
4. the period from disease onset to admission was less than 72 hours.

SAH patients were excluded if they were diagnosed with other relevant diseases or severe blood coagulation function problems.

The study was approved by the Biochemical Ethics Committee of West China Hospital, which waived the requirement for informed consent based on the study's retrospective design.

2.2. Clinical features

After admission, patients received standard treatment based on SAH management guideline.[2] The severity of patients was assessed using the World Federation of Neurosurgical Societies (WFNS) grade at admission and all evaluations were completed within 72 hours after disease onset. All relevant patient information, such as sex, age, WFNS grade, admission blood pressure, and temperature were collected. Medication history, including treatment for hypertension and diabetes mellitus, and history of smoking and alcohol abuse were also reviewed.

Red blood cell (RBC) count, WBC count, NLR, PLR, AFR, blood coagulation function, and blood glucose data were extracted from the medical records. In addition, the outcome was evaluated according to the modified Rankin scale (mRS) at 30 days. The mRS measures the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. Patients with mRS scores of 0–2 (scores ranging from "no symptoms" to "slight disability") were considered as having a good outcome, whereas those with mRS scores above 3 (scores ranging from "moderate disability" to "death") were defined as having a poor outcome.

2.3. Statistical analysis

IBM SPSS Statistics Version 22 (IBM Corp., Armonk, NY) was used for all statistical analyses. The unpaired *t* test was used for analysis of normally distributed continuous variables. Categorical data were analyzed using the Fisher exact test or Pearson Chi-Squared test. $P < .05$ was considered as statistically significant. Multivariate analysis was employed to confirm independent risk factors in combination with binary logistic regression analysis to identify confounders among potential independent predictors. Receiver operating characteristic (ROC) analysis was conducted to evaluate the predictive ability of AFR.

3. Results

A total of 440 patients with SAH treated from December 2018 to November 2019 were included in our study. Their clinical characteristics are shown in Table 1. There were 138 men (31.36%) and 302 women (68.64%) with a mean age of 56.75 ± 11.19 years (Table 1). Based on an mRS score of 0–2 at 30 days, 279 patients (63.41%) were classified as having a good outcome. The remaining 161 patients (36.59%) exhibited poor outcomes with a score above 3 (Table 1). There were significant differences between the 2 groups in terms of age ($P < .001$), the modified Fisher scale score ($P < .001$), and the WFNS grade ($P < .001$). Patients with poor outcomes were more likely to have a larger volume of hematoma and worse neurological function at admission, and to be of older age. No significant difference was found between patients with good and poor outcomes with regards to history of smoking, alcohol abuse, hypertension, diabetes, blood pressure, or body temperature (Table 1).

Based on the blood test results, the average WBC count was $12.74 \pm 4.72\,10^9$/L among all patients with SAH (Table 2). However, patients with poor outcomes had a higher WBC count (14.82 ± 5.47) than those with favorable outcomes (11.54 ± 3.74;

Table 2

Blood tests at admission.

	MRS ≤ 2 (n=279)	MRS ≥ 3 (n=161)	P
RBC (10^{12}/L)	4.28±0.55	4.38±0.60	.065
WBC (10^9/L)	11.54±3.74	14.82±5.47	<.001*
Neutrophils (10^9/L)	10.02±3.63	12.86±5.16	<.001*
Lymphocytes (10^9/L)	1.11±0.57	1.36±0.99	.003*
Platelets (10^9/L)	168.84±54.80	175.27±62.25	.276
GLU (mmol/L)	7.72±2.09	9.76±3.31	<.001*
PT (s)	11.35±0.77	11.36±0.90	.894
APTT (s)	26.34±3.02	26.01±3.27	.295
INR	0.96±0.07	0.96±0.08	.895
Albumin (g/L)	43.51±3.10	43.30±4.74	.615
Fibrinogen (g/L)	2.63±0.67	3.34±6.74	.184
NLR	11.27±6.83	13.14±8.52	.018*
PLR	182.70±95.04	181.57±140.95	.92
AFR	17.92±7.11	16.36±4.68	.013*

AFR = albumin-fibrinogen ratio, APTT = activated partial thromboplastin time, GLU = blood glucose, INR = international normalized ratio, MRS = modified Rankin scale, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio, PT = prothrombin time, RBC = red blood cell, WBC = white blood cell.

* $P<.05$.

$P<.001$). Further investigation revealed that both increasing neutrophil and lymphocyte counts contributed to WBC count elevation in patients with unfavorable outcomes. The average blood glucose in patients with poor outcomes was 9.76±3.31 mmol/L, which was significantly higher than that of patients with favorable outcomes (7.72±2.09; $P<.001$). Nevertheless, no difference was found in RBC counts, platelet counts, or blood coagulation function between patients with poor outcomes and those with good outcomes.

As 2 major components of AFR, there was no significant difference in the individual levels of albumin and fibrinogen. The mean AFR of all SAH patients involved was 16.85±6.37. SAH patients with a good outcome had a higher AFR ($P=.013$) and a lower NLR ($P=.018$) than patients with a poor outcome, while the PLR did not significantly differ between the 2 groups.

Multivariate logistic regression analysis was performed to identify independent predictors of poor outcome after SAH (Table 3). AFR (odds ratio 0.935, 95% CI 0.883–0.991, $P=.023$), age ($P<.001$), WFNS grade ($P<.001$), WBC count ($P=.007$), and blood glucose ($P=0.026$) were strongly correlated with the outcome of patients with SAH. However, the modified Fisher scale, NLR, and PLR were not identified as predictors of SAH prognosis. A ROC analysis was also performed to estimate

Table 3

Logistic regression for predictors of poor outcome.

	OR	95% CI	P
WBC count	1.105	1.027–1.189	.007
GLU	1.125	1.014–1.247	.026
Age	1.056	1.031–1.082	<.001
WFNS grade	2.445	1.776–3.366	<.001
Modified Fisher Scale	1.112	0.821–1.507	.492
NLR	0.997	0.945–1.052	.913
PLR	1.000	0.997–1.004	.797
AFR	0.935	0.883–0.991	.023

AFR = albumin-fibrinogen ratio, CI = confidence interval, GLU = blood glucose, NLR = neutrophil-lymphocyte ratio, OR = odds ratio, PLR = platelet-lymphocyte ratio, WBC = white blood cell, WFNS = World Federation of Neurosurgical Societies.

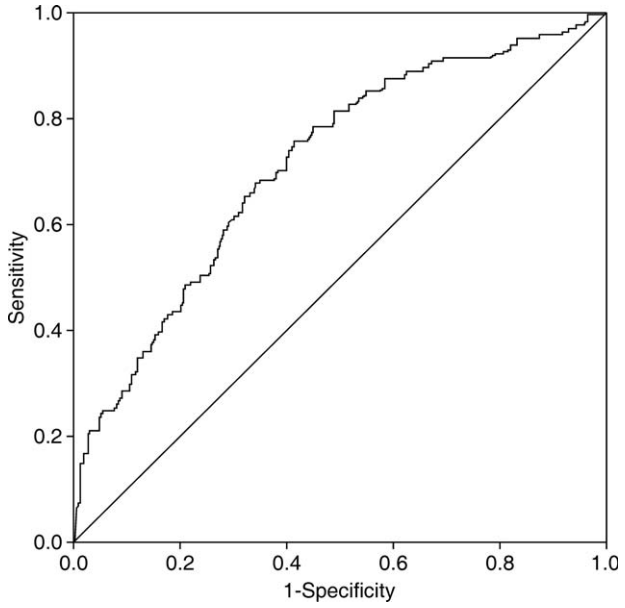

Figure 1. Receiver operating characteristic curves analysis of albumin-fibrinogen ratio for outcome prediction after subarachnoid hemorrhage.

the ability of AFR at admission to predict the 30-day prognosis (Fig. 1). The results showed an area under the curve of 0.713, which shows a good predictive value of AFR in predicting the prognosis of SAH patients.

4. Discussion

SAH is characterized as an intracranial neurovascular disease that is associated with sudden and intolerable headache.[29] Recent evidence from both epidemiological studies and basic research on SAH pathophysiology has determined that inflammation plays a critical role during disease development.[30] Combinatory parameters, such as NLR and PLR, have also been demonstrated to be closely related to the prognosis of SAH.[12–14] The results of our retrospective study indicate a potential correlation of AFR, age, WFNS grade, blood glucose, and WBC count with outcomes of SAH patients. Similar results were found in previous studies that age, WFNS grade, blood glucose, and WBC count were predictors for SAH patients.[31] This research provides preliminary evidence that lower serum fibrinogen and higher albumin levels may be associated with a favorable outcome in SAH patients. However, NLR and PLR were found to be not significantly associated with the prognosis of SAH patients in this study, which was different from previous studies regarding NLR and PLR.[12,32] AFR was believed to be more stable than NLR and PLR, but this can be biased by opportunistic infection.

Albumin constitutes two-thirds of the body's total proteins, and helps to maintain oncotic pressure, blood viscosity, and the permeability of the microvasculature.[33,34] This protein family has been reported to be an anti-inflammatory marker that is significantly downregulated with increases in C-reactive protein and interleukin (IL)-6 after a metabolic response.[33,35] An increase in albumin could inhibit the expression of vascular cell adhesion molecule-1, thus modulating adhesive interactions between neutrophils and the endothelium.[36,37] Notably, albumin was also observed to exert anti-inflammatory effects through

the inhibition of microglial polarization.[38] Moreover, albumin possesses unique intravascular neuroprotective effects, including reduction of brain edema, enhancement of neuronal survival, and maintenance of blood–brain barrier integrity in patients and animal models of cerebrovascular diseases.[39–41] In addition, a previous clinical trial has demonstrated that 1.25 g/kg/d albumin is safe for patients with SAH and significantly improves the prognosis.[28] The other component of AFR, fibrinogen, is a precursor of fibrin and can accelerate platelet aggregation.[42] Both fibrinogen and fibrin can increase proinflammatory cytokine levels in the circulatory system and are considered inflammatory markers.[43] Several studies have already demonstrated that plasma fibrinogen levels are correlated with the outcomes of patients with SAH.[22,23,26] An increase in fibrinogen-positive vessels was also observed in SAH animal models, which exhibited significant vasoconstriction of the neurovascular system and neuronal cell death.[44] However, with the exception of the current report, few previous studies have attempted to use a combination of albumin and fibrinogen to predict the course of cerebral vascular diseases.

After SAH, erythroclasis can also trigger the MAPK signaling pathway, leading to severe inflammation.[30] Sterile inflammation in cerebral vascular diseases has long been recognized.[45,46] These immune responses not only exacerbate the infiltration of monocytes, but also polarize macrophages into a proinflammatory phenotype, thus further elevating local levels of DAMPs and cytokines.[47] Previous studies found that DAMPs serve as endogenous toll-like receptor 4 ligands and interact with inflammatory cytokines to increase the secretion of tumor necrosis factor and IL-1β, ultimately causing vasoconstriction, meningitis, and cerebritis in patients with cerebral vascular diseases.[48] Considering the close relationship between bleeding-triggered sterile inflammation and the development of SAH, an inflammation-related marker that can help determine the appropriate treatment approach during the perioperative phase as well as predict the prognosis is urgently required. The AFR is calculated according to the circulating levels of fibrinogen and albumin, and previous studies have revealed that it is related to the prognosis of several vascular diseases. A recent prospective study found that AFR was associated independently with the severity of coronary artery disease and prognosis.[49] Moreover, AFR could predict the severity of retinal vein occlusion.[50] This raised our interest in using AFR as an indicator of neurovascular disease. Although albumin and fibrinogen were not individually associated with the outcome of SAH patients, we reported here for the first time that AFR could be used as an independent prognostic factor in SAH patients. Based on our study, it is assumed that AFR could represent the severity of neuroinflammation after SAH. For patients with a high level of AFR at admission, specific treatment should be conducted, including but not limited to anti-inflammation therapy and nutritional therapy. Nevertheless, further intensive studies should be conducted to determine the optimal therapeutic methods for those patients.

4.1. Limitations

Some limitations to our retrospective study need to be acknowledged. First, all patients were from a single clinical center, which might have introduced potential bias in patient selection. Second, we only had access to AFR values at admission; obtaining the AFR at different stages could provide more prognostic value. In addition, only the functional outcomes at 30 days were available, and the association between AFR and long-term outcomes is unclear. The difference of AFR in the 2 groups (mRS $\leq$2 and mRS $\geq$3) is small, and multitest correction of AFR was not conducted in this study.

4.2. Future directions

Further prospective studies with a multicenter design and large sample size are warranted to validate the role of AFR in predicting the prognosis of SAH patients.

In conclusion, AFR, age, WFNS grade, blood glucose, and WBC count at admission were significantly associated with the prognosis of SAH patients. As a simple, effective, and safe biomarker, AFR could be of great value to neurosurgeons and physicians attempting to evaluate the outcomes of SAH patients. Lower AFR levels might be associated with unfavorable functional outcome at 30 days. However, more relevant studies are needed to validate the conclusions.

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