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Can albumine to INR ratio predict prognosis in patients with subarachnoid hemorrhage

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Abstract

Aneurysmal subarachnoid hemorrhage (aSAH) is among the neurovascular diseases requiring urgent intervention, characterized by high rates of mortality and morbidity. Systemic inflammatory response and coagulation disorders play a critical role in the prognosis of aSAH patients. This study investigates the prognostic and diagnostic value of the albumin-International Normalized Ratio (INR) ratio (AIR) in predicting 28-day mortality in aSAH patients. This retrospective, single-center study included 71 adult patients diagnosed with aSAH, confirmed through imaging modalities. Demographic, clinical, and laboratory data of the patients (albumin, INR, neutrophil count, and other inflammatory indices) were analyzed. The primary endpoint was determined as 28-day mortality. ROC analysis was performed to evaluate the diagnostic performance of the AIR and other indices. The 28-day mortality rate was found to be 39.4% (n=28). In patients who developed mortality, median AIR values and albumin levels were significantly lower ($p<0.001$), while INR and neutrophil counts were significantly higher ($p<0.001$). AIR demonstrated superior performance compared to other indices in predicting 28-day mortality, with a sensitivity of 89.3% and an area under the curve (AUC) of 0.839. Multivariable logistic regression analysis confirmed AIR as an independent predictor of mortality. This study revealed that AIR is a reliable and practical prognostic biomarker for predicting short-term mortality in aSAH patients. AIR outperformed other inflammatory and coagulation markers. Considering its ease of calculation and clinical applicability, AIR could serve as a valuable tool for patient risk stratification and management.

Keywords: Subarachnoid hemorrhage, prognosis, mortality, biomarker

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe neurovascular condition associated with high mortality and morbidity, despite advancements in diagnostic and therapeutic approaches in healthcare, and requires urgent intervention. Epidemiological studies indicate that the incidence of aSAH ranges between 6 and 10 cases per 100,000 annually, with 30-day mortality rates varying from 35% to 50% [1]. Approximately 30% of surviving patients are left with moderate to severe functional dependency [2].

Recent research has demonstrated that the systemic inflammatory response following aSAH significantly influences the prognosis of the disease [3]. The inflammatory process affects the severity of neurological damage and contributes to the development of secondary complications such as vasospasm and delayed cerebral ischemia [4]. In this context, serum albumin levels are significant indicators of both the inflammatory response and nutritional status. Studies have shown that hypoalbuminemia (<3.5 g/dL) at presentation is associated with in-hospital mortality [5,6].

Coagulation system parameters also impact the prognosis of aSAH patients. The International Normalized Ratio (INR), a commonly used measure to evaluate the coagulation system, reflects activated prothrombin levels. Elevated INR values, particularly at presentation, are associated with increased mortality rates and worse neurological outcomes [7]. Recent studies have also shown that high INR levels at presentation may increase the likelihood of aneurysmal rupture [8].

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Inflammatory marker ratios are increasingly gaining attention for prognostic evaluations. When the literature was examined, it was reported that neutrophil-albumin ratio (NAR) and lactate albumin ratio predicted mortality [9,10]. Additionally, recent studies have found that the D-dimer/albumin ratio is associated with poor outcomes [11]. Similarly, the albumin-fibrinogen ratio can be used as a prognostic marker [12].

Research has also suggested the potential utility of microalbuminuria and systemic inflammatory response markers in aSAH patients [13]. However, the Albumin-INR Ratio (AIR) has not been extensively studied as a prognostic marker in aSAH patients. This ratio could be considered a biomarker reflecting both the coagulation system and inflammatory response.

The aim of this study is to investigate the prognostic and diagnostic value of AIR, which can be easily obtained from routine laboratory tests, in predicting 28-day mortality in aSAH patients and to evaluate its contribution to existing prognostic models.

Material and Methods

Study Design and Participants

This single-center study was conducted by retrospectively evaluating the data of patients who presented to the Emergency Department (ED) of a tertiary education and research hospital between 2018 and 2024. The study commenced following approval from the Ordu University Clinical Research Ethics Committee (Ethics Committee Approval No: 2024/107, Date: 26.07.2024). All stages of the study adhered to the ethical principles outlined in the Declaration of Helsinki.

Patients aged 18 years and older with a diagnosis of SAH based on computed tomography (CT) between 2018 and 2024 were retrospectively evaluated. Patients diagnosed with aSAH based on CT angiography or magnetic resonance angiography results were included in the study.

Patients under the age of 18, pregnant individuals, those presenting with trauma, patients using anticoagulants, individuals with a history of chronic liver disease, patients presenting to the ED with cardiac arrest, those with a history of immunodeficiency, those diagnosed with non-aneurysmal SAH after evaluation, and those with incomplete data in their records were excluded from the study.

Sample Size Calculation

Sample size was determined using the G*Power program. Since no studies in the literature compared the diagnostic performance of AIR in predicting 28-day mortality in aSAH patients, a pilot study was conducted with 30 patients. The effect size for AIR was determined as 1.09 in the pilot study. For a power of 0.95 and a type I error level of 0.05, the sample size was calculated as 58 patients, with 41 in the survival group and 17 in the mortality group.

Data Collection and Measurement

Demographic characteristics, vital parameters assessed at ED presentation, and laboratory data obtained from blood samples (white blood cells [WBC], neutrophils, lymphocytes, hemoglobin, hematocrit, platelets, glucose, serum electrolytes [sodium, potassium, chloride, calcium], urea, creatinine, albumin, coagulation parameters [prothrombin time (PT), partial thromboplastin time (PTT), and INR], and lactate values from blood gas samples) were recorded. Indices calculated from this data included NAR, Nneutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and AIR, defined as follows:

NAR: Neutrophil count / Serum albumin

NLR: Neutrophil count / Lymphocyte count

PLR: Platelet count / Lymphocyte count

SII: Neutrophil count x Platelet count / Lymphocyte count

AIR: Serum albumin / INR

The 28-day mortality of patients was evaluated through the hospital information management system and the national health database. The primary endpoint of the study was the 28-day mortality status of patients diagnosed with aSAH.

Statistical Analysis

Statistical analysis was performed using SPSS v.26 and JAMOVI. The normality of data distribution was assessed using histograms and the Kolmogorov-Smirnov test. Variables were presented as mean±standard deviation, medians with interquartile ranges, frequencies, and percentages. Intergroup differences were analyzed using the Student's t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and the chi-square test for categorical variables. Statistical significance was set at $p<0.05$.

Univariable and multivariable logistic regression models were used to evaluate the relationship between neutrophils, albumin, INR, NAR, AIR, and 28-day mortality. The performance of variables with a p-value <0.05 in multivariable analysis for predicting 28-day mortality was assessed using Receiver Operating Characteristic (ROC) curve analysis. The area under the curve (AUC) was used to determine diagnostic performance. (AUC=0.5 indicates no discrimination, and AUC=1 indicates perfect discrimination). Sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (-LR) of the variables were calculated.

Results

The study was conducted on 71 patients who met the inclusion and exclusion criteria (Figure 1). The mean age of the patients was determined as 60.97±18.85 years, and 52.1% (n=37) were male. The primary outcome, 28-day mortality, occurred in 39.4% (n=28) of patients.

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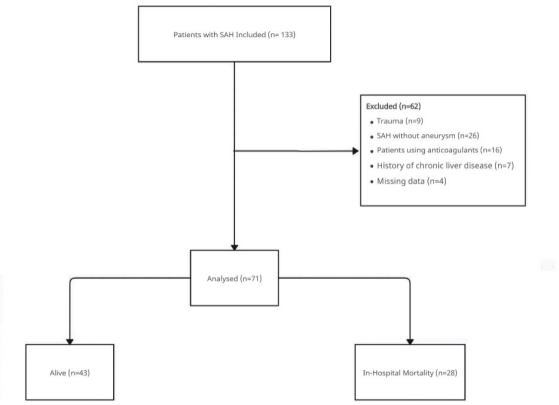

Figure 1. Flowchart of study

No statistically significant relationship was found between gender and 28-day mortality (p=0.774), whereas increased age was associated with higher 28-day mortality rates (p=0.019). No significant relationship was observed between vital signs measured at presentation and 28-day mortality (p>0.05). Compared to survivors, patients who died within 28 days had significantly lower median albumin and mean AIR values and higher median neutrophil and INR levels. A statistically significant association was found between neutrophils, albumin, AIR, INR, and 28-day mortality (p-values <0.001). The relationship between the demographic, clinical, and laboratory parameters of the patients and 28-day mortality is shown in Table 1.

Table 1. Evaluation of the relationship between clinical and laboratory findings and 28-day mortality in patients with SAH

	In hospital mortality (n=71)		
	Survivors (n=43)	**Non-survivors (n=28)**	**p**
Age	56.79±18.02	67.39±18.6	**0.019**
Sex; n (%)			
Male	20 (58.8)	14 (41.2)	0.774
Female	23 (62.2)	14 (37.8)	
SBP	160.26±20.3	168.46±17.19	0.082
DBP	90.67±11.28	92.79±8.06	0.394
MAP	113.87±13.64	118.01±10.39	0.176
Pulse pressure	69.58±12.74	75.68±12.34	0.050
WBC	11.13±4.29	11.15±5.21	0.986
Hemoglobin	13.27±1.97	13.16±2.39	0.837
Neutrophils	5.40 (3.20-7.90)	9.40 (5.98-14.15)	**<0.001**
Lymphocyte	1.57 (1.19-2.8)	1.44 (0.6-2.1)	0.106
Platelet	232.49±62.65	207.18±69.11	0.115
NLR	2.55 (1.43-5.71)	8.07 (3.01-17.13)	**<0.001**
PLR	112.56 (87.39-193.42)	143.4 (85.27-306.21)	0.359
SII	610 (287.08-1487.83)	1644.89 (573.42-3202.55)	**0.005**
Glucose	123 (111-150)	136 (112.25-176.5)	0.219
Creatinine	0.85 (0.64-0.93)	0.89 (0.7-1.15)	0.235
Sodium	139 (138-141)	138 (135.25-141)	0.274
Potassium	3.89±0.45	4.04±0.56	0.241
Albumine	4 (3.7-4.4)	3.2 (2.7-3.68)	**<0.001**
PT	9.1 (8.6-9.7)	10.15 (8.8-10.98)	**0.014**
PTT	25.53±3.72	26.83±5.18	0.222
INR	1.01 (0.95-1.08)	1.15 (1.02-1.28)	**<0.001**
NAR	1.34 (0.84-2.02)	2.91 (2.17-4.46)	**<0.001**
AIR	3.87±0.63	2.76±0.92	**<0.001**
Lactate	1.9 (1.3-3.1)	2.15 (1.43-2.9)	0.600

Values are presented as mean±SD, median (25th and 75th quartile); AIR: albumine to INR ratio, DBP: diastolic blood pressure, INR: international normalized ratio, MAP: mean arterial pressure, NAR: neutrophil to albumin ratio, NLR: neutrophil to lymphocyte ratio, PT: protrombin time, PTT: partial prothrombin time, SBP: systolic blood pressure, SD: standart deviation, SII: systemic immune-inflammation index, WBC: white blood cell

To evaluate the diagnostic performance of the parameters in predicting 28-day mortality in aSAH patients, ROC analysis was performed (Figure 2). An AIR cutoff value of 3.713 was determined, yielding the highest AUC (0.839) and sensitivity (89.3%) for predicting 28-day mortality. The AUC for NAR was 0.834, with a sensitivity of 78.6%. Details of the performance

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characteristics of the parameters in predicting 28-day mortality are shown in Table 2.

In univariate logistic regression analysis, neutrophils, albumin, NLR, SII, NAR, AIR, and INR were identified as predictors of 28-day mortality (p-values<0.05). When age was added to each parameter, their independent effects on predicting 28-day mortality were calculated using multivariate logistic regression analysis. Accordingly, neutrophils, albumin, NLR, SII, NAR, AIR, and INR were independently associated with 28-day mortality (p-values <0.05). Details of the univariate and multivariate logistic regression analyses are presented in Table 3.

Table 2. Cutoff points and performance characteristics of laboratory findings in predicting 28-day mortality

Parameters	AUC	95% CI	Cutoff	Sensitivity	Specificity	+LR	-LR	p values
Neutrophil	0.760	(0.647-0.873)	9.15	0.536	0.860	3.83	0.54	**<0.001**
Albumin	0.779	0.652-0.907	3.75	0.821	0.744	3.21	0.24	**<0.001**
INR	0.762	0.648-0.876	1.13	0.536	0.884	4.62	0.52	**<0.001**
NAR	0.834	(0.736-0.932)	2.167	0.786	0.814	4.23	0.26	**<0.001**
NLR	0.756	(0.640-0.871)	6.636	0.607	0.837	3.72	0.47	**<0.001**
SII	0.696	(0.568-0.824)	1500.777	0.571	0.767	2.45	0.56	**0.005**
AIR	0.839	0.742-0.936	3.713	0.893	0.651	2.56	0.16	**<0.001**

AIR: albumin to INR ratio, AUC: areas under the curve, CI: confidence interval, INR: international normalized ratio, NAR: neutrophils to albumin ratio, NLR: neutrophil to lymphocyte ratio, SII: systemic immune-inflammation index

Table 3. Logistic regression analysis of prognostic factors in predicting 28-day mortality in patients with SAH

	Model 1*		Model 2**	
Parameters	**Odds ratio (%95 CI)**	**p value**	**Odds ratio (%95 CI)**	**p value**
Neutrophil	1.283 (1.106-1.489)	**0.001**	1.307 (1.119-1.526)	**0.001**
Albumin	0.456 (0.216-0.96)	**<0.001**	0.216 (0.089-0.521)	**0.001**
NAR	3.059 (1.708-5.480)	**<0.001**	3.471 (1.804-6.472)	**<0.001**
NLR	1.143 (1.036-1.262)	**0.008**	1.140 (1.036-2-1.260)	**0.010**
SII	1.000 (1.000-1.001)	**0.023**	1.000 (1.000-1.001)	**0.019**
INR	13.6153 (13.472-136008.72)	**0.002**	2264.774 (15.330-334593.179)	**0.002**
AIR	0.167 (0.071-0.392)	**<0.001**	0.156 (0.063-0.387)	**<0.001**

AIR: albumin to INR ratio, CI: confidence interval, INR: international normalized ratio, NAR: neutrophil to albumin ratio, NLR: neutrophil to lymphocyte ratio, SAH: subarachnoid hemorrhage, SII: systemic immune-inflammation index; *Model 1: Unadjusted model; **Model 2: Each parameter adjusted for age and sex

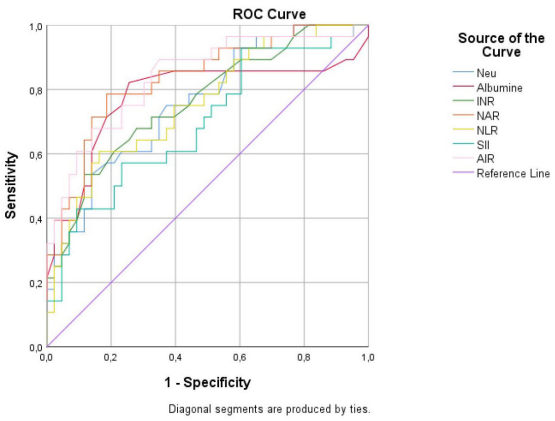

Figure 2. ROC curve of shock ındex and ıts derivatives in predicting 28-days mortality; AIR: albumine to INR ratio, INR: international normalized ratio, NAR: neutrophil to albumin ratio, Neu: neutrophil, NLR: neutrophil to lymphocyte ratio, ROC: receiver operating characteristics, SII: systemic immune-inflammation index

Discussion

aSAH is one of the most fatal pathologies leading to cerebrovascular events. Consequently, numerous studies have evaluated mortality in aSAH patients using parameters like albumin, an indicator of inflammatory response, and INR, a marker of coagulation. This highlights the potential utility of the AIR parameter, derived from the ratio of these two diagnostic tests, in predicting mortality in aSAH patients.

Systemic inflammatory response plays a critical role in the pathophysiology of aSAH. Following aneurysm rupture, red blood cells filling the subarachnoid space activate oxidative stress and inflammatory responses. The resulting neuroinflammation has been implicated in neuronal cell death. Excessive activation of the inflammatory response has been shown to correlate with poor prognosis in aSAH patients [9,14]. Shortly after the hemorrhagic event, a large number of neutrophils migrate to the affected

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area, peaking during the early stages [15]. Through interactions with activated endothelial cells, neutrophils exacerbate the inflammatory response, leading to brain edema, blood-brain barrier disruption, hypoperfusion, and neuronal cell damage [16]. Zhang et al. demonstrated in their study that elevated peripheral neutrophil counts in aSAH patients are associated with increased risks of mortality, hospital-acquired infections, and delayed neurological deficits [17]. In the current study, we identified neutrophil count as an independent predictor of 28-day mortality in aSAH patients. Increased neutrophil counts were associated with higher mortality risk.

Albumin, one of the most abundant proteins in plasma, serves as a negative acute-phase reactant and a marker of nutritional status. It plays several roles, including regulating oncotic pressure, transporting various molecules in plasma, and serving as an extracellular antioxidant defense mechanism [18]. Albumin also exerts neuroprotective effects by modulating microvascular permeability, inhibiting endothelial cell apoptosis, and exhibiting anti-inflammatory and antioxidant properties. Additionally, albumin reduces blood-brain barrier permeability [12]. Studies have reported an association between hypoalbuminemia and poor outcomes and complications in SAH patients [5,9,11]. Consistent with previous studies, we found that decreased albumin levels were associated with increased 28-day mortality in the current study. The cutoff value for albumin was 3.75, with a sensitivity of 82.1%. Furthermore, we identified the NAR, a combined index of neutrophil count and albumin levels, as an independent predictor of 28-day mortality in aSAH patients. Zhang et al. found in their study that NAR outperformed other inflammatory markers in predicting mortality in aSAH patients [9]. Another study also demonstrated that NAR exhibited superior performance compared to other inflammatory indices in predicting mortality [3]. Consistent with the literature, we found that NAR had the highest AUC values for predicting 28-day mortality after AIR among inflammatory indices in the current study.

Can et al. demonstrated in their study that elevated INR levels are associated with the development of aSAH. When analyzing patients separately based on anticoagulant use, they suggested that anticoagulant use had protective effects against aneurysm rupture, whereas high INR values made patients without anticoagulants more susceptible to rupture [7]. In the current study, we excluded patients using anticoagulants and demonstrated that elevated INR levels were associated with increased 28-day mortality risk. However, INR had low sensitivity but high specificity.

Considering the neuroprotective effects of albumin on inflammatory response and the impact of INR on coagulation, we developed AIR to predict the prognosis in aSAH patients. As a combined index of inflammation and coagulation mechanisms in aSAH pathophysiology, AIR independently predicted 28-day mortality. Our findings demonstrated that AIR is an independent predictor of 28-day mortality. Decreased AIR values were associated with increased 28-day mortality in aSAH patients. With an AUC of 0.839 and a sensitivity of 89.3%, AIR outperformed neutrophils (AUC 0.760, sensitivity 53.6%), albumin (AUC 0.779, sensitivity 82.1%), NLR (AUC 0.756, sensitivity 60.7%), SII (AUC 0.659, sensitivity 57.1%), NAR (AUC 0.834, sensitivity 78.6%), and INR (AUC 0.762, sensitivity 53.6%) in predicting 28-day mortality.

Limitations

This study has several limitations that should be acknowledged: First, the study is a single-center, retrospective analysis, which may introduce selection bias and limit the generalizability of findings to other populations or clinical settings. Second, the relatively small sample size may affect statistical power and the robustness of the results. Third, while AIR demonstrated significant prognostic value, its performance in combination with existing clinical scoring systems was not assessed in this study. Such evaluations could provide additional insights. Finally, the retrospective design of the study limits the ability to establish causal relationships. Larger, prospective cohort studies are needed to validate these findings and investigate their practical applicability.

Conclusion

This study demonstrates that the AIR is a promising prognostic biomarker for predicting 28-day mortality in patients with aSAH. Our findings indicate that low AIR values are independently associated with an increased risk of mortality. Moreover, AIR outperformed other inflammatory indices such as NAR, neutrophil count, and albumin in terms of sensitivity and AUC values for predicting 28-day mortality. These results suggest that AIR, reflecting both inflammatory and coagulation dynamics, could serve as a practical and cost-effective biomarker for assessing the prognosis of aSAH patients in clinical practice. Prospective and multicenter studies are warranted to validate these findings and evaluate its applicability in different clinical settings.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethical approval for this retrospective study was obtained from the Ordu University Clinical Research Ethics Committee (Ethics Committee Approval No: 2024/107, Date: 26.07.2024).

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