Association of Serum Blood Urea Nitrogen to Albumin Ratio with in-Hospital Mortality in Patients with Acute Ischemic Stroke: A Retrospective Cohort Study of the eICU Database

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Background: Albumin (ALB) and blood urea nitrogen (BUN) are both associated with the prognosis of acute ischemic stroke (AIS). A recent prognostic marker, the BUN/ALB ratio (BAR), has been suggested as a simple and sensitive method to predict certain acute diseases.

Aims: To determine the predictive value of BAR in relation to the risk of in-hospital mortality among AIS patients.

Study Design: Retrospective cohort study with data acquired from the e-intensive care unit (eICU) collaborative research database.

Methods: Cox regression analysis was employed to assess the relationship between in-hospital mortality and BAR, with hazard ratios (HRs) and 95% confidence intervals. Subgroup analysis of acute pulmonary embolism, acute myocardial infarction (AMI), thrombolysis, thrombectomy, and septic shock was performed to further examine this relationship. The predictive value of BAR and BAR multivariate models for in-hospital mortality was evaluated and compared to BUN, ALB, the Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score, and the Sequential Organ Failure Assessment Score (SOFA).

Results: Among the 1,635 eligible patients, 226 (13.81%) died during hospitalization. An elevated serum BAR level was associated with an increased in-hospital mortality risk (HR: 1.3) after covariates were adjusted. Additionally, this positive association was observed in patients without AP, AMI, thrombolysis, history of thrombectomy, or septic shock (all; $p < 0.05$). The efficacy of the BAR multivariate model in predicting in-hospital mortality among AIS patients was superior to that of both APACHE IV and SOFA, with an area under the curve of 0.87.

Conclusion: Serum BAR exhibits the potential to identify AIS patients with high mortality risk, which may contribute to enhanced disease surveillance and risk stratification.

INTRODUCTION

Stroke has been a significant global cause of mortality and lifelong disability, causing immense economic burden over the past few decades.[1,2] Acute ischemic stroke (AIS) is the most prevalent form of stroke, affecting approximately 700,000 individuals annually.[3,4] AIS results from hypoxia and nutrient deficiency caused by the cerebral artery occlusion that induces a local inflammatory immune response.[5] Therefore, certain biological indicators of inflammation and nutritional status play a vital role in identifying high-risk populations and monitoring AIS progress to appropriately modify therapeutic strategies and vastly enhance patient outcomes.

Albumin (ALB) has been a well-established potent indicator of malnutrition and inflammation (Arques[7], 2018). In animal models and clinical trials, serum ALB has been demonstrated to function as a neuroprotector.[6] Research reveals that hypoalbuminemia is linked to poor prognosis in AIS patients.[6,7] Serum blood urea nitrogen (BUN) is a critical parameter that can indicate patients' kidney function, hemodynamic status, and protein metabolism level. Elevated BUN at admission has been observed to be independently linked to increased in-hospital mortality risk in AIS.[8] A prognostic marker, the BUN to ALB ratio (BAR), has been recently proposed as a simple and sensitive indicator of prognosis.[9] Zeng et al.[10] demonstrated that an elevated BAR was a reliable and independent predictor for in-hospital mortality in patients with acute exacerbation of chronic obstructive pulmonary disease, with an area under the curve (AUC) of 0.87. Zou et al.[11] discovered that BAR was an easily accessible and independent predictor of 30-day mortality as well as severity in patients with *E. coli*

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Received: August 16, 2024 **Accepted:** August 29, 2024 **Available Online Date:** xxxxxx • **DOI:** 10.4274/balkanmedj.galenos.2024.2024-8-77

Available at www.balkanmedicaljournal.org

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Cite this article as: Wenhan Li W, Qing Huang Q, Ke Zhan K. Association of Serum Blood Urea Nitrogen to Albumin Ratio with in-Hospital Mortality in Patients with Acute Ischemic Stroke: A Retrospective Cohort Study of the eICU Database. Balkan Med J.;

bacteremia. However, the role of serum BAR in AIS patients has not been fully investigated.

Herein, we aimed to investigate the relationship between serum BAR and in-hospital mortality in AIS patients, evaluate the predictive value of BAR, provide insights on high-risk population identification, and monitor and modify treatment strategies in AIS in a timely manner.

MATERIALS AND METHODS

Data on participants

This retrospective cohort study included data of adult AIS patients that were extracted from the e-intensive care unit (eICU) collaborative research database, which contains information pertaining to 200,859 ICU admissions of 139,367 patients during 2014-2015 at 208 hospitals in the United States.[12] The eICU-CRD version 2.0 was accessed using Google BigQuery, and structured query language scripts were employed to acquire relevant data. The complete code is available on Github (https://github.com/CONDUITlab/eICU-CRD/tree/master).[13] EICU-CRD includes comprehensive de-identified records, including details pertaining to demographics, diagnoses, and treatment.[14]

This study initially included 3,379 AIS patients. The diagnosis of AIS was defined using ICD-9[15] and ICD-10-CM codes.[16] We also extracted data from the fields "ais," "acute cerebral infarct," and "AIS." The study excluded patients hospitalized in the ICU < 24 hours and those without information on their BUN/ALB levels or survival status. A total of 1,635 patients were finally eligible. The eICU database has been granted ethical approval by the relevant ethics committee, and the patients who are involved have provided informed consent. Since the data were publicly accessible, the requirement for ethical approval was waived by the ethics committee of our hospital.

Measurement of BAR level

The BUN (mg/dl) to ALB (g/dl) ratio was used to calculate the serum BAR. Based on the cut-off value calculated by the X-tile software,[9] the serum BAR was classified into two levels: BAR level ≥ 5.28 and BAR level < 5.28.

In the analyses, included both the continuous variable and categorical variable of ALB and BUN. The ALB concentrations were divided into ALB ≥ 3.5 g/dl and ALB < 3.5 g/dl based on the median value, while the BUN concentrations were classified as BUN ≥ 19 mg/dl and BUN < 19 mg/dl using the same method.[2,17]

Potential confounding factors

Variables selected as potential covariates in this study included age, sex, ethnicity, ventilation use, vasopressor use, thrombolysis, thrombectomy, antiplatelet agents, anticoagulation agents, acute kidney injury (AKI), acute pulmonary embolism (APE), renal replacement therapy, hypertension, chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), liver diseases, acute myocardial infarction (AMI), septic shock, cerebral hemorrhage, surgical treatment, blood transfusion, height, weight, heart rate, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiration rate (RR), temperature, Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score, white blood cell (WBC), lymphocyte count, hemoglobin (HB) levels, platelet count, red blood cell distribution width (RDW), bilirubin concentration, international normalized ratio (INR), creatinine levels, prothrombin time (PT), levels of glucose, bicarbonate, potassium (K), sodium (Na), and chloride, Sequential Organ Failure Assessment (SOFA) score, and multiple organ dysfunction syndrome (MODS). The information was initially recorded within 24 hours of hospital admission.

Outcome and follow-up duration

The primary outcome was in-hospital mortality, which was defined as patients' survival status at the time of ICU discharge, as documented in the hospital department records. The Social Security Bureau documented the time of death through the out-of-hospital social security account, which served as the endpoint of the follow-up.

Statistical analysis

The normality assumption was evaluated using the Shapiro-Wilk test. The normally distributed data were described by mean ± standard deviation. The Levene's test was used to assess the variance homogeneity. The t-test was employed to compare normally distributed data that exhibited variance homogeneity between two groups, while the Welch's t-test was employed to compare normally distributed data that did not exhibit variance homogeneity. Non-normally distributed data were described using medians and quartiles [M (Q_1, Q_3)], and the Mann-Whitney U rank test was employed for comparison. Categorical data were presented as frequency and constituent ratio [n (%)]. The chi-square test (χ^2) was employed to compare the two groups.

The confounding factors for in-hospital mortality were determined using univariate Cox regression and incremental analyses. Variables with a p value of < 0.05 were considered statistically significant and incorporated in the multivariate model adjustment. The association between serum BAR and in-hospital mortality in AIS patients was investigated using univariate and multivariate Cox regression analyses. When considering AIS treatment modalities, thrombolysis should be included in the covariates, with hazard ratios (HRs) and 95% confidence intervals (CIs). A two-sided $p < 0.05$ was deemed statistically significant. Multivariate models were adjusted for specific covariates (age, ethnicity, ventilation use, vasopressor use, thrombolysis, antiplatelet agents use, AKI, APE, septic shock, Glasgow Coma Scale (GCS), WBC, platelets, bilirubin, INR, PT, K, and MODS). The relationship between BAR and in-hospital mortality was further investigated through subgroup analysis of APE, AMI, thrombolysis, thrombectomy, and septic shock.

The predictive efficacy of BAR, BUN, and ALB for in-hospital mortality in AIS patients was compared using the DeLong's test. The time-dependent receiver operator characteristic (ROC) curves were constructed to represent the predictive value of BAR, BUN, and ALB. This function is applicable in both the conventional survival

setting and the competing risks setting, which involves estimating the cumulative/dynamic time-dependent ROC curve using the inverse probability of censoring weighting. We also constructed a BAR multivariate model involving both BAR and variables that were substantially associated with in-hospital mortality, including vasopressor use, COPD, temperature, GCS, total bilirubin, platelets, INR, and thrombolysis. The predictive value of the BAR multivariate model on in-hospital mortality in AIS was compared to that of SOFA and APACHE IV scores, by determining the C-indexes of these three prediction systems.

Statistical analysis

Statistical analysis was conducted using the SAS 9.4 software (SAS Institute, Cary, NC, USA) and R software version 4.2.2 (2022-10-31 ucrt) (Institute for Statistics and Mathematics, Vienna, Austria). Variables that were missing values were depicted in the Supplementary Table 1 and were supplemented using multiple imputation. This process generated a complete data set from a data set that was missing values, because of repeated simulation using the "mice" package of R. The Supplementary Table 2 illustrates the sensitivity analysis of the characteristics of the participants before and after multiple imputation of missing data.

TABLE 1. Characteristics of AIS Patients.

Variables	Total (n = 1635)	BAR < 5.28 (n = 831)	BAR ≥ 5.28 (n = 804)	p
Age, years, M (Q_1, Q_3)	69 (59, 80)	65 (55, 75)	73 (63, 82)	<0.001
Sex, n (%)				0.178
Female	802 (49.05)	394 (47.41)	408 (50.75)	
Male	833 (50.95)	437 (52.59)	396 (49.25)	
Ethnicity, n (%)				0.164
African American	190 (11.62)	103 (12.39)	87 (10.82)	
Asian	29 (1.77)	13 (1.56)	16 (1.99)	
Caucasian	1227 (75.05)	626 (75.33)	601 (74.75)	
Hispanic	90 (5.50)	37 (4.45)	53 (6.59)	
Native American	2 (0.12)	0 (0.00)	2 (0.25)	
Other/unknown	97 (5.93)	52 (6.26)	45 (5.60)	
Ventilation use, n (%)				<0.001
No	1211 (74.07)	666 (80.14)	545 (67.79)	
Yes	424 (25.93)	165 (19.86)	259 (32.21)	
Vasopressor use, n (%)				<0.001
No	1476 (90.28)	778 (93.62)	698 (86.82)	
Yes	159 (9.72)	53 (6.38)	106 (13.18)	
Thrombolysis, n (%)				<0.001
No	1162 (71.07)	559 (67.27)	603 (75.00)	
Yes	473 (28.93)	272 (32.73)	201 (25.00)	
Thrombectomy, n (%)				0.080
No	1620 (99.08)	820 (98.68)	800 (99.50)	
Yes	15 (0.92)	11 (1.32)	4 (0.50)	
Antiplatelet agents, n (%)				0.243
No	1388 (84.89)	697 (83.87)	691 (85.95)	
Yes	247 (15.11)	134 (16.13)	113 (14.05)	
Anticoagulation agents, n (%)				0.115
No	1619 (99.02)	826 (99.40)	793 (98.63)	
Yes	16 (0.98)	5 (0.60)	11 (1.37)	
Renal replacement therapy, n (%)				<0.001
No	1590 (97.25)	827 (99.52)	763 (94.90)	
Yes	45 (2.75)	4 (0.48)	41 (5.10)	
AKI, n (%)				<0.001
No	1463 (89.48)	807 (97.11)	656 (81.59)	
Yes	172 (10.52)	24 (2.89)	148 (18.41)	

TABLE 1. continued

Variables	Total (n = 1635)	BAR < 5.28 (n = 831)	BAR ≥ 5.28 (n = 804)	p
APE, n (%)				0.024
No	1618 (98.96)	827 (99.52)	791 (98.38)	
Yes	17 (1.04)	4 (0.48)	13 (1.62)	
Hypertension, n (%)				0.104
No	1157 (70.76)	603 (72.56)	554 (68.91)	
Yes	478 (29.24)	228 (27.44)	250 (31.09)	
COPD, n (%)				0.090
No	1547 (94.62)	794 (95.55)	753 (93.66)	
Yes	88 (5.38)	37 (4.45)	51 (6.34)	
DM, n (%)				<0.001
No	1405 (85.93)	746 (89.77)	659 (81.97)	
Yes	230 (14.07)	85 (10.23)	145 (18.03)	
Liver disease, n (%)				0.072
No	1623 (99.27)	828 (99.64)	795 (98.88)	
Yes	12 (0.73)	3 (0.36)	9 (1.12)	
AMI, n (%)				<0.001
No	1583 (96.82)	821 (98.80)	762 (94.78)	
Yes	52 (3.18)	10 (1.20)	42 (5.22)	
Septic shock, n (%)				<0.001
No	1589 (97.19)	826 (99.40)	763 (94.90)	
Yes	46 (2.81)	5 (0.60)	41 (5.10)	
Cerebral hemorrhage, n (%)				1.000
No	1633 (99.88)	830 (99.88)	803 (99.88)	
Yes	2 (0.12)	1 (0.12)	1 (0.12)	
Surgical treatment, n (%)				0.768
No	1360 (83.18)	689 (82.91)	671 (83.46)	
Yes	275 (16.82)	142 (17.09)	133 (16.54)	
Blood transfusion, n (%)				0.424
No	1618 (98.96)	824 (99.16)	794 (98.76)	
Yes	17 (1.04)	7 (0.84)	10 (1.24)	
Height, cm, M (Q_1, Q_3)	168 (160, 177.8)	170.18 (162.6, 177.8)	167.6 (160, 175.3)	0.002
Weight, kg, M (Q_1, Q_3)	79.38 (66.8, 94)	79.6 (68, 94.42)	78.96 (65.5, 93.35)	0.127
BMI, kg/m^2, M (Q_1, Q_3)	27.47 (23.88, 32.14)	27.58 (24.12, 31.89)	27.42 (23.79, 32.38)	0.826
Heart rate, bpm, M (Q_1, Q_3)	81 (70, 95)	80 (70, 94)	82 (70, 97)	0.144
SBP, mmHg, M (Q_1, Q_3)	146 (126, 165)	148 (130, 168)	143 (121, 163)	<0.001
DBP, mmHg, M (Q_1, Q_3)	79 (66, 92)	82 (70, 94)	75 (62, 89)	<0.001
RR, M (Q_1, Q_3)	18 (16, 21)	18 (16, 21)	18 (16, 22)	0.222
Temperature, °C, M (Q_1, Q_3)	37 (36, 37)	37 (37, 37)	37 (36, 37)	0.026
APACHE IV score, M (Q_1, Q_3)	51 (38, 68)	43 (33, 56)	61 (47, 82)	<0.001
GCS, M (Q_1, Q_3)	12 (7, 14)	13 (8, 14)	10 (6, 14)	<0.001
WBC, K/mcl, M (Q_1, Q_3)	9.3 (7.3, 12.5)	8.9 (7.2, 11.6)	9.8 (7.41, 13.62)	<0.001
Lymphocytes, (%), M (Q_1, Q_3)	17 (9.8, 26.3)	19.5 (12, 28.9)	14 (8, 23.18)	<0.001
Platelet, K/mcl, M (Q_1, Q_3)	216 (174, 265.5)	224 (184, 270)	207 (161, 260.25)	<0.001
Hemoglobin, g/dl, M (Q_1, Q_3)	13.2 (11.4, 14.55)	13.9 (12.4, 14.9)	12.4 (10.6, 13.9)	<0.001
RDW, (%), M (Q_1, Q_3)	14 (13.2, 15.15)	13.7 (13.05, 14.5)	14.4 (13.6, 15.6)	<0.001

TABLE 1. continued

Variables	Total (n = 1635)	BAR < 5.28 (n = 831)	BAR ≥ 5.28 (n = 804)	p
Total bilirubin, mg/dl, M (Q_1, Q_3)	0.6 (0.4, 0.8)	0.5 (0.4, 0.78)	0.6 (0.4, 0.9)	0.033
Creatinine, mg/dl, M (Q_1, Q_3)	1 (0.79, 1.32)	0.84 (0.7, 1)	1.26 (0.97, 1.8)	<0.001
INR, M (Q_1, Q_3)	1.07 (1, 1.2)	1 (1, 1.1)	1.1 (1, 1.26)	<0.001
PT, sec, M (Q_1, Q_3)	13.2 (12, 14.5)	12.9 (11.6, 14)	13.6 (12.3, 15.4)	<0.001
Glucose, mg/dl, M (Q_1, Q_3)	128 (105, 161)	123 (103, 150.5)	134 (108, 180.25)	<0.001
Bicarbonate, mmol/l, M (Q_1, Q_3)	25 (22, 27)	25 (23, 27)	24 (22, 27)	0.007
Na, mmol/l, M (Q_1, Q_3)	139 (136, 141)	139 (136, 141)	139 (136, 142)	0.061
K, mmol/l, M (Q_1, Q_3)	4 (3.7, 4.36)	3.9 (3.6, 4.2)	4.1 (3.7, 4.5)	<0.001
Chloride, mmol/l, M (Q_1, Q_3)	104 (100, 107)	104 (101, 106)	104 (100, 108)	0.004
SOFA, M (Q_1, Q_3)	5 (4, 8)	4 (4, 6)	5 (4, 8)	<0.001
MODS, n (%)				<0.001
No	1074 (65.69)	640 (77.02)	434 (53.98)	
Yes	561 (34.31)	191 (22.98)	370 (46.02)	
BUN, mg/dl, M (Q_1, Q_3)	19 (13, 26)	14 (11, 16)	26 (21, 37)	<0.001
ALB, g/dl, M (Q_1, Q_3)	3.5 (3.1, 3.9)	3.8 (3.4, 4.1)	3.3 (2.8, 3.6)	<0.001
In-hospital mortality, n (%)				<0.001
Survival	1409 (86.18)	763 (91.82)	646 (80.35)	
Death	226 (13.82)	68 (8.18)	158 (19.65)	
Survival time, days, M (Q_1, Q_3)	5.75 (3.37, 9.99)	5.04 (3.04, 8.88)	6.67 (3.75, 11.34)	<0.001

AIS, acute ischemic stroke; BAR, blood urea nitrogen and albumin ratio; M, median; Q_1, 1st quartile; Q_3, 3rd quartile; AKI, acute kidney injury; APE, acute pulmonary embolism; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; AMI, acute myocardial infarction; BMI, body mass index; SBP, Systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; GCS, Glasgow Coma Scale; WBC, white blood cell count; RDW, red blood cell distribution width; INR, international normalized ratio; PT, prothrombin time; Na, sodium; K, potassium; SOFA, Sequential Organ Failure Assessment Score; MODS, Multiple organ dysfunction syndrome; BUN, blood urea nitrogen; ALB, albumin; Statistics, t-test, rank sum test, chi-square test and Fisher's exact test.

RESULTS

The characteristics of AIS patients

The flow chart of the study procedure is depicted in Figure 1. Initially, 3,379 adult AIS patients were included. Those who were hospitalized in the ICU for less than 24 hours (n = 639), those lacking data related to their BUN or ALB levels (n = 1,078) or survival data (n = 26), were excluded. Finally, 1,635 study participants were eligible.

The characteristics of AIS patients in different BAR level groups are shown in Table 1. Of the eligible patients, 226 (13.82%) died during hospitalization. The total population had a mean age of 69 years, with 802 (49.05%) females and 833 (50.95%) males. The median serum ALB (3.8 vs. 3.3 g/dl) and BUN (14 vs. 26 mg/dl) concentrations were substantially different between the low BAR level group and the high BAR level group. The median APACHE IV scores in these two groups were 43 vs. 61, and the median SOFA scores were respectively 4 and 5. Additionally, significant differences were detected in the following parameters: ventilation use, thrombolysis, vasopressor use, AKI, renal replacement therapy, APE, DM, AMI, septic shock, height, SBP, DBP, RR, temperature, GCS, WBC, lymphocytes, platelet levels, HB levels, RDW, total bilirubin, creatinine, INR, PT, MODS, and levels of glucose, bicarbonate, Na, K, and chloride (all; $p < 0.05$).

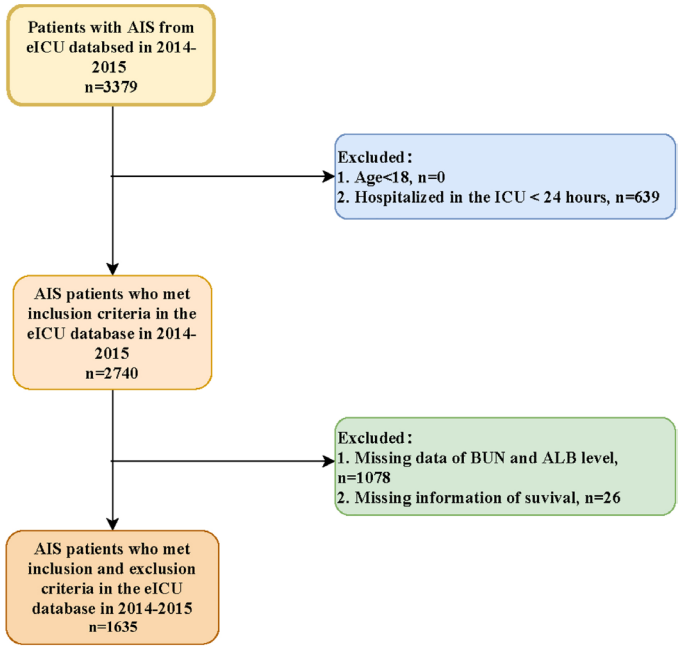

FIG. 1. Flow chart depicting participant screening process.
AIS, acute ischemic stroke; eICU, e-intensive care unit; BUN, blood urea nitrogen; ALB, albumin.

TABLE 2. Covariates Linked to in-Hospital Mortality in AIS Patients.

Variables	HR (95% CI)	p
Age	1.01 (1.01-1.02)	0.008
Sex		
Female	Ref	
Male	0.96 (0.74-1.24)	0.749
Ethnicity		
African American	Ref	
Asian	0.88 (0.20-3.79)	0.862
Caucasian	2.00 (1.23-3.25)	0.005
Hispanic	1.61 (0.80-3.25)	0.183
Native American	-	-
Other/unknown	1.92 (0.98-3.77)	0.057
Ventilation use		
No	Ref	
Yes	2.61 (1.98-3.43)	<0.001
Vasopressor use		
No	Ref	
Yes	2.01 (1.49-2.71)	<0.001
Thrombolysis		
No	Ref	
Yes	0.66 (0.46-0.95)	0.026
Thrombectomy		
No	Ref	
Yes	0.49 (0.07-3.48)	0.474
Antiplatelet agents		
No	Ref	
Yes	0.58 (0.38-0.88)	0.011
Anticoagulation agents		
No	Ref	
Yes	0.95 (0.31-2.98)	0.935
Renal replacement therapy		
No	Ref	
Yes	0.91 (0.50-1.68)	0.773
AKI		
No	Ref	
Yes	1.39 (1.01-1.91)	0.043
APE		
No	Ref	
Yes	2.15 (1.06-4.36)	0.034
Hypertension		
No	Ref	
Yes	0.88 (0.66-1.17)	0.374
COPD		
No	Ref	
Yes	1.40 (0.91-2.16)	0.126
DM		
No	Ref	
Yes	1.11 (0.79-1.55)	0.547
Liver disease		
No	Ref	
Yes	1.71 (0.76-3.86)	0.198
AMI		
No	Ref	
Yes	1.44 (0.85-2.43)	0.178
Septic shock		
No	Ref	
Yes	2.61 (1.73-3.95)	<0.001
Cerebral hemorrhage		
No	Ref	
Yes	-	0.971
Surgical treatment		
No	Ref	
Yes	0.85 (0.62-1.17)	0.317
Blood transfusion		
No	Ref	
Yes	1.41 (0.63-3.18)	0.406
Height	1.00 (0.99-1.01)	0.654
Weight	1.00 (1.00-1.01)	0.675
BMI	1.00 (1.00-1.00)	0.921
Heart rate	1.00 (1.00-1.01)	0.125
SBP	1.00 (0.99-1.00)	0.586
DBP	1.00 (0.99-1.00)	0.222
RR	1.01 (0.99-1.04)	0.191
Temperature	0.86 (0.74-1.00)	0.055
APACHE IV score	1.02 (1.02-1.03)	<0.001
GCS	0.80 (0.77-0.83)	<0.001
WBC	1.03 (1.01-1.05)	<0.001
Lymphocytes	0.99 (0.98-1.00)	0.089
Platelet	0.99 (0.99-0.99)	0.003
Hemoglobin	1.03 (0.98-1.09)	0.289
RDW	1.03 (0.98-1.09)	0.274
Bilirubin	1.11 (1.02-1.21)	0.016
Creatinine	1.04 (0.97-1.11)	0.244
INR	1.24 (1.04-1.47)	0.015
PT	1.02 (1.01-1.04)	0.032
Glucose	1.00 (1.00-1.00)	0.115
Bicarbonate	0.98 (0.95-1.00)	0.085
Na	1.03 (1.00-1.05)	0.060
K	1.27 (1.05-1.53)	0.012
Chloride	1.01 (0.99-1.03)	0.382
MODS		
No	Ref	
Yes	2.14 (1.62-2.82)	<0.001

AIS, acute ischemic stroke; HR, hazard ratio; CI, confidence interval; Ref, reference; AKI, acute kidney injury; APE, acute pulmonary embolism; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; AMI, acute myocardial infarction; BMI, body mass index; SBP, Systolic blood pressure; DBP, diastolic blood pressure; RR, respiratory rate; APACHE IV, Acute Physiology and Chronic Health Evaluation IV; GCS, Glasgow Coma Scale; WBC, white blood cell count; RDW, red blood cell distribution width; INR, international normalized ratio; PT, prothrombin time; Na, sodium; K, potassium; MODS, Multiple organ dysfunction syndrome.

Screening for the covariates associated with in-hospital mortality

Table 2 illustrates the selected covariates. The univariate Cox regression analysis revealed that in-hospital mortality was significantly correlated with age, ethnicity, ventilation use, vasopressor use, thrombolysis, thrombectomy, antiplatelet agents use, AKI, APE, septic shock, APACHE IV score, GCS, WBC, platelet levels, total bilirubin concentration, INR, PT, K, and MODS. Then, following stepwise regression, the final selected covariates were incorporated in adjustment of multivariate models.

Association between BAR and in-hospital mortality

Table 3 depicts the correlation between BAR and in-hospital mortality. After adjusting for covariates, both serum BUN concentration ≥ 19 mg/dl [HR: 1.65, 95% CI: (1.22-2.22)] and BAR ≥ 5.28 [HR: 1.39, 95% CI: (1.01-1.91)] were observed to be associated with an elevated in-hospital mortality risk.

Further subgroup analysis of common comorbidities was conducted. Table 4 demonstrates the investigation of the association of BAR with in-hospital mortality in AMI, APE, thrombolysis, thrombectomy and septic shock subgroups.

The results revealed that the positive association between BAR and in-hospital mortality risk was also significant in patients without APE (HR: 1.40, 95% CI: 1.02-1.93), AMI (HR: 1.39, 95% CI: 1.01-1.92), thrombolysis (HR: 1.47, 95% CI: 1.04-2.09), or septic shock (HR: 1.42, 95% CI: 1.03-1.97), and a history of undergoing thrombectomy (HR: 1.39, 95% CI: 1.01-1.91).

Predictive value of BAR on in-hospital mortality in AIS patients

Figure 2 illustrates the ROC curves of the predictive value of BAR, BUN, and ALB on in-hospital mortality. Both in univariate analysis and multivariate analysis, it was evident that the AUC of time related-ROC for BAR was greater than that of BUN or ALB.

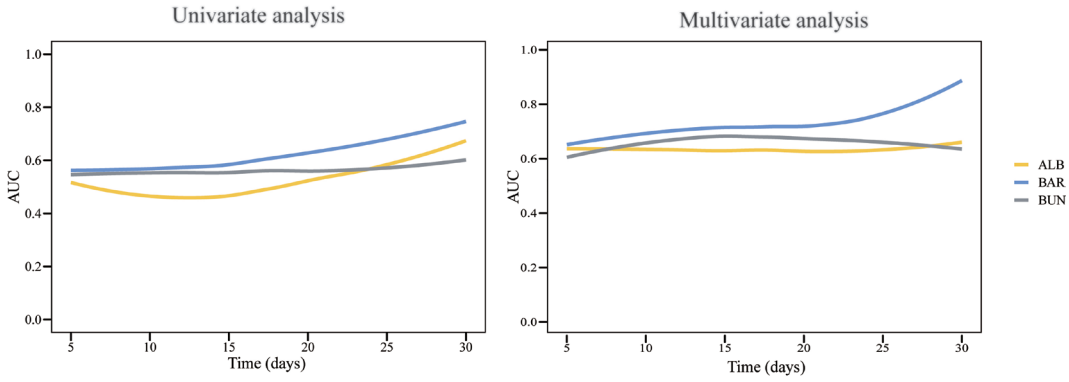

FIG. 2. ROCs of the efficacy of BAR, BUN and ALB in predicting in-hospital mortality in AIS patients.
AUC, area under the curve; ROC, receiver operator characteristic; BAR, BUN/ALB ratio; BUN, blood urea nitrogen; ALB, albumin.

TABLE 3. Association Between Serum BAR Level and the Risk of in-hospital mortality in AIS Patients.

	Crude model		Adjusted model	
Variables	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
ALB	0.95 (0.84-1.08)	0.418	1.14 (0.99-1.30)	0.063
BUN	1.14 (1.04-1.24)	0.006	1.06 (0.95-1.19)	0.324
BAR	1.11 (1.02-1.21)	0.020	1.01 (0.90-1.13)	0.928
ALB < 3.5 g/dl	Ref		Ref	
ALB ≥ 3.5 g/dl	0.73 (0.52-1.01)	0.056	1.03 (0.73-1.45)	0.866
BUN < 19 mg/dl	Ref		Ref	
BUN ≥ 19 mg/dl	1.97 (1.49-2.60)	<0.001	1.65 (1.22-2.22)	0.001
BAR < 5.28	Ref		Ref	
BAR ≥ 5.28	1.84 (1.38-2.44)	<0.001	1.39 (1.01-1.91)	0.041

BAR, blood urea nitrogen/albumin ratio; AIS, acute ischemic stroke; HR, hazard ratio; CI, confidence interval; ALB, albumin; BUN, blood urea nitrogen; Ref, reference. Model adjusted for age, ethnicity, ventilation use, vasopressor use, thrombolysis, antiplatelet agents, acute kidney injury, acute pulmonary embolism, septic shock, Glasgow Coma Scale, white blood cell, platelets, total bilirubin, international normalized ratio, prothrombin time, potassium, multiple organ dysfunction syndrome.

TABLE 4. Relationship Between BAR and In-Hospital Mortality in AMI, APE, Thrombolysis, Thrombectomy, and Septic Shock Subgroups.

Subgroups	HR (95% CI)	p
Non-APE (n = 1618)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	1.00 (0.70-1.42)	0.979
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	1.65 (1.22-2.24)	0.001
BAR < 5.28	Ref	
BAR ≥ 5.28	1.40 (1.02-1.93)	0.037
APE (n = 17)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	-	-
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	-	-
BAR < 5.28	Ref	
BAR ≥ 5.28	-	-
Non-AMI (n = 1584)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	1.09 (0.76-1.57)	0.652
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	1.71 (1.26-2.33)	<0.001
BAR < 5.28	Ref	
BAR ≥ 5.28	1.39 (1.01-1.92)	0.046
AMI (n = 52)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	0.73 (0.12-4.63)	0.742
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	0.53 (0.02-17.64)	0.721
BAR < 5.28	Ref	
BAR ≥ 5.28	0.54 (0.02-17.32)	0.727
Non-thrombolysis (n = 1162)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	1.06 (0.74-1.52)	0.746
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	1.75 (1.26-2.43)	<0.001
BAR < 5.28	Ref	
BAR ≥ 5.28	1.47 (1.04-2.09)	0.031
Thrombolysis (n = 473)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	0.92 (0.21-4.15)	0.918
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	1.25 (0.56-2.77)	0.589
BAR < 5.28	Ref	
BAR ≥ 5.28	1.19 (0.53-2.67)	0.673
Non-thrombectomy (n = 1620)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	1.03 (0.73-1.46)	0.849
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	1.65 (1.22-2.23)	0.001
BAR < 5.28	Ref	
BAR ≥ 5.28	1.39 (1.01-1.91)	0.041
Thrombectomy (n = 15)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	-	-
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	-	-
BAR < 5.28	Ref	
BAR ≥ 5.28	-	-
Non-septic shock (n = 1589)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	1.13 (0.76-1.67)	0.541
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	1.67 (1.23-2.28)	0.001
BAR < 5.28	Ref	
BAR ≥ 5.28	1.42 (1.03-1.97)	0.033
Septic shock (n = 46)		
ALB < 3.5 g/dl	Ref	
ALB ≥ 3.5 g/dl	0.49 (0.17-1.37)	0.172
BUN < 19 mg/dl	Ref	
BUN ≥ 19 mg/dl	3.25 (0.31-34.62)	0.329
BAR < 5.28	Ref	
BAR ≥ 5.28	0.95 (0.14-6.52)	0.958

BAR, blood urea nitrogen/albumin ratio, APE, acute pulmonary embolism, AMI, acute myocardial infarction, HR, hazard ratio, CI, confidence interval, ALB, albumin, BUN, blood urea nitrogen, Ref, reference. -, the risk ratio cannot be calculated due to the sample size is too small. APE subgroups adjusted for age, ethnicity, ventilation use, vasopressor use, thrombolysis, antiplatelet agents, acute kidney injury (AKI), septic shock, Glasgow Coma Scale (GCS), white blood cell (WBC), platelets, total bilirubin, international normalized ratio (INR), prothrombin time (PT), potassium, and multiple organ dysfunction syndrome (MODS); AMI, thrombolysis, thrombectomy, and septic shock subgroups all adjusted for age, ethnicity, ventilation use, vasopressor use, thrombolysis, antiplatelet agents, AKI, APE, septic shock, GCS, WBC, platelets, total bilirubin, INR, PT, potassium, MODS.

TABLE 5. Efficacy of the BAR Multivariate Model in Predicting in-Hospital Mortality in AIS Patients.

Variables	C-index (95% CI)	p
BAR multivariate model	0.789 (0.760-0.818)	Ref
APACHE IV	0.712 (0.675-0.749)	0.001
SOFA	0.683 (0.646-0.720)	<0.001

BAR, blood urea nitrogen/albumin ratio, AIS, acute ischemic stroke, CI, confidence interval, Ref, reference. APACHE IV, Acute Physiology and Chronic Health Evaluation IV, SOFA, Sequential Organ Failure Assessment Score. BAR multivariate model: including BAR, age, ethnicity, ventilation use, vasopressor use, thrombolysis, antiplatelet agents use, acute kidney injury, acute pulmonary embolism, septic shock, Glasgow Coma Scale, white blood cell, platelets, bilirubin, international normalized ratio, prothrombin time, potassium, multiple organ dysfunction syndrome.

Additionally, we calculated the C-index of the BAR multivariate model, the APACHE IV score, and the SOFA score to assess their efficacy in predicting in-hospital mortality (Table 5). The findings revealed that compared to the BAR multivariate model [C-index: 0.789, 95% CI: (0.760-0.818)], both APACHE IV [C-index: 0.712, 95% CI: (0.675-0.749)] and SOFA scores [C-index: 0.683, 95% CI: (0.646-0.720)] exhibited lower C-indexes, indicating a superior prediction value of BAR multivariate model for in-hospital mortality than the other two scoring systems.

DISCUSSION

This study examined the link between BAR and in-hospital mortality risk in AIS patients. The results indicated that a higher serum BAR was associated with an elevated in-hospital mortality risk. This positive correlation was also significant in patients who had not experienced APE, AMI, thrombolysis, thrombectomy, or septic shock. Furthermore, the efficacy of BAR and its multivariate model in predicting in-hospital mortality is superior to both ALB and BUN, as well as the APACHE IV and SOFA scores.

We did not find any other study that explored the role of BAR in AIS prognosis. According to recent studies, BAR has the potential to serve as a mortality predictor in both pneumonia and ICU patients.[18-20] Zhao et al.[9] reported that a higher BAR level at the time of ICU admission was associated with a higher four-year all-cause mortality risk in AMI patients, and thus, it may serve as an independent predictor. Dundar et al.[21] revealed that an increased BAR could predict in-hospital mortality among older emergency department patients. A cohort study conducted by Ye et al.[22] suggested that BAR was linked to poor prognosis in patients undergoing cardiac surgery and may offer prognostic information regarding in-hospital mortality. Similarly, the current study revealed that serum BAR exhibited a positive association with in-hospital mortality risk in AIS patients even after adjusting for a variety of potential confounding factors.

The BUN to ALB ratio is determined by the ratio of BUN to ALB. The serum BUN level has been identified as a predictor of mortality in various acute diseases, including AMI, pneumonia, acute pancreatitis, AIS, and APE.[8,20,23-26] Also, studies have reported that an elevated serum BUN concentration at the time of ICU admission is directly linked to mortality.[27,28] Pan et al.[29] indicated that the maximal serum BUN level, which was examined during an ICU stay, could independently predict mortality in critically ill older patients. Furthermore, the role of ALB in disease prognosis has garnered significant attention in recent decades. After a ten-year follow-up, Plakht et al.[30] demonstrated that a decreased serum ALB level is substantially associated with long-term all-cause mortality in AMI survivors. Xia et al.[31] also discovered that in initial-onset AMI patients, a low baseline ALB level was an independent predictor of long-term cardiovascular, all-cause, and cardiac mortality. In the present study, we observed that BAR exhibited a significantly superior efficacy for predicting in-hospital mortality in AIS patients. These findings fill the gap in research on this population, indicating that the combination of these two indicators may provide a more complete picture of AIS patients' risk of death than either indicator alone. Potentially complicated and diverse mechanisms may underlie BAR's potential to predict in-hospital mortality in AIS patients. Increasing evidence indicates that inflammation is a significant factor in the AIS process.[5,32] The anti-inflammatory effect of ALB was observed at physiological concentrations by selectively inhibiting the expression of vascular cell adhesion molecule-1 and monocyte adhesion in human aortic endothelial cells that were induced by tumor necrosis factor-alpha.[33] Inflammatory biomarkers, including lipoprotein-associated phospholipase A2 and C-reactive protein, are associated with hypoalbuminemia, as well as significant factors in risk stratification after AIS.[34] In addition, since ALB is an extracellular antioxidant, the increase in reactive oxygen species and free radicals worsens the long-term prognosis for AIS patients with hypoalbuminemia.[35]

Research suggests that BAR exhibits higher efficacy and sensitivity in predicting mortality in patients with acquired pneumonia than BUN or ALB, although they are both independent predictors of mortality.[18,19,36] This study also revealed that BAR demonstrated a substantially higher AUC value of ROC in predicting in-hospital mortality in AIS patients than ALB or BUN. Dundar et al.[21] reported that AUC and ORs obtained from BAR were superior to those calculated from BUN and ALB in predicting mortality among older patients. In predicting mortality, Ryu et al.[20] indicated that AUC and OR values corresponding to BAR were higher than those corresponding to ALB. BUN and ALB are easily accessible parameters in emergency services; however, performing a combined evaluation by proportioning them may be more advantageous than evaluating them separately.[37] Moreover, we compared the predictive value BAR multivariate model with that of APACHE IV and SOFA scores, and found that the BAR model demonstrated a superior prediction performance for in-hospital mortality in AIS compared to the APACHE IV and SOFA scores. Zhao et al.[9] also observed that the AUC of BAR-based predictive model was greater than those of SOFA score. This indicates a more favorable prognostic efficiency for 4-year mortality after AMI, which could be easily and rapidly calculated in routine clinical practice. Our study findings suggest that it may be more meaningful to evaluate BAR in AIS patients, and use it as a biomarker for prognosis, as this may enable physicians to assess the clinical condition of AIS patients from two distinct perspectives.

Also, the C-index of BAR multivariate model, APACHE IV score and SOFA score in this study were respectively 0.789, 0.712, and 0.683. Nevertheless, additional study is required to validate the advantage of serum BAR in predicting mortality compared to BUN or ALB.

There were several limitations in our study. The eICU database is a public multi-center database in the U.S. and is representative to a certain extent. However, the conclusions we have drawn are still limited to the American population and therefore cannot be generalized. There was evident selection bias due to the substantial number of deleted patients who lacked BUN or ALB data. However, based on sensitivity analysis and existing literature, our conclusion that BAR is significantly associated with in-hospital mortality in AIS patients after excluding potential confounding factors is relatively robust. The sample size in APE and thrombectomy subgroups was insufficient to explore the association between BAR and in-hospital mortality. Although we compared the predictive performance of the BAR multivariate model with APACHE IV and SOFA scores, other scoring systems, such as the National Institutes of Health Stroke Scale, which provide significant data regarding factors influencing hospitalization-related mortality in AIS patients, were not included in the eICU database. Additionally, prospective cohort studies with a larger sample size are still required to investigate the causal relationship between BAR and mortality risk in AIS patients.

In conclusion, serum BAR exhibits a positive association with in-hospital mortality risk in AIS patients. Additionally, BAR and its multivariate model both demonstrated reliable predictive value for in-hospital mortality in AIS. Our findings suggested that serum BAR exhibits the potential to identify patients with high mortality risk, which may be beneficial for the disease surveillance and risk stratification of AIS.

Ethics Committee Approval: Since the data were publicly accessible, the requirement for ethical approval was waived by the ethics committee of our hospital.

Informed Consent: The patients who are involved have provided informed consent.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- W.L.; Design- W.L.; Data Collection or Processing- Q.H., K.Z.; Analysis and/or Interpretation- Q.H., K.Z.; Writing- W.L.; Critical Review- W.L.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: The authors declared that this study received no financial support.

Supplementary Table 1: https://balkanmedicaljournal.org/uploads/pdf/SUPLLEMENT--TABLE%201.pdf

Supplementary Table 2: https://balkanmedicaljournal.org/uploads/pdf/SUPLLEMENT--TABLE%202.pdf

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