Prognostic significance of the blood urea nitrogen-to-serum albumin ratio in patients with septic shock

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Abstract. The blood urea nitrogen-to-serum albumin ratio (BAR) has been linked to clinical outcomes in multiple critical illnesses; however, its prognostic value in patients with septic shock remains inconclusive. The present retrospective observational study involved 120 patients with septic shock, who were classified into a survivor group (n=97) and a non-survivor group (n=23) based on discharge outcomes. Within 24 h of ICU admission, important clinical and laboratory data were collected and compared between the two groups. Multivariate logistic regression analysis identified BAR [odds ratio (OR)=1.052; 95% confidence interval (CI):1.014-1.117; P=0.012] and the Acute Physiology and Chronic Health Evaluation II (APACHE II; OR=1.096; 95% CI:1.014-1.185; P=0.030) as independent risk factors for in-hospital mortality in these patients. Receiver operating characteristic (ROC) curve analysis showed that the area under the curve (AUC) of BAR for predicting in-hospital mortality was 0.707. At the optimal cutoff value of 13.62, BAR had a sensitivity of 73.9% and a specificity of 63.9%. Further, the AUC of the multivariable model [including BAR, diastolic blood pressure (DBP), APACHE II, and partial pressure of carbon dioxide (PCO_2)] was 0.859 (95% CI:0.778-0.939; P<0.001); the optimal cutoff value was 0.154; the sensitivity was 87% and the specificity was 74.2%, which was markedly improved over single BAR or APACHE II. Therefore, BAR emerged as a valid independent predictor of in-hospital mortality in patients with septic shock and may serve as a simple, readily accessible biomarker for the early risk stratification in this patient population. The BAR model incorporating DBP, APACHE II and PCO_2 demonstrated high discrimination and stratification efficiency for patient mortality risk.

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Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. When accompanied by hyperlactatemia or fluid-refractory hypotension, it is classified as septic shock. The incidence of sepsis is alarmingly high. In 2017 alone, there were 48.9 million cases worldwide, with an annual standardized incidence rate of 677.5 per 100,000 individuals and an annual standardized mortality rate of 148.1 per 100,000 individuals. For patients in the intensive care unit (ICU), sepsis and septic shock are critical determinants of mortality prognosis (1). Although numerous research efforts and clinical measures over the past few decades have improved the speed of sepsis diagnosis and treatment, sepsis, specifically septic shock, still exhibits a high mortality rate. Therefore, early identification of patients at high risk of poor outcomes is critical for optimizing management.

Currently, the Acute Physiology and Chronic Health Evaluation II (APACHE II) is a widely used scoring system for evaluating disease severity (2); however, it has several limitations. For example, in young patients with severe sepsis but without chronic organ dysfunction, the risk of adverse outcomes may be significant; however, the APACHE II score could still be low (3). The Sequential Organ Failure Assessment (SOFA) score is primarily used to objectively describe the degree of organ dysfunction (4). However, certain variables in the SOFA score exhibit known limitations, such as the possibility that elevated bilirubin may be due to hemolysis rather than liver dysfunction, while the Glasgow Coma Scale (GCS) is not only challenging to assess but also inherently subjective (5). Hence, developing simple and objective biomarkers for early risk stratification in patients with septic shock has important clinical significance.

Blood urea nitrogen (BUN), an important parameter providing information about renal function, protein metabolism and tissue perfusion (6), is markedly correlated, at elevated

levels, with poor prognosis in patients with sepsis (7-9). Albumin (ALB) plays a critical role in maintaining colloid osmotic pressure while also exerting antioxidant and anti-inflammatory effects, and hypoalbuminemia is also closely associated with poor prognosis in sepsis (10). The blood urea nitrogen-to-serum albumin ratio (BAR), which combines the two, has been shown to be an independent predictor of prognosis for critically ill patients with pneumonia (11) and sepsis (12,13). Nevertheless, the predictive value of BAR in patients with septic shock has not been fully examined. Therefore, the aim of the present study was to evaluate the predictive performance of BAR with respect to the survival prognosis of patients with septic shock.

Materials and methods

Participants and procedures. The present retrospective study initially included a total of 224 patients with shock from the intensive care database of the First Affiliated Hospital of Anhui Medical University (Anhui, China). Clinical data collected within 24 h of ICU admission includes 34 candidate variables, included age, sex, height, weight, history of hypertension, history of diabetes, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), APACHE II score, SOFA score and results of relevant laboratory blood tests. The blood test items included white blood cell count (WBC), hemoglobin (HBG), platelet count (PLT), C-reactive protein (CRP), procalcitonin (PCT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALB, globulin (GLO), total bilirubin (TBIL), creatinine (CREA), BUN, BAR, glucose (GLU), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), D-Dimer (D-D), pH, bicarbonate (HCO_3^-), partial pressure of carbon dioxide (PCO_2), oxygenation index (PaO_2/FiO_2 ratio, FPR) and lactic acid (LAC). Unit conversion is required when calculating BAR: BUN (mg/dl)=urea (mmol/l)x2.8; ALB (g/dl)=ALB (g/l)/10. The present study was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University [approval no. PJ2022-01-09(1)], in accordance with the Declaration of Helsinki and the relevant applicable Chinese regulations on biomedical research involving human subjects. Written informed consent was obtained from all of the participants or their legal representatives for their participation in the study. The present study strictly adhered to the ethical principles and standards set forth by the aforementioned-mentioned ethics committee.

During the data preprocessing phase, the missing data rates for height (118 missing cases, representing 52.7%) and weight (119 missing cases, representing 53.1%) both exceeded 10%. Consequently, these variables were excluded from the pool of candidate variables and were not considered in the subsequent analysis.

Inclusion and exclusion criteria for study participants. The criteria for inclusion in the study were as follows: Participants aged ≥18 years who met the diagnostic criteria for septic shock as defined by Sepsis 3.0 (14). The exclusion criteria were as follows: Age <18 years; ICU stay <48 h; late-stage brain herniation; cardiogenic, hypovolemic, or obstructive shock; and missing data >10%. The number of missing BUN and ALB key variables and individual missing variables exceeded 10% of the total number of current variables.

Missing value processing and statistical analysis. Among the 224 initially screened cases, we excluded those aged under 18 years (1 case), those with an ICU stay of <48 h (24 cases), those with late-stage cerebral hernia (11 cases) and those with non-septic shock (25 cases). Subsequently, 29 patients with simultaneous missing values for both BUN and ALB were excluded because BAR could not be calculated. Among the remaining 134 cases, an individual-level missing data assessment was conducted for 32 continuous variables, and 14 patients with >3 missing variables (that is, exceeding 10% of the total number of current variables) were further excluded. Ultimately, 120 patients with septic shock were included in the analysis and were divided into a survival group (97 cases) and a death group (23 cases) based on their clinical outcomes at discharge.

In the final dataset comprising 120 cases, a small number of scattered missing values were observed among the continuous variables, as detailed below: SBP was missing in one case (0.8%), DBP in one case (0.8%), APACHE II score in one case (0.8%), SOFA score in one case (0.8%), CRP in two cases (1.7%), PCT in five cases (4.2%) and HCO_3^- in two cases (1.7%), with no missing values for the remaining variables (15). These missing values were imputed using the mean interpolation method stratified by survival status. Specifically, the mean values of each variable were calculated separately for the survival and death groups, and the missing values within each group were then filled with the corresponding group mean. All univariate and multivariate analyses were conducted based on the complete dataset after imputation.

Statistical analyses were performed using SPSS 26.0 (IBM Corp.), GraphPad Prism 8.0 (Dotmatics) and SPLS online statistical platform (https://www.spls.cn). For count data, the results were presented intuitively as frequency (N) and proportion (%), employing either the χ^2 test or Fisher's exact test, to evaluate differences among various groups. Quantitative data with a normal distribution were expressed as mean ± standard deviation, while comparisons between groups were conducted using the unpaired Student's t-test (or Welch's t-test when equal variances were not assumed). Conversely, for quantitative data without a normal distribution, results were presented using the median (M) and interquartile range (Q1-Q3). Intergroup comparisons were conducted using the Mann-Whitney U test. Further, for variables demonstrating statistically significant differences between the two groups, univariate logistic regression analysis was carried out on the interpolated variables, while determination of the multivariate model was conducted through Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis. Independent risk factors were identified using multivariate logistic regression analyses. To assess the diagnostic accuracy of the indicators in predicting the risk of in-hospital mortality in patients with septic shock, the present study applied the receiver operating characteristic (ROC) curve and calculated the area under the ROC curve, the Youden index, sensitivity and specificity. A two-sided P-value of <0.05 was considered to indicate a statistically significant difference (16). The stability of the model was validated internally using bootstrap resampling.

Table I. Comparison of clinical data between two groups of patients with septic shock.

Variable	Survival group (n=97)	Death group (n=23)	P-value
Age (range), years	64 (48.5-73)	68 (42-72)	0.942
Male, n (%)	70 (72.2)	18 (78.3)	0.552
Hypertension, n (%)	28 (28.9)	9 (39.1)	0.338
Diabetes, n (%)	16 (16.5)	2 (8.7)	0.537
SBP (range), mmHg	86 (78.5-98)	68 (56-88)	0.000[a]
DBP (range), mmHg	50 (44-55)	38 (30-51)	0.000[a]
HR, bpm	123.47±23.29	136.04±29.09	0.029[a]
APACHEII (range)	20 (15-26)	30 (22-34)	0.000[a]
SOFA (range)	9 (6-12)	11 (9-14.25)	0.006[a]
WBC (range), $x10^{9}$/l	12.77 (7.10-17.46)	17.87 (11.81-21.88)	0.077
HBG, g/l	101.26±27.25	101.35±27.25	0.989
PLT (range), $x10^{9}$/l	145.78±98.84	125.57±77.54	0.362
CRP (range), mg/l	146.56 (68.44-200)	200 (66-200)	0.962
PCT (range), pg/ml	7.2 (1.64-37.67)	11.83 (2.90-37.21)	0.294
ALT (range), U/l	42 (25-140)	91 (27-540)	0.084
AST (range), U/l	60 (34-167)	128 (33-1328)	0.081
ALB, g/l	32.99±5.84	32.74±6.76	0.855
GLO, g/l	24.41±5.21	24.63±4.48	0.857
TBIL (range), μmol/l	20.4 (13.25-32.55)	28.1 (15-43.3)	0.191
CREA (range), μmol/l	96 (59.15-202.6)	132.3 (99.3-375.8)	0.072
BUN (range), mmol/l	13.66 (10.09-19.69)	21.33 (13.31-131.60)	0.003[a]
BAR (range), mg/g	11.29 (8.22-18.56)	18.49 (11.94-30.72)	0.002[a]
GLU (range), mmol/l	10.4 (7.68-14.5)	13.24 (9.7-19.1)	0.135
PT (range), sec	16.6 (15.2-19.5)	20.5 (16.9-24.2)	0.010[a]
APTT (range), sec	44.4 (39.7-53.95)	56.9 (41.7-90.7)	0.013[a]
FIB, g/l	4.75±1.95	4.95±2.17	0.667
D-Dimer (range), mg/ml	5.84 (2.445-12.67)	5.07 (2.23-11.95)	0.992
pH (range)	7.494 (7.423-7.527)	7.476 (7.43-7.556)	0.918
HCO_3^- (range), mmol/l	27.2 (23.55-31.65)	27.8 (22.6-37)	0.314
PCO_2 (range), mmHg	42.2 (36.75-49.45)	51.1 (35.6-64.5)	0.035[a]
PFR (range), mmHg	240.72±97.03	223.45±113.73	0.460
LAC (range), mmol/l	2.46 (1.59-4.23)	6.65 (3.25-14.44)	0.000[a]

[a]P<0.05. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; APACHEII, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell count; CRP, C-reactive protein; HBG, hemoglobin; PLT, platelet count; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; GLO, globulin; TBIL, total bilirubin; CREA, creatinine; BUN, blood urea nitrogen; BAR, blood urea nitrogen-to-albumin ratio; GLU, glucose; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; D-Dimer, D-dimer; pH, potential of hydrogen; HCO_3^-, bicarbonate; PCO_2, partial pressure of carbon dioxide; PFR, oxygenation index; LAC, lactic acid.

Results

Inclusion in the septic shock patient screening process. Based on the inclusion and exclusion criteria, a total of 120 patients with septic shock were ultimately included from 224 patients presenting with shock. Of the included patients, 97 were in the survivor group and 23 were in the non-survivor group (Fig. 1).

Patient demographics and baseline clinical characteristics. In a baseline cohort of 120 patients with septic shock, the median age of those in the survivor group (N=97) was 64 years, whereas the median age of those in the non-survivor group (N=23) was 68 years (Fig. 1). The two groups did not differ in age with respect to statistical significance (P=0.942). Of the patients in the survivor group 70 were male, representing 72.2% of the cohort; by contrast, the non-survivor group comprised 18 male patients, accounting for 78.3%. Sex distribution did not differ significantly between the groups (P=0.552). Additional analysis showed no statistically significant differences in the prevalence of hypertension, history of diabetes, or laboratory parameters, including WBC, HBG, PLT, CRP, PCT, ALT, AST, ALB, GLO, TBIL, CREA, GLU, FIB, D-D, PH, HCO_3^- and PFR (P>0.05). Conversely, patients in the non-survivor group exhibited markedly higher values for HR, APACHE II,

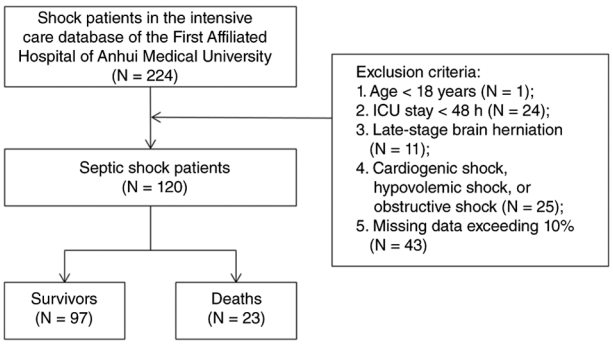

Figure 1. Inclusion in the septic shock patient screening process.

SOFA, PT, APTT, BUN, BAR, LAC and PCO_2 than those in the survivor group, while showing comparatively lower SBP and DBP values. As illustrated in Table I and Fig. 2, all of the observed differences were statistically significant (P<0.05).

Analysis of risk factors for in-hospital mortality in patients with septic shock. Based on the results of the univariate logistic regression analysis, a total of 11 variables were identified as statistically significant (P<0.05): SBP, DBP, HR, APACHE II, SOFA, BAR, PT, APTT, PCO_2 and LAC. However, ALB showed no statistical significance (P=0.854) (Table II). Because of the high correlation between BUN and BAR (Spearman's r=0.930; VIF=7.386), collinearity was avoided by including 10 variables other than BUN in LASSO regression (10-fold cross-validation; λ.1se criterion). Finally, five nonzero coefficient variables were selected, namely, DBP, BAR, PCO_2, LAC and APACHE II, for inclusion in the multivariate logistic regression, and the backward stepwise regression method (likelihood ratio method) was employed. After LAC (P=0.504) was removed, the final model retained four independent predictive factors, namely, DBP, BAR, PCO_2 and APACHE II. The results showed that DBP [odds ratio (OR)=0.920; 95% confidence interval (CI): 0.871-0.972; P=0.03] serves as a protective factor against in-hospital mortality in patients with septic shock, whereas BAR (OR=1.064; 95% CI:1.014-1.117; P=0.012) and APACHE II (OR=1.096; 95% CI:1.014-1.185; P=0.020) emerged as independent risk factors for in-hospital mortality in this patient population. Notably, PCO_2 did not show statistical significance (P=0.056; Table III, Fig. 3). The collinearity diagnosis indicated that the VIF of each variable in the final model was <2.0, indicating that the final model had no significant multicollinearity.

Model prediction performance and internal validation. The ROC curve analysis showed that the AUC for BAR in predicting in-hospital mortality due to septic shock was 0.707 (95% CI:0.596-0.817; P=0.002), with a Youden index of 0.378. The optimal diagnostic cutoff value was established at 13.62, yielding a diagnostic sensitivity of 73.9% and a specificity of 63.9%. The AUC of the APACHE II score was 0.783 (95% CI:0.678-0.887), the optimal cutoff value was 29.5, sensitivity was 56.5%, and specificity was 88.7%. The AUC of the multivariable model, including DBP, BAR, PCO_2 and APACHE II, was 0.859 (95% CI:0.778-0.939), which was markedly improved over the single BAR and APACHE II indicators. As illustrated in Table IV and Fig. 4, the optimal cutoff value for this model was 0.154, corresponding to a sensitivity of 87.0% and a specificity of 74.2%.

Table II. Univariate logistic regression for in-hospital mortality in septic shock.

Variable	P-value	Odds ratio (95% CI)
HR, bpm	0.033[a]	1.020 (1.002-1.038)
SBP, mmHg	0.001[a]	0.957 (0.932-0.983)
DBP, mmHg	0.000[a]	0.904 (0.861-0.951)
APACHEII	0.000[a]	1.150 (1.072-1.223)
SOFA	0.007[a]	1.190 (1.046-1.353)
BUN, mmol/l	0.006[a]	1.049 (1.014-1.085)
BAR, mg/g	0.009[a]	1.052 (1.013-1.094)
PT, sec	0.044[a]	1.041 (1.001-1.082)
APTT, sec	0.009[a]	1.015 (1.004-1.027)
PCO_2, mmHg	0.012[a]	1.029 (1.006-1.052)
LAC, mmol/l	0.000[a]	1.165 (1.071-1.267)

[a]P<0.05. SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; APACHEII, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; BUN, blood urea nitrogen; BAR, blood urea nitrogen-to-albumin ratio; ALB, albumin; PT, prothrombin time; APTT, activated partial thromboplastin time; PCO_2, partial pressure of carbon dioxide; LAC, lactic acid; CI, confidence interval.

The bootstrap self-sampling method (5,000 resamples) was used for internal validation of the model. The 95% CIs obtained through the bias corrected and accelerated method (BCa) for BAR, DBP and PACHE II did not include 0, consistent with the direction of the original multiple regression results and maintained stable significance (17). The lower limit of the BCa 95% CI for PCO_2 was slightly below 0 (-0.005 to 0.078; P=0.027), indicating a relatively weak effect (Table V). The aforementioned results indicated no significant overfitting in this model, and the predictive performance exhibited good internal consistency.

Comparison of predictive performance between BAR and BUN-based combined models. To further investigate whether BAR provides additional predictive information superior to that provided by BUN, a BAR-based combined model (comprising BAR, DBP, APACHE II and PCO_2) and a BUN-based combined model (comprising BUN, DBP, APACHE II and PCO_2) were constructed and their goodness of fit and predictive performance were compared.

The AIC of the BAR model was 88.182, while the AIC of the BUN model was 88.776 (ΔAIC=-0.594), indicating that the marginal fitting efficiency of the BAR model was improved over that of the BUN model. After the removal of BAR, the model χ^2 decreased by 6.620 (P=0.010), whereas after BUN was removed, the χ^2 decreased by 6.026 (P=0.014). Therefore, the contribution of BAR to the model was slightly greater than that of BUN. The ROC curve analysis revealed that the AUC of the BAR-based combined model was 0.859 (95% CI:0.778-0.939), whereas the BUN-based combined model

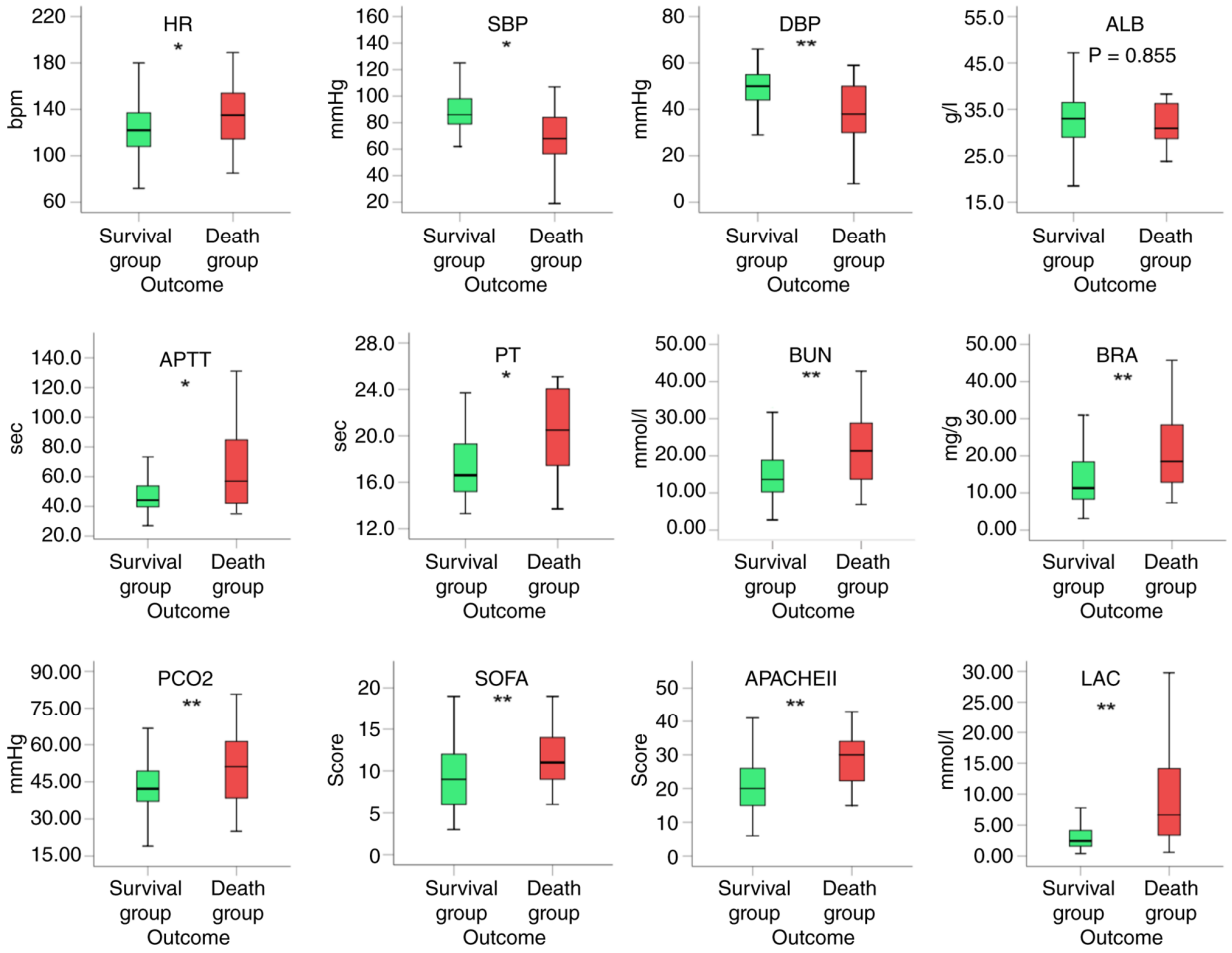

Figure 2. Comparison of key clinical data between the survivor and non-survivor groups. *P<0.05, **P<0.01. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALB, albumin; APTT, activated partial thromboplastin time; PT, prothrombin time; BUN, blood urea nitrogen; BAR, blood urea nitrogen-to-serum albumin ratio; PCO_2, partial pressure of carbon dioxide; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; LAC, lactic acid.

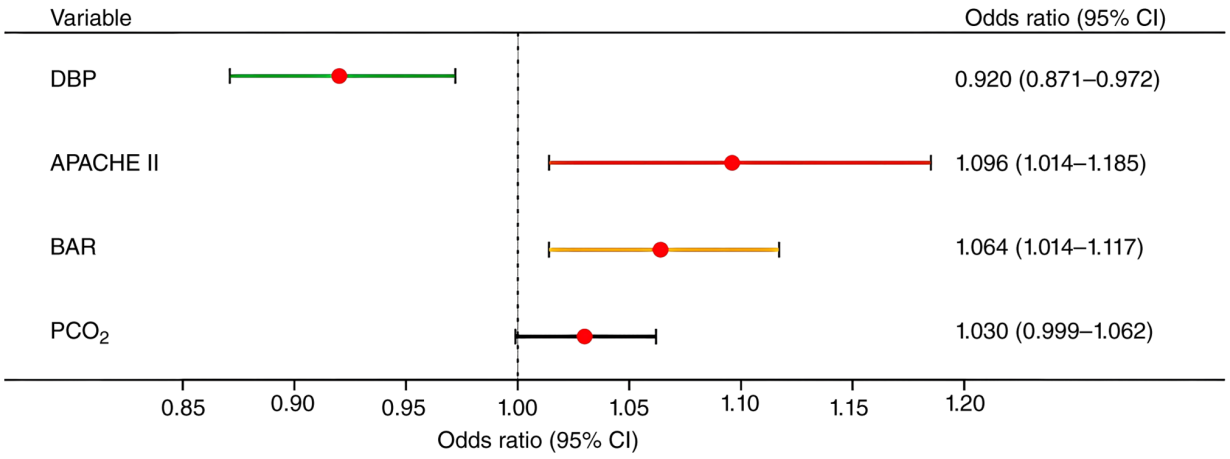

Figure 3. Predictors of in-hospital mortality in patients with septic shock. DBP, diastolic blood pressure; APACHE II, Acute Physiology and Chronic Health Evaluation II; BAR, blood urea nitrogen-to-serum albumin ratio; PCO_2, partial pressure of carbon dioxide; CI, confidence interval.

had an AUC of 0.853 (95% CI:0.770-0.935), with no statistically significant difference between the two (ΔAUC=+0.006; P=0.842). These findings indicated that the predictive performance of the two models was essentially comparable (Table VI). Therefore, BAR and BUN were largely equivalent in statistical performance; however, BAR exhibited a marginally improved model fit and a higher variable contribution.

Mortality risk stratification by BAR alone vs. the multivariable model. Based on the optimal cutoff value for

Table III. Multivariate logistic regression for in-hospital mortality in septic shock.

Variable	P-value	Odds ratio (95% CI)
DBP, mmHg	0.003[a]	0.920 (0.871-0.972)
APACHEII	0.030[a]	1.096 (1.014-1.185)
BAR, mg/g	0.012[a]	1.052 (1.014-1.117)
PCO_2, mmHg	0.056[a]	1.030 (0.999-1.062)

[a]P<0.05. DBP, diastolic blood pressure; APACHEII, Acute Physiology and Chronic Health Evaluation II; BAR, blood urea nitrogen-to-albumin ratio; PCO_2, partial pressure of carbon dioxide; CI, confidence interval.

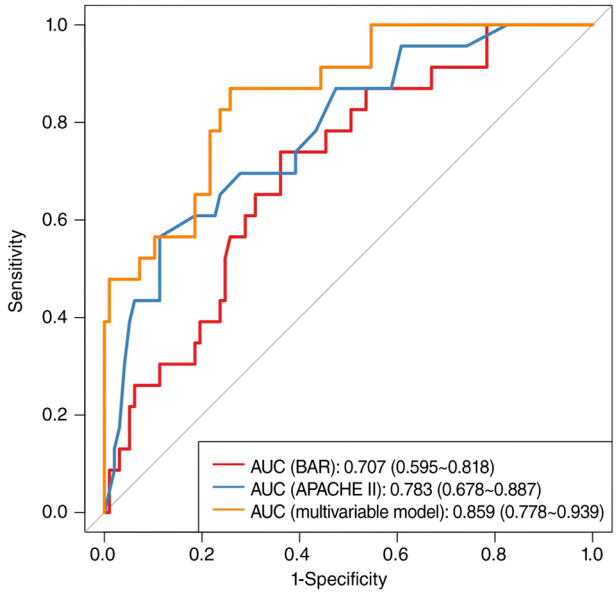

Figure 4. ROC curves of BAR, APACHE II and the multivariable prediction model. ROC, receiver operating characteristic; BAR, blood urea nitrogen-to-serum albumin ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II; AUC, area under the curve.

predicting mortality using BAR (13.62), patients were divided into a high-risk group (BAR ≥13.62) and a low-risk group (BAR <13.62). The mortality rate in the high-risk group was significantly higher than that in the low-risk group [32.7% (17/52) vs. 8.8% [6/68]; χ^2=10.836; P=0.001], signifying a significant stratified effect of elevated BAR on mortality risk. Based on the optimum cutoff value (0.154) of the BAR-based combined model for risk stratification, the mortality rate in the high-risk group (predicted probability ≥0.154) was significantly higher than that in the low-risk group [predicted probability <0.154; 44.4% (20/45) vs. 4.0% (3/75); χ^2=29.694; P<0.001]. The BAR-based combined model demonstrated markedly improved hierarchical performance than a single BAR indicator (Table VII).

Discussion

The present study revealed that BAR was an independent risk factor for in-hospital mortality in patients with septic shock, with an optimal cutoff value of 13.62. The predictive efficacy of BAR was validated in the high-risk group of patients with septic shock. Prior studies confirmed the predictive value of BAR in patients with sepsis. For example, Cai *et al* (12)'s retrospective analysis of 13,464 patients with sepsis indicated that for every five units of increase in BAR, the risk of in-hospital mortality correspondingly increased by 8%. Min *et al* (13) also confirmed that the ICU mortality rate among patients with sepsis (BAR ≥7.93) was markedly higher than that of the low-BAR group. Moreover, BAR has demonstrated good prognostic potential in other critically ill populations, such as acute pancreatitis (18) and chronic heart failure (19). The present study extended this finding to the subgroup of septic shock, further supporting the universality of BAR as a prognostic biomarker across critically ill patient populations.

In the present study, compared with other predictive indicators, the APACHE II score was also confirmed as an independent risk factor for in-hospital mortality in patients with septic shock. This revelation is consistent with the advantage of using APACHE II as a comprehensive scoring system covering multiple physiological parameters (3). By contrast, as an objective laboratory indicator, BAR can avoid the evaluation bias of subjective indicators inherent in the APACHE II scoring scale and is easier to monitor dynamically.

In the present study, DBP was employed as a protective factor against in-hospital mortality in patients with septic shock (OR=0.920; P=0.003), indicating an 8% reduction in the risk of mortality for every 10 mmHg increase in DBP. This insight aligns with a number of research findings, such as a significant correlation between 24-h mean DBP<59 mmHg and 28-day mortality risk from septic shock (20), DBP<70 mmHg and adverse cardiovascular events in patients with coronary heart disease (21), and DBP<55 mmHg and cardiovascular events (22). As the principal driver of coronary artery perfusion, DBP may lead to myocardial ischemia, particularly in patients with septic shock who often exhibit impaired coronary artery reserve function. Low DBP further aggravates myocardial injury (23). However, research conducted in Japan has shown that, compared with a MAP target of 65-70 mmHg, a higher target of 80-85 mmHg does not improve the prognosis of elderly patients with septic shock (24). The aforementioned evidence implies that DBP should be regarded as an independent target for hemodynamic management of septic shock, rather than solely focusing on mean arterial pressure.

The present study also compared the predictive performance of the BAR-based combined model with that of the BUN-based combined model. The AIC of the BAR model (88.182) was lower than that of the BUN model (88.776), and the contribution of BAR to the model (likelihood ratio test P=0.010) was slightly higher than that of BUN (P=0.014). However, the difference in AUC between the two models was not statistically significant (ΔAUC=+0.006; P=0.842). This suggested that BAR and BUN possess essentially equivalent statistical power, with BAR exhibiting a marginally superior model fit and a higher variable contribution. Li *et al* (8) found a nonlinear relationship between BUN and 30-day mortality in patients with sepsis, with an inflection point at 41.1 mg/dl, indicating that the predictive performance of BUN may have a threshold effect. By integrating ALB information, BAR

Table IV. ROC Analysis of BAR, BUN, APACHE II and the multivariable model for mortality prediction.

Variable	BAR	BUN	APACHE II	Multivariable model
AUC	0.707	0.699	0.783	0.859
P-value	0.002	0.003	<0.001	<0.001
95% CI	0.596-0.817	0.585-0.817	0.678-0.887	0.778-0.939
Youden's index	0.378	0.362	0.452	0.612
Sensitivity	73.9%	0.609	56.5%	87%
Specificity	63.9%	0.753	88.7%	74.2%
Optimal cutoff value	13.62	19.57	29.5	0.154

ROC, receiver operating characteristic; BAR, blood urea nitrogen-to-albumin ratio; BUN, blood urea nitrogen; APACHEII, Acute Physiology and Chronic Health Evaluation II; AUC, the area under the curve; CI, confidence interval.

Table V. Bootstrap internal validation of the multivariate model (5,000 resamples).

Variable	β coefficient	Original SE	Bootstrap SE	Bias	Original P-value	Bootstrap P-value	BCa 95% CI	
							Lower	Upper
BAR	0.062	0.025	0.811	0.009	0.012	0.011	0.006	0.182
DBP	-0.083	0.028	0.67	-0.008	0.003	0.001	-0.147	-0.044
APACHEII	0.063	0.040	0.111	0.006	0.020	0.009	0.003	0.222
PCO_2	0.030	0.016	0.069	0.003	0.056	0.027	-0.005	0.078
Constant	-2.692	1.894	0.988	-0.204	0.155	0.163	-7.608	1.269

BAR, blood urea nitrogen-to-albumin ratio; DBP, diastolic blood pressure; APACHEII, Acute Physiology and Chronic Health Evaluation II; PCO_2, partial pressure of carbon dioxide; BCa, bias corrected acceleration method; CI, confidence interval; SE, standard error.

Table VI. Predictive performance comparison: BAR model vs. BUN model.

Model	-2Log Likelihood	AIC	BIC	Nagelkerke R^2	Core Variable P-value (Likelihood Ratio Test)
BAR model	0.707	88.182	102.119	0.446	0.010
BUN model	0.002	88.776	102.713	0.440	0.014
Difference (Δ)	13.62	-0.594	-0.594	+0.006	-

BAR, blood urea nitrogen-to-albumin ratio; BUN, blood urea nitrogen; AIC, akaike information criterion; BIC, bayesian information criterion.

Table VII. Univariate logistic regression for in-hospital mortality in septic shock.

Variable	Group	Total (N)	Deaths, N (%)	χ^2	P-value
BAR	Low-risk	68	5 (8.8)		
	High-risk	52	17 (32.7)	10.836	0.001[a]
Multivariable Model	Low-risk	75	3 (4.0)		
	High-risk	45	20 (44.4)	29.694	<0.001[a]

[a]P<0.05. BAR, blood urea nitrogen-to-albumin ratio.

may partially correct the nonlinear characteristics of BUN, resulting in more stable model-fit performance.

The predictive model developed by combining BAR with DBP, APACHE II and PCO_2 yielded an AUC of 0.859,

markedly outperforming individual BAR or APACHE II indicators. Risk stratification based on the combined model revealed a mortality rate as high as 44.4% in the high-risk group and only 4.0% in the low-risk group, with stratification performance far superior to that of the single BAR indicator (32.7% vs. 8.8%). This indicated that combining BAR (reflecting renal perfusion/inflammatory status), DBP (reflecting circulatory function) and APACHE II (reflecting overall disease severity) substantially enhances the ability to identify mortality risk in patients with septic shock. This finding is also consistent with previous studies highlighting prediction strategies that integrate multiple indicators (23,24). In the present study, LASSO regression and bootstrap internal validation effectively controlled the risk of overfitting, with the adjusted BAR yielding a BCa 95% CI of 0.006-0.182 (P=0.011), thereby confirming the robustness of the model.

In the multivariate analysis, ALB did not enter the final model (single factor P=0.854), which does not align with some previous research conclusions. Xiao *et al* (25) reported that serum albumin ≤25 g/l is an independent risk factor for predicting mortality in ICU patients with fungal bloodstream infection and that supplementing with human albumin may improve hemodynamic parameters and short-term survival in patients with liver cirrhosis and septic shock (10). However, subsequent large-sample randomized controlled trials targeting septic shock populations did not confirm that supplementing albumin improves 28- or 90-day survival rates and, in some cases, it may even increase the risk of adverse reactions, including pulmonary edema (26,27). The aforementioned discrepancies suggest that the prognostic value of ALB may be influenced by multiple factors, including basic liver and kidney function, fluid resuscitation strategy, and timing and dosage of albumin administration. When the predictive value of ALB is limited, BAR compensates for the shortcomings of ALB's single indicator by combining BUN indicators.

The mechanism whereby BAR predicts poor prognosis in patients with septic shock may involve multiple pathological and physiological disorders. First, sepsis-induced systemic inflammatory response may lead to renal microcirculation dysfunction and acute kidney injury, resulting in reduced BUN excretion. Further, high catabolic metabolism enhances protein breakdown and enhances BUN generation, and higher BUN is associated with increased mortality in patients with sepsis (7,8). Second, elevated BUN may also serve as an indirect marker for neural hormone activation, such as the renin angiotensin aldosterone system and antidiuretic hormone system (28), which plays a central role in the pathological progression of vascular paralysis and organ hypoperfusion in septic shock. Third, capillary leakage induced by inflammation causes the extravascular migration of ALB, along with impaired liver synthesis function, leading to hypoalbuminemia (10). By integrating the two opposing but jointly reflecting disease severity processes into a single indicator, BAR provides more comprehensive prognostic information than either BUN or ALB.

The present study was subject to several limitations. First, the retrospective, single-center design of the study may introduce selection bias. Second, the sample size was relatively small. Third, a limited number of baseline indicators were considered, which may have affected the final conclusions of the predictive model. Fourth, the outcome measure in the present study was in-hospital mortality, with no follow-up on 28-day mortality. Finally, while dynamic changes in the BAR value may provide greater clinical value for assessing patients with septic shock, the present study lacked relevant data on this aspect.

In conclusion, BAR emerged as a readily available and promising biomarker for early risk stratification of in-hospital mortality in patients with septic shock. The prediction model constructed by combining BAR with DBP, PCO_2, APACHE II, and other indicators has high predictive performance, which can provide reference for clinical practitioners to identify high-risk patients early, initiate prevention strategies for septic shock, and optimize treatment plans. However, the conclusions require validation through additional studies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JL and ZW were responsible for writing, methodology, and data curation. SY and MS were responsible for supervision, project administration and conceptualization. JL and MS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University [approval no. PJ2022-01-09(1)], in accordance with the Declaration of Helsinki and the relevant applicable Chinese regulations on biomedical research involving human subjects. Written informed consent was obtained from all of the participants or their legal representatives for their participation in the study. The present study strictly adhered to the ethical principles and standards set forth by the aforementioned-mentioned ethics committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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