# ORIGINAL RESEARCH Analysis of the Value of the Blood Urea Nitrogen to Albumin Ratio as a Predictor of Mortality in Patients with Sepsis

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Purpose: At present, simple, accurate, and efficient prognostic tools for the evaluation of cases with early-stage sepsis in the emergency department (ED) are lacking. An increased blood urea nitrogen to albumin ratio (BAR) has previously been shown to be a valuable biomarker with predictive utility in several diseases. The relationship between BAR and sepsis patient outcomes, however, is not well-understood. This exploration was thus developed for the exploration of the link between BAR values and the short-term prognosis of cases with sepsis.

Methods: This was a retrospective cohort research of sepsis cases admitted to the West China Hospital of Sichuan University ED from July 2015 to June 2016. Laboratory data were collected upon ED admission, and 7-day all-cause mortality was the primary study endpoint. Relationships between BAR values and APACE II and SOFA scores were generated assessed with correlation coefficient heatmaps. Independent risk factors were identified through multivariate analyses, with the curves of receiver operating characteristic (ROC) being employed to gauge the value of BAR as a predictor of the risk of mortality in sepsis cases.

Results: In sum, 801 patients participated in the present investigation. BAR values were strongly correlated with APACHE II and SOFA scores. In a multivariate logistic regression assessment, BAR was identified as an independent predictor of mortality among patients with sepsis (HR=1.032, 95% CI: 1.010-1.055, P=0.004). BAR exhibited an AUC of 0.741 (95% CI: 0.688-0.793, P<0.001) when used to predict patient mortality risk, with 5.27 being the optimal BAR cut-off.

**Conclusion:** We found that BAR can be used as a reliable biomarker to predict mortality in patients with sepsis. Keywords: sepsis, blood urea nitrogen-to-albumin ratio, risk factors, prognosis

#### Introduction

Sepsis is one of the pervasive reasons for mortality all over the world, imposing substantial medical and economic burdens on affected individuals and society as a whole.<sup>1-3</sup> The 2016 international consensus for sepsis and septic shock (Sepsis-3) benchmark recently defined sepsis as a form of life-threatening organ dysfunction arising as a result of abnormal responses to infection.<sup>4</sup> Effectively identifying patients at a high risk of severe sepsis during the early stages of this disease is thus critically important as it has the potential to lower rates of multiple organ failure and associated patient mortality.

Multiple systems have been developed to gauge the severity of sepsis and to approximate the prognosis of affected patients,<sup>5</sup> comprising the sequential organ failure assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation (APACHE) II score, both of which are used to identify patients with a bad prognosis.<sup>6,7</sup> Both of these scores, however, are dependent on many whole-body physiologic parameters and are thus challenging to measure, limiting their use

during the initial stages of patient evaluation in the Emergency Department (ED).<sup>8,9</sup> As such, there is a clear need to identify reliable biomarkers that can be readily assessed to predict the sepsis patient prognosis during the early stages of disease.

A growing body of evidence suggests that elevations in levels of blood urea nitrogen (BUN) and decreases in serum albumin levels are closely associated with sepsis severity. Moreover, an increase in the BUN to albumin ratio (BAR) has been confirmed to be a robust predictor of outcomes for cases with a range of diseases, such as chronic obstructive pulmonary disease (COPD), COVID-19, and critical illnesses.<sup>10–13</sup> The role of BAR as a prognostic factor for sepsis patients, however, has not been assessed in prior reports. Here, we therefore sought to evaluate the value of BAR as a predictor of mortality risk among sepsis patients.

# **Materials and Methods**

#### Study Design

This was a single-center retrospective cohort research developed for the assessment of the relationship between BAR levels and the odds of negative achievements in sepsis cases. All patients or their legal proxies provided informed consent for study participation prior to enrollment. The public and patients were not included in designing, conducting, reporting, or disseminating research plans. This study was consistent with the Declaration of Helsinki, and was confirmed through the Human Ethical Committee of West China Hospital of Sichuan University (number: 2019 (373)).

#### Study Population

Data used for the present exploration were obtained from the West China Hospital retrospective sepsis database. Specifically, data were obtained for cases with sepsis evaluated in the ED of West China Hospital of Sichuan University between July 2015 and June 2016. Patients eligible for inclusion in this analysis were individuals  $\geq 18$  years old that met the Sepsis-3 definition and were admitted within 3 days following disease onset.<sup>4</sup> Contributors were excluded from this research if they were pregnant, exhibited malignant tumors, presented to the ED in cardiac arrest necessitating immediate cardiopulmonary resuscitation, required long-term hemodialysis, exhibited chronic kidney disease or exhibited incomplete data.

#### Data Collection

Data collected for patients included in this study included demographic details, medical history, vital signs, laboratory findings, and associated diagnosis. Analyzed laboratory parameters included pH, lactate (Lac), base excess (BE), hemoglobin (Hb), platelet (PLT) count, white blood cell (WBC) count, bilirubin, hematocrit (HCT), albumin (ALB), creatinine (Cr), blood urea nitrogen (BUN), triglyceride (TG), aspartate aminotransferase (ALT), alanine aminotransferase (AST), prothrombin time (PT), and activated partial thromboplastin time (APTT) values. BAR was calculated by dividing the BUN of a patient at admission by their ALB level. SOFA and APACHE II scores for patients were estimated by physicians based on baseline data following ED admission.

# Endpoints and Follow-Up

The patients received a structured telephone interview-based follow-up call at 28 days post-ED admission. The primary study endpoint was 7-day all-cause mortality, while secondary endpoints included mechanical ventilation (MV), the incidence of ICU admission (AICU), and 28-day mortality. AICU was described as patient admission to the ICU owing to unstable vital signs, severe hydroelectrolyte imbalance, severe dystrophy, and a requirement for organ support. MV was described as a requirement for invasive or non-invasive ventilation as a consequence of hypoxic respiratory failure.<sup>14</sup> Patients were separated into survival and non-survival groups based on their 7-day survival status.

# Statistical Analysis

The Kolmogorov–Smirnov assessment was employed to evaluate whether continuous variables conformed to a normal distribution, with those that did being expressed as means ±standard deviations and scrutinized via Student's t-tests. Non-normally distributed continuous variables were presented as medians [interquartile range (IQR)] and were scrutinized via

Mann–Whitney *U*-tests. Non-continuous variables were presented as frequencies (proportions) and scrutinized employing  $\chi^2$  or Fisher's exact test as appropriate. Relationships between BAR values, APACHE II scores, and SOFA scores in patients with sepsis were assessed using a correlation coefficient heat map, with the Pearson's correlation test being used to define correlation coefficients. The utility of BAR as an independent predictor of short-term mortality in sepsis patients was assessed through an analysis of multivariate logistic regression. The area under the receiver operating characteristic (ROC) curve (AUC) for BAR, APACHE II, and SOFA scores was calculated to gauge the ability of these different metrics to predict the odds of 7-day mortality in septicemic cases. The AUC values for these variables were compared via the DeLong test. The maximum Youden index was utilized to select an optimal BAR cut-off value for stratifying patients into two subgroups, with rates of adverse events being compared between these groups (including AICU, MV, and 28day mortality) via Fisher's exact test or  $\chi^2$  test. A two-sided P < 0.05 was the threshold of significance, and all outcomes were evaluated employing SPSS 26.0 (IBM Corporation, NY, USA), MedCalc Statistical Software v 19, and R V.3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

#### Baseline Characteristics

In sum, 801 sepsis cases participated in this survey (mean age:  $57.37\pm17.73$  years old; 64.4% male). These patients exhibited respective median SOFA and APACHE II scores of 5 (IQR 3–8) and 15 (IRQ 11–20). Of these cases, 722 (90.14%) survived for 7 days, while 79 (9.86%) died during this period. Clinical data were compared between these two groups of patients, revealing significant differences in heart rate, respiratory rate, mean arterial pressure, SpO<sub>2</sub>, PH, lactate, base excess, platelet count, aspartate aminotransferase, serum albumin, BUN, BAR, creatinine, activated partial thromboplastin time, prothrombin time, SOFA scores, and APACHE II scores between groups (P<0.05, Table 1). No other clinical characteristics were found to vary between these groups (P>0.05, Table 1).

## Correlations Between BAR Values and SOFA and APACHE II Scores

Next, we explore the relationship between BAR values and both the APACHE II scores and SOFA scores for sepsis patients through Pearson's correlation analyses. This approach revealed that BAR values and SOFA scores were associated n (r=0.47, P<0.001, Figure 1), with a similarly strong positive correlation being observed between BAR values and APACHE II scores (r=0.34, P<0.001, Figure 1).

# Evaluation of the Diagnostic Performance of BAR Values as Predictors of the Odds of 7-Day Mortality Among Sepsis Patients

Next, we examined the utility of BAR, APACHE II, and SOFA scores as predictors of 7-day mortality among sepsis patients using ROC curves. The AUC values for these curves indicated that BAR values exhibited good predictive utility (AUC =0.741, 95% CI: 0.688–0.793, P<0.001) that was not inferior to SOFA (0.772, 95% CI 0.732–0.813) or APACHE II (0.772, 95% CI 0.732–0.813) performance, with no significant differences among these indicators (P>0.05) (Figure 2). The optimal BAR value for the estimation of 7-day mortality among sepsis patients was 5.27, yielding respective sensitivity and specificity values of 86.08% and 50.00%.

## The Relationship Between BAR Values and Adverse Outcomes

Septic patients were next classified into groups with high BAR values (BAR $\geq$ 5.27) and low BAR values (BAR<5.27) based on the optimal BAR cut-off value. Rates of adverse events including AICU, MV, and 28-day mortality were then compared between these groups, revealing that the rates of all three of these events were significantly increased among patients with high BAR values relative to those with low BAR values (P<0.05) (Figure 3).

## Risk Factors Associated with Sepsis Patient Mortality

Next, the collected data were subjected to multivariate and univariate binary logistic regression assessments. In univariate assessments, reduced MAP, SpO<sub>2</sub>, pH, BE, PLT, and ALB values and elevated HR, RR, Lac, BUN, BAR, Cr, PT, and

Characteristic	Total Patients (n=801)	Survivors (n=722)	Non-Survivors (n=79)	Р	
The general information					
Age (years)	57.37±17.73	57.07±17.77	60.11±17.24	0.140	
Male, n (%)	516 (64.4)	467 (64.7)	49 (62.0)	0.640	
T (°C)	36.9 (36.5, 38.0)	36.9 (36.6, 38.0)	36.7 (36.5, 37.6)	0.058	
HR (time)	107 (95, 123)	106 (95, 122)	114 (101, 130)	0.002	
RR (time)	22 (21, 25)	22 (21, 24)	24 (22, 28)	<0.001	
MAP (mmHg)	89.67 (76.50, 100.33)	90.00 (77.67, 100.33)	78.67 (68.67, 98.67)	0.006	
SpO2 (%)	96 (92, 98)	96 (93, 98)	94 (90, 97)	0.005	
Laboratory test results					
PH	7.44 (7.34, 7.48)	7.44 (7.39, 7.48)	7.39 (7.30, 7.46)	<0.001	
Lac (mmol/L)	1.5 (1.2, 2.1)	1.4 (1.1, 2.0)	2.6 (1.4, 2.8)	<0.001	
BE (mmol/L)	22.1 (19.3, 25.4)	22.55 (19.80, 25.50)	19.30 (15.80, 21.30)	<0.001	
WBC (×10 <sup>9</sup> /L)	11.71 (7.52, 16.33)	11.74 (7.59, 16.29)	11.69 (6.03, 17.03)	0.672	
HB (g/L)	III.33±29.66	113.94±29.53	108.82±30.65	0.161	
НСТ	0.34 (0.29, 0.40)	0.34 (0.29, 0.40)	0.35 (0.28, 0.39)	0.438	
PLT (×10 <sup>9</sup> /L)	160 (93, 240)	163 (97, 246)	119 (55, 191)	<0.001	
Bilirubin (µmol/L)	12.70 (8.30, 21.90)	12.40 (8.30, 21.48)	16.00 (8.70, 23.20)	0.140	
ALT (U/L)	36.0 (15.0, 55.5)	26.0 (16.0, 54.0)	29.0 (14.0, 85.0)	0.514	
AST (U/L)	34.0 (22.0, 64.5)	33.0 (21.0, 63.0)	43.0 (26.0, 125.0)	0.003	
ALB (g/dl)	3.22 (2.79, 3.72)	3.28 (2.82, 3.76)	2.84 (2.43, 3.12)	<0.001	
BUN (mg/dl)	18.17 (12.33, 29.37)	17.44 (12.06, 27.22)	29.29 (17.30, 49.22)	<0.001	
BAR	5.67 (3.73, 9.82)	5.28 (3.62, 8.75)	10.45 (5.90, 18.25)	<0.001	
Cr (µmol/L)	79.0 (60.5, 123.0)	77.0 (60.0, 109.0)	123.0 (74.0, 240.0)	<0.001	
TG (mmol/L)	1.11 (0.80, 1.65)	1.11 (0.81, 1.64)	1.08 (0.70, 1.68)	0.570	
PT (s)	13.6 (12.4, 15.4)	13.6 (12.4, 15.2)	15.4 (13.0, 18.9)	<0.001	
APTT (s)	34.1 (28.9, 40.5)	33.8 (28.9, 39.7)	38.2 (29.7, 52.3)	<0.001	
Scoring system					
SOFA (score)	5 (3, 8)	4 (2, 7)	6 (9, 14)	<0.001	
APACHE II (score)	15 (11, 20)	15 (11, 19)	22 (17, 26)	<0.001	

Table I Comparison of Baseline Data of Patients with Different Prognosis

Abbreviations: T, temperature; HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure; SpO2, oxyhemoglobin saturation; Lac, lactate; BE, base excess; WBC, white blood cell; HB, hemoglobin; HCT, haematocrit; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; BUN, blood urea nitrogen; BAR, blood urea nitrogen-to-albumin ratio; Cr, creatinine; TG, triglyceride; PT, prothrombin time; APTT, activated partial thromboplastin time; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II.

APTT values were all identified as risk factors associated with patient 7-day mortality. Following adjustment for age, sex, HR, RR, MAP, SpO2, pH, Lac, BE, PLT, ALB, BUN, Cr, PT, and APTT levels, BAR values were identified as an independent predictor of mortality risk among sepsis patients (HR=1.032, 95% CI: 1.010–1.055, *P*=0.004). In addition, RR, pH, Lac, ALB, and PT were described as independent predictors of patient mortality. For further details regarding the results of these logistic regression analyses, see Table 2.

# Discussion

Sepsis and associated multiple organ failure are among the leading causes of global mortality, posing a serious threat to human quality of life.<sup>15</sup> At present, however, efforts to accurately gauge sepsis severity in affected patients in a timely manner remain difficult.<sup>16</sup> Several scoring systems and clinical biomarkers have been leveraged for the prognostic evaluation of sepsis patients, but owing to the complex nature of this condition, no specific clinical indicator has been reliably shown to predict outcomes in this patient population.<sup>17</sup> While the SOFA and APACHE II scores have been employed to estimate sepsis patient mortality in a clinical setting, with higher scores being positively correlated with higher rates of mortality,<sup>18–20</sup> these scoring systems are time-consuming, complex, and tedious, limiting their more widespread utilization.

BUN levels are commonly employed as a serum biomarker when evaluating renal function, and are routinely utilized in clinical practice owing to the associated ease of measurement.<sup>21,22</sup> BUN levels have previously been reported to be

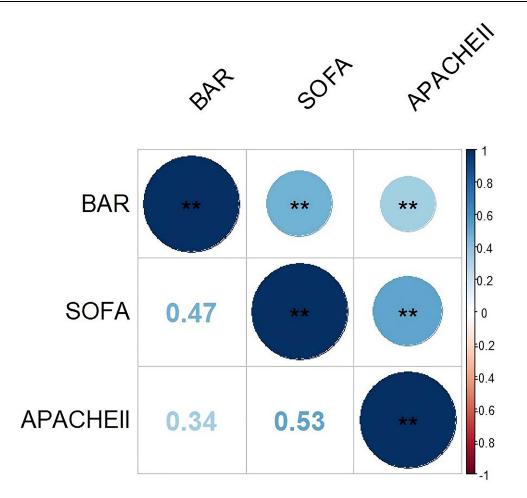


Figure I Correlation coefficient heatmap. \*\*P<0.001.

Variables		AUC(95% CI)	SE	<i>P</i> -value	P for comparison
BAR		0.741 (0.688-0.793)	0.027	<0.001	Ref
SOFA	⊢∙⊣	0.786 (0.730-0.841)	0.028	<0.001	0.143
APACHE II	¦ ⊢●−1	0.761 (0.708-0.815)	0.027	<0.001	0.491
	0.6 0.7 0.8 0.9	1.0			

Figure 2 AUC of BAR and other predictive scoring systems for 7-day sepsis mortality.

closely correlated with several diseases including primary aldosteronism (PA), acute pancreatitis (AP), and primary pulmonary hypertension (PPH) and are often used to stratify these patients according to disease severity.<sup>23–25</sup> BUN levels have also been employed in the context of sepsis patient evaluation in recent years, and have been shown to be a key risk factor associated with poor sepsis patient prognosis.<sup>26,27</sup> In line with these previous reports, we found that non-surviving sepsis patients exhibited significantly elevated BUN levels as compared to survivors. Further sepsis progression has the potential to result in multiple organ dysfunction, which is the primary reason for mortality among sepsis cases.<sup>28</sup> The

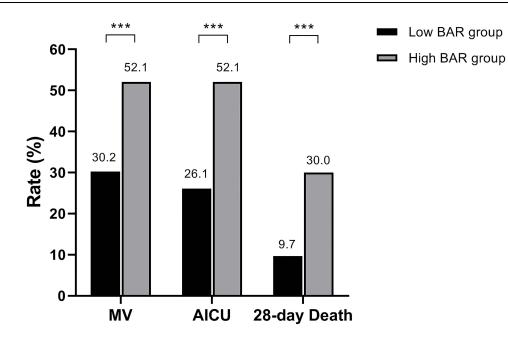


Figure 3 MV, AICU and 28-day death in the different BAR groups. \*\*\*P<0.001.

kidneys are generally the first and most significantly damaged vital in patients suffering from septicemia.<sup>29</sup> Consistently, BUN levels can serve as an indicator of renal function, rising in the context of renal failure.

Albumin accounts for ~60% of plasma protein,<sup>30</sup> playing key physiological roles as a transporter of various compounds, a robust antioxidant, and a regulator of colloidal osmotic pressure within the plasma.<sup>31</sup> In addition to offering valuable clinical insight regarding patient nutritional status, albumin levels are also associated with acute inflammatory activity in patients.<sup>32</sup> A growing body of evidence has demonstrated the important role played by albumin in the onset and progression of septicemia, underscoring its utility as a prognostic biomarker in the evaluation of septic patients.<sup>33,34</sup> There are several likely explanations for these findings. For one, severe sepsis can cause systemic inflammation that results in increased vascular permeability and the consequent extravascular leakage of serum albumin, thus resulting in hypoproteinemia outside of the vasculature and causing substantial fluid retention within tissues while simultaneously reducing effective circulating blood volumes, further contributing to the incidence of systemic organ damage.<sup>35,36</sup> Moreover, the liver is often one of the first and most profoundly affected organs in septicemic patients, and severe damage that exceeds the compensatory capabilities of the liver can compromise albumin synthesis.<sup>37</sup> Early human serum albumin supplementation has been shown to decrease the incidence of sepsis-related mortality, contributing to better therapeutic achievements in sepsis cases.<sup>38</sup>

Recent articles have highlighted the promise of the BAR as a prognostic inflammation-related biomarker in patients with a range of diseases, but its value in the context of sepsis patient evaluation remains unclear. Here, we therefore explored the utility of BAR values as a predictor of sepsis patient prognosis. This study is the first to our knowledge to have reported increased BAR levels in sepsis patient serum. We also found that serum lactate levels were significantly elevated in patients that did not survive relative to those that did. Higher SOFA and APACHE II scores are generally considered to be indicative of more severe disease and a poorer prognosis. Here, we found that BAR levels were significantly positively correlated with SOFA and APACHE II scores. We then plotted ROC curves and determined the corresponding AUC values as a means of gauging the relative prognostic accuracy of BAR values, SOFA scores, and APACHE II scores when used to evaluate sepsis patients. These analyses revealed that all three approaches were able to effectively establish the risk of 7-day mortality among sepsis patients in the ED. While BAR values performed comparably to SOFA and APACHE II scores, it is important to note that these latter two methods necessitate complex calculations that make their use in an emergency situation impractical. In contrast, BAR values can be readily measured and calculated. To further confirm our findings, cases were separated into two cohorts

Variable	Univariable Analysis				Multivariable Analysis			
	OR	P	95% CI for HR		OR	Р	95% CI for HR	
			Lower	Upper	1		Lower	Upper
Age	1.010	0.148	0.996	1.024				
Gender	0.892	0.640	0.552	1.440				
т	0.921	0.278	0.793	1.069				
HR	1.017	0.004	1.005	1.028				
RR	1.067	<0.001	1.031	1.104	1.064	0.002	1.024	1.107
MAP	0.983	0.009	0.970	0.996				
SpO2	0.968	0.008	0.945	0.992				
PH	0.000	<0.001	0.000	0.005	0.041	0.043	0.020	0.910
Lac	1.359	<0.001	1.235	1.495	1.261	<0.001	1.129	1.408
BE	0.902	<0.001	0.864	0.942				
WBC	1.009	0.501	0.983	1.035				
НВ	0.994	0.145	0.986	1.002				
НСТ	0.168	0.210	0.010	2.734				
PLT	0.996	0.001	0.993	0.998				
Bilirubin	1.002	0.400	0.998	1.006				
ALT	1.000	0.575	1.000	1.001				
AST	1.000	0.425	1.000	1.000				
ALB	0.325	<0.001	0.219	0.483	0.523	0.005	0.333	0.821
BUN	1.021	<0.001	1.013	1.028				
BAR	1.056	<0.001	1.036	1.076	1.032	0.004	1.010	1.055
Cr	1.002	0.003	1.001	1.002				
TG	0.963	0.677	0.808	1.149				
РТ	1.053	<0.001	1.026	1.081	1.031	0.005	1.010	1.054
APTT	1.027	<0.001	1.016	1.038				

Table 2 Univariable and Multivariable Logistic Regression Analyses of the Various Features Associated with Fatal Outcomes inPatients with Sepsis

Notes: Adjusted for age, sex, HR, RR, MAP, SpO<sub>2</sub>, PH, Lac, BE, PLT, ALB, BUN, Cr, PT and APTT.

Abbreviations: T, temperature; HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure; SpO2, oxyhemoglobin saturation; Lac, lactate; BE, base excess; WBC, white blood cell; HB, hemoglobin; HCT, haematocrit; PLT, platelet count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; BUN, blood urea nitrogen; BAR, blood urea nitrogen-to-albumin ratio; Cr, creatinine; TG, triglyceride; PT, prothrombin time; APTT, activated partial thromboplastin time.

according to their BAR values. Further analyses exhibited that there were substantial discrepancies between these two groups with respect to secondary endpoints including AICU, MV, and 28-day mortality. As such, BAR values can be readily leveraged to monitor therapeutic responses and/or deterioration in sepsis patients in the ED.

# Limitations

There are certain limitations to these analyses. For one, this was a retrospective single-center research with a small sample size, potentially subjecting these achievements to selection bias. Therefore, the analysis does not adjust for potential confounders. Although the sample size was relatively small, according to the sample size calculations the minimum number required for each group was met. Second, we did not conduct any external validation, and these results thus ought to be validated in the next large-scale investigations. Lastly, it is possible that dynamic changes in BAR values may offer greater prognostic value for the evaluation of sepsis patients, but we failed to test this possibility in the present study.

# Conclusion

In conclusion, BAR value at admission is an easily measured biomarker that is positively correlated with sepsis severity, with a higher BAR value being indicative of a poorer sepsis patient prognosis.

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# Disclosure

The authors have no potential conflicts of interest to disclose.

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