Prognostic impact of blood urea nitrogen to albumin ratio on patients with sepsis: A retrospective cohort study

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Article

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Abstract

Objective

To investigate the ability of the ratio of blood urea nitrogen (BUN) to serum albumin ratio (BAR) in patients with sepsis in intensive care units (ICUs) to predict the prognosis of short-and long-term death.

Methods

Data were derived from the Medical Information Market in the Intensive Care IV (MIMIC-IV v2.0) database, with septic patients defined by SEPSIS-3. 30-day mortality for the primary outcome and 360-day mortality for the secondary outcome. Kaplan-Meier (KM) Survival curves were plotted to describe differences in BAR mortality in different subgroups, and area under the curve (AUC) analysis was performed to a comparison of BAR + SOFA and sequential organ failure assessment (SOFA) performance. Multivariate Cox regression models, restricted cubic spline curves (RCS), and subgroup analysis were used to ascertain the correlation between BAR and 30-day mortality and 360-day mortality.

Results

A total of 7656 eligible patients with a median BAR of 8.0 mg/g were enrolled in the study, with 3837 patients in the ≤8.0 group and 3819 in the BAR > 8.0 group, with 30-day mortality rates of (19.1% and 38.2%; P < 0.001)The area under the curve (AUC) was 0.718 (95% CI: 0.705–0.731) for SOFA + BAR and 0.703 (95% CI: 0.690–0.716) for SOFA. In the subgroup analysis, BAR remained an isolated risk element for patient death. For 360-day all-cause mortality, the same pattern was observed after adjustment for the same confounders.

Conclusion

As a clinically inexpensive and readily available parameter, BAR can be a valuable forecaster of prognosis in patients with sepsis in the intensive care unit.

1. Introduction

Sepsis is a symptom of infection-induced physiological, pathological and biochemical abnormalities. Despite the decreasing trend in sepsis morbidity and mortality over the years, there are still 48.9 million cases of sepsis, of which 11 million resulted in death as of 2017. Severe sepsis can cause acute multi-organ dysfunction, surviving patients with sepsis often have long-term consequences such as impaired immune function, cognitive function, and mental health, which affect the long-term health-related quality of life and survival. Many biomarkers and multiple scoring systems are used to predict the prognosis of
patients with sepsis; however, these tools are either expensive or not readily available\textsuperscript{7-9}. We aimed to explore convenient laboratory markers to predict the prognoses of patients with sepsis. Blood urea nitrogen (BUN) is the main product of protein metabolism in the human body and is mainly excreted by the kidneys. In the presence of excessive protein catabolism or reduced glomerular filtration, BUN levels rise, which is an essential parameter for the patient's renal status and protein catabolism metabolism\textsuperscript{10}. Albumin is also one of the commonly used assays in clinical laboratories and has a significant effect on numerous physiological mechanisms\textsuperscript{11}. Increased microvascular permeability in inflammatory states alters the distribution of intra- and extravascular albumin, resulting in decreased serum albumin concentrations in many critically ill patients\textsuperscript{12}. The impact of BUN and albumin on the prognoses of patients with sepsis has been demonstrated\textsuperscript{13,14}. To our knowledge, the effectiveness of the predictive value of the urea nitrogen to serum albumin ratio (BAR), calculated as the quotient of BUN and albumin, has not been investigated in patients with sepsis. For this reason, we first sought to determine the correlation between BAR and prognosis in septic patients in the ICU.

2. Materials And Methods

2.1 Data sources

Data were obtained from the Marketplace for Intensive Care Medical Information IV (MIMIC-IV version 2.0) database\textsuperscript{15}, an open-source and free database developed by the associated laboratories at the Massachusetts Institute of Technology (MIT). The database records clinical data (e.g., patient baseline information, baseline vital signs, imaging tests, complications, medication use, and diagnoses) for patients admitted to a single-center intensive care unit from 2008 to 2019. MIMIC-IV is an updated clinical database that incorporates contemporary data and improves many aspects of MIMIC-, which was formerly a widely accepted database and has undergone intensive analysis for academic purposes. This study obtained database access authorized by the relevant institution (certificate number: 39168475).

2.2 Selection criteria

According to the latest definition of sepsis, SEPSIS-3, adult patients diagnosed with sepsis at the time of admission were entered into this research. In addition, for patients reentering the intensive care unit, only patients who were admitted to the intensive care unit for the first time were considered for this study. We further excluded for lack of blood urea nitrogen or serum albumin and patients who spent less than 24 hours in the intensive care unit (Fig. 1).

2.3 Data Collection

The following variables were extracted from the MIMIC-IV database. Patient demographic characteristics (age, gender), vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation), laboratory parameters (red blood cells, white blood cells, platelets, hemoglobin, serum electrolytes, serum creatinine, glucose), and comorbidities (congestive heart failure, chronic lung disease, liver disease, kidney disease, malignancy, peripheral vascular disease) upon admission. Extraction of data from the database using

2.4 Statistical analysis

The analysis of statistical data was performed using R, version 4.1.2 for Windows ("http://www.r-project.org/) and Free Statistics analysis platform. All reported P values are two-tailed, and P < 0.05 values were considered statistically significant. Continuous variables were represented as median ± interquartile difference; categorical variables were represented as frequencies; t-tests and X^2 tests were for comparison of differences between groups. KM survival curves were plotted for different subgroups according to the restricted cubic spline (RCS) model and Sequential Organ Failure Assessment (BAR) to show survival at 30 and 360 days in sepsis patients and compared using nonlinear regression and log-rank tests, respectively. Multivariate Cox regression models were used to estimate the association between BAR and all-cause mortality in sepsis. The multivariable Cox regression model was used to predict the interaction with BAR and all-cause sepsis mortality. The results of multivariate Cox regression models showed risk ratios (HRs) and risk ratios with 95% confidence intervals (CIs). The model I adjusted for age and sex. Model II was adjusted for age, heart rate, blood pressure, respiratory rate, oxygen saturation, comorbidities, erythrocytes leukocytes platelets hemoglobin serum potassium serum creatinine, SOFA, hemoglobin SAPS II. The comparison of the forecast efficiency of SOFA + BAR with BAR was performed by ROC analysis. The comparison of AUC between models was evaluated by the DeLong test. Subgroup analyzes were used to assess the association between BAR and 30- and 360-day mortality, including age, sex, comorbidity, SOFA score, and SAPS II score

2.5 Outcomes

The principal outcome indicator was post-ICU mortality 30 days after admission and the minor outcome indicator was post-ICU mortality 360 days after admission.

3. Results

3.1 Population characteristics

A series of 7656 patients fulfilling the SEPSIS-3 diagnostic criteria with blood urea nitrogen and albumin data during 24 hours in the ICU and completed follow-up were selected for this study, and the data criteria selection process is shown in Figure 1. **Figure 1** Flow chart of the study

The baseline characteristics of the study population are presented in Table 1, patients in the high BAR group tended to be older, had a higher proportion of males, and had more comorbidities and adverse clinical signs such as high respiratory rate, high white blood cell count; potassium, creatinine, glucose, and severity scores, and lower blood pressure, oxygen saturation, red blood cells, hemoglobin platelets, and blood calcium levels compared to patients with low BAR (≤ 8.0). Additionally, patients in the high BAR group had higher mortality rates at 30 and 360 days than in the low groups.
Table 1 Characteristics of the study patients by BAR levels
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BAR levels</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 7656)</td>
<td>BAR ≤ 8.0 (n = 3837)</td>
</tr>
<tr>
<td>Age (years), Median (IQR)</td>
<td>64.0 (53.0, 76.0)</td>
<td>61.0 (49.0, 73.0)</td>
</tr>
<tr>
<td>Gender, F, n (%)</td>
<td>3285 (42.9)</td>
<td>1761 (45.9)</td>
</tr>
</tbody>
</table>

**Basic vital signs, Median (IQR)**

<table>
<thead>
<tr>
<th></th>
<th>Value (IQR)</th>
<th>Value (IQR)</th>
<th>Value (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>88.2 (76.4, 100.4)</td>
<td>87.8 (76.4, 100.2)</td>
<td>88.6 (76.3, 100.8)</td>
<td>0.255</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>112.7 (103.8, 125.0)</td>
<td>115.1 (105.5, 127.8)</td>
<td>110.6 (102.4, 122.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>61.4 (55.0, 68.8)</td>
<td>63.4 (57.1, 71.1)</td>
<td>59.0 (53.0, 66.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>75.6 (69.5, 83.2)</td>
<td>77.9 (71.7, 85.7)</td>
<td>73.2 (67.6, 80.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Respiratory rate (bpm)</td>
<td>19.7 (17.2, 22.8)</td>
<td>19.3 (17.1, 22.3)</td>
<td>20.1 (17.4, 23.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SPO2 (%)</td>
<td>97.1 (95.7, 98.5)</td>
<td>97.3 (95.8, 98.6)</td>
<td>97.0 (95.5, 98.4)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Comorbidities, n (%)**

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Value (n, %)</th>
<th>Value (n, %)</th>
<th>Value (n, %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>2335 (30.5)</td>
<td>871 (22.7)</td>
<td>1464 (38.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chronic Pulmonary Disease</td>
<td>1949 (25.5)</td>
<td>883 (23)</td>
<td>1066 (27.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>1770 (23.1)</td>
<td>339 (8.8)</td>
<td>1431 (37.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Liver disease</td>
<td>1046 (13.7)</td>
<td>401 (10.5)</td>
<td>645 (16.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td>1235 (16.1)</td>
<td>568 (14.8)</td>
<td>667 (17.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>817 (10.7)</td>
<td>326 (8.5)</td>
<td>491 (12.9)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Laboratory parameters, Median (IQR)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (IQR)</th>
<th>Value (IQR)</th>
<th>Value (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cell (103/µL)</td>
<td>3.4 (2.9, 4.0)</td>
<td>3.6 (3.1, 4.2)</td>
<td>3.3 (2.8, 3.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>White blood cell (103/µL)</td>
<td>11.7 (7.8, 16.8)</td>
<td>11.3 (7.7, 15.9)</td>
<td>12.1 (8.0, 17.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>182.0 (118.0, 258.0)</td>
<td>195.0 (132.0, 264.0)</td>
<td>166.0 (105.5, 247.0)</td>
<td>&lt; 0.001</td>
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<td>----------------------</td>
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</tr>
<tr>
<td>Platelet (103/µL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemoglobin (mg/dL)</td>
<td>10.4 (8.8, 11.9)</td>
<td>11.0 (9.4, 12.6)</td>
<td>9.8 (8.4, 11.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>potassium (mEq/L)</td>
<td>4.1 (3.7, 4.6)</td>
<td>4.0 (3.6, 4.4)</td>
<td>4.3 (3.8, 4.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>sodium (mEq/L)</td>
<td>139.0 (135.0, 142.0)</td>
<td>139.0 (136.0, 141.0)</td>
<td>138.0 (134.0, 142.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>calcium (mEq/L)</td>
<td>8.1 (7.6, 8.7)</td>
<td>8.2 (7.6, 8.7)</td>
<td>8.1 (7.5, 8.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>creatinine (mg/dL)</td>
<td>1.1 (0.8, 1.9)</td>
<td>0.8 (0.6, 1.1)</td>
<td>1.7 (1.2, 2.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>glucose (mg/dL)</td>
<td>130.0 (104.0, 173.0)</td>
<td>127.0 (104.0, 165.0)</td>
<td>133.0 (104.0, 183.0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Scoring systems, Median (IQR)

<table>
<thead>
<tr>
<th></th>
<th>7.0 (4.0, 10.0)</th>
<th>5.0 (3.0, 8.0)</th>
<th>9.0 (6.0, 12.0)</th>
<th>&lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPSII</td>
<td>40.0 (31.0, 51.0)</td>
<td>35.0 (27.0, 43.0)</td>
<td>47.0 (38.0, 57.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>2191 (28.6)</td>
<td>731 (19.1)</td>
<td>1460 (38.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>360-day mortality</td>
<td>3315 (43.3)</td>
<td>1192 (31.1)</td>
<td>2123 (55.6)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: mean arterial pressure; SOFA: sequential organ failure score; SAPS II: simplified acute physiology score II

### 3.2 Relationship between BAR and patient mortality

We used RCS to develop a model to assess the relationship between BAR at ICU admission and 30- and 360-day mortality. The model incorporated P < 0.05 variables in the analysis as confounders, with the cutoff point being a BAR of 8.0 at the time of admission.

In Fig. 2, the HR increases rapidly until after the cutoff value and then decreases in the rate of increase (nonlinear P < 0.001). Overall, the HR curve shows an increasing trend, indicating that the risk of patient death increases with increasing BAR at the time of ICU admission. The sample was separated into a high BAR group (BAR > 8.0, n = 3819) and a low BAR group (BAR ≤ 8.0, n = 3837) according to the optimal cutoff value.

In Fig. 3, we plotted the KM survival curves of different groups, which were markedly lower in the high-BAR group than in the low-BAR group. For the two curves, the difference was certified by the log-rank test.
(P < 0.001). In Table 2, multivariate Cox regression models showed that the high BAR group was related to an enhanced risk of in-hospital mortality to the hospital when in comparison to the low BAR group in 30-day mortality as an outcome (HR = 1.182, 95% CI: 1.065 - 1.313, P = 0.002) and in 360-day mortality as an outcome (HR = 1.246, 95% CI: 1.145 - 1.355, P < 0.001). Overall, higher levels of BAR at ICU admission predicted higher mortality.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate model</th>
<th>Model I</th>
<th>Model II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CIs)</td>
<td>P</td>
<td>HR (95% CIs)</td>
</tr>
<tr>
<td>30-day all-cause mortality</td>
<td>1.032(1.029 - 1.035)</td>
<td>&lt; 0.001</td>
<td>1.031(1.028 - 1.034)</td>
</tr>
<tr>
<td>BAR ≤ 8.0</td>
<td>Reference</td>
<td>-</td>
<td>Reference</td>
</tr>
<tr>
<td>BAR &gt; 8.0</td>
<td>2.272(2.079 - 2.483)</td>
<td>&lt; 0.001</td>
<td>2.071(1.892 - 2.267)</td>
</tr>
<tr>
<td>360-day all-cause mortality</td>
<td>1.032(1.030 - 1.035)</td>
<td>&lt; 0.001</td>
<td>1.030(1.028 - 1.033)</td>
</tr>
<tr>
<td>BAR ≤ 8.0</td>
<td>Reference</td>
<td>-</td>
<td>Reference</td>
</tr>
<tr>
<td>BAR &gt; 8.0</td>
<td>2.195(2.045 - 2.357)</td>
<td>&lt; 0.001</td>
<td>1.969(1.832 - 2.116)</td>
</tr>
</tbody>
</table>

HR: hazard ratio; CIs: confidence intervals.
Model I covariates were adjusted for age and sex.
Model II covariates were adjusted for age, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiration, oxygen saturation, congestive heart failure, kidney disease, malignancy, severe liver disease, peripheral vascular disease, red blood cells, white blood cells, platelets, haemoglobin, serum potassium, Serum creatinine, SOFA, and SAPS II.

### 3.3 ROC curve analysis

Figure 4A shows the predictive value of SOFA alone and BAR + SOFA for 30-day mortality in patients with sepsis. The AUC of the receiver operating characteristic curve for BAR + SOFA for 30-day mortality was 71.81%, 95%CI: (70.54 ~ 73.08%); higher than the AUC (95% CI) for SOFA: 70.33% (69.03 ~ 71.63%), (P < 0.001), and the results remained consistent in 360-day mortality as an outcome (Fig. 4B).

### 3.4 Subgroup Analysis

In order to explore further whether BAR was still an independent prognostic element in subgroups of certain sepsis patients, we made exploratory subgroup analyses for age, sex, comorbidity, and severity scores. Forest plots showed that BAR was an independent prognostic factor in all subgroups with 30-day mortality as the outcome (Fig. 5A). In addition, similar results were shown in the 360-day mortality. Except
for the interaction in patients with malignancy and renal disease (Fig. 5B), higher BAR still predicted higher mortality in all subgroups.

4. Discussion

We retrospectively analyzed 7,656 eligible patients in the MIMIC-IV (V2.0) database to examine the association between BAR and short- and long-term mortality in patients with sepsis. Multivariate Cox regression indicated that higher BAR values at ICU admission were an independent risk factor and that high BAR levels predicted higher mortality. In addition, we compared the area under the curve of BAR, blood urea nitrogen, and albumin using a ROC curve analysis. The AUC of BAR at ICU admission was significantly better than that of blood urea nitrogen and albumin and with a fairly good predictive value of mortality, with better prediction of short-term mortality than long-term mortality.

The pathophysiology of sepsis is a complex process of the host's response to infection, localizing and controlling bacterial invasion while initiating the repair of damaged tissues. One of its mechanisms is the production of pro-and anti-inflammatory mediators. Sepsis occurs when the release of pro-inflammatory mediators in response to infection excessively or disproportionally (the so-called cytokine storm), leads to various organ dysfunctions.

In sepsis, increased microvascular permeability in an inflammatory state alters the intra- and extravascular distribution of albumin, resulting in lower serum albumin concentrations in critically ill patients. TNF-α and interleukin-1 can inhibit the transcription of albumin genes, thereby reducing serum albumin levels. Kendall et al. have confirmed that low serum albumin level is associated with poor prognosis in patients with sepsis. As a well-known indicator of renal function, BUN can also reflect the complex interrelationship between a patient's nutritional status, protein metabolism, and renal condition. In patients with sepsis, RBF-independent microcirculatory dysfunction in the renal parenchyma is characterized by inflammatory mediators, immune cell infiltration, nitric oxide synthase dysregulation, redistribution of blood flow from the renal medulla to the renal cortex, with some degree of renal medullary deoxygenation, and often complicated by acute kidney injury. Critically ill patients are in a high proteolytic state, and these factors can lead to elevated BUN levels in patients with sepsis. The effect of BUN on the prognoses of patients with sepsis has also been demonstrated. Recently, BAR has been used as a new biomarker to assess the prognoses of various diseases and is an important prognostic factor for death in various diseases (lung cancer, gastrointestinal bleeding, community-acquired pneumonia, and other diseases). Our study reported a strong correlation between BAR values and 30- and 360-day mortality in patients with sepsis, with a good predictive value.

The MIMIC-IV (v2.0) database, released in June 2022, contains a large number of sepsis patients with complete follow-up data, providing us with data to support our study of the long-term prognosis of sepsis patients. The wealth of patient data in this database allowed us to perform ideal stratification and subgroup analyses. Despite the important findings we have highlighted, there were some limitations to...
this study. First, as with all retrospective analyses, other confounding factors may exist and we adjusted for some common confounders to ensure the correctness of our conclusions. Second, we excluded patients with multiple admissions with confirmed sepsis and only retained patients with their first confirmed sepsis. The potential for selection bias existed. Finally, some patients were excluded from this study due to a lack of data, which may have led to bias in the results of this study. A larger multi-center prospective study is necessary for future validation.

5. Conclusion

In brief, we observed that high BAR was significantly associated with increased all-cause mortality in patients with sepsis and that BAR was a simple and effective biomarker in adults with sepsis.

Declarations

Data availability The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors’ Contributions Yuhe WANG and Shan GAO performed the data analyses and drafted the manuscript; Lei HONG and Tingting HOU assisted with data analyses. Huihui LIU and Meng LI contributed to data interpretation and manuscript preparation; Yong ZHANG designed the conception of the study and helped to revise the manuscript.

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Conflict of Interest The authors declare that there is no conflict of interest.

Ethical approval This study does not contain any work with human participants conducted by any of the authors.

References


Figures

Figure 1

Flow chart of the study
Figure 2

The relationship between admission BAR and the risk of death in patients with sepsis. HR is indicated by the black solid line and 95% CI is indicated by the grey-shaded area.

Figure 3

Kaplan-Meier curve presenting the relationship between BAR grouping and sepsis mortality.
Figure 4

Receiver operator characteristic curve analysis for mortality of patients with sepsis.
**Figure 5**

Forest plot for subgroup analysis of the relationship between mortality and BAR...