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ORIGINAL RESEARCH

Association Between Blood Urea Nitrogen to Serum Albumin Ratio and Mortality in Critically Ill Patients With Chronic Obstructive Pulmonary Disease: A Retrospective Study

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Background: Epidemiological studies suggest that elevated blood urea nitrogen (BUN) and reduced serum albumin could independently predict adverse clinical outcomes in patients with chronic obstructive pulmonary disease (COPD). However, the predictive performance of BUN-albumin ratio (BAR) in critically ill patients with COPD remains to be confirmed. This study aimed to investigate the association between BAR and all-cause mortality in intensive care unit (ICU) patients with COPD.

Methods: This was a retrospective study that included COPD patients with BUN and serum albumin value on the first day of each ICU admission and data were obtained from the eICU Collaborative Research Database. The included COPD patients were divided into three groups stratified by BAR tertiles (T1-T3). Multivariate logistic regression and Cox proportional hazards models were used to examine the association between BAR and all-cause in-hospital and ICU mortality, respectively. Kaplan–Meier curves were plotted to evaluate survival differences among three groups and discrepancies were compared with the log–rank test.

Results: A total of 4037 patients were included in the final analysis and the in-hospital and ICU mortality rates were 11.79% and 6.51%, respectively. The multivariate logistic regression analyses showed that continuous BAR was a significant risk predictor of in-hospital mortality (OR: 1.039, 95% CI: 1.026–1.052, $P < 0.001$) and ICU mortality (OR: 1.030, 95% CI: 1.015–1.045, $P < 0.001$) in fully adjusted model. The Cox proportional hazards models revealed that patients in the highest BAR tertile (T3) were significantly associated with higher risk of in-hospital mortality (HR: 1.983, 95% CI: 1.419–2.772, $P < 0.001$) and ICU mortality (HR: 2.166, 95% CI: 1.373–3.418, $P < 0.001$). The Kaplan–Meier curves showed that the survival differences of all-cause mortality were statistically significant in three tertile groups (log-rank $P < 0.0001$). Correlated subgroup analyses indicated that this positive association might vary in certain population settings.

Conclusion: High level of BAR is associated with the increasing all-cause mortality in critically ill patients with COPD. As an innovative and promising biomarker, BAR might be useful in predicting high risk of death in patients with COPD.

Keywords: chronic obstructive pulmonary disease, blood urea nitrogen, serum albumin, all-cause mortality, intensive care unit

Introduction

Chronic obstructive pulmonary disease (COPD), a progressive airway inflammatory disease, is characterized by irreversible airflow limitation caused by smaller breathing tubes, most commonly induced by tobacco smoke.[1,2] COPD has become a major global public health concern with the prevalence increased to an estimated 384 million people worldwide.[3,4] According to the World Health Organization, COPD is the third most common cause of death worldwide and the economic burden is estimated to be above $50 billion in the United States.[5,6] A wide variety of risk factors are associated with COPD, including occupational exposures, asthma, air pollution, environmental tobacco smoke, infections, and low socioeconomic status.[7] The proportion of patients admitted to the intensive care unit (ICU) due to respiratory failure is increasing and COPD was recognized as a risk factor for increased

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morbidity and mortality in ICU patients.[8] Thus, early detection for patients with COPD at high risk of mortality is necessary and may assist in risk stratification and providing clinical decision support.

An ideal biomarker should be easy and repeatable to measure, helpful in medical decision making and able to give accurate results.[9] Previous studies suggested that the blood eosinophil count, total serum IgG levels and sputum microbiome are associated with the poor prognosis with COPD patients.[10–12] However, due to lack of progress in modifying the clinical outcomes in this highly heterogeneous disease, there is still intense need in developing novel biomarkers in COPD.[13]

In recent years, blood urea nitrogen to serum albumin ratio (BAR), an emerging prognostic biomarker, has been demonstrated associated with adverse clinical outcomes in patients with heart failure, gastrointestinal bleeding and coronary heart disease.[14–16] In addition, other studies have also demonstrated that BAR serves as a predictor of poor outcomes in cardiac surgeries,[17] including coronary artery bypass grafting and heart valve transplantation, and functions as a novel indicator for assessing the severity and prognosis of idiopathic pulmonary hypertension.[18] Elevated blood urea nitrogen (BUN) levels, which indicate neurohormonal activation and low cardiac input, were associated with disease severity with respect to COPD.[19] Serum albumin, produced by the liver, is essential for maintaining the osmotic pressure and nutrition. Previous studies revealed that hypoalbuminemia was independently associated with increased mortality in COPD.[20,21] A study conducted by Zeng Z et al has found that BAR was a strong and independent predictor of in-hospital and 90-day all-cause mortality in patients with acute exacerbation of COPD.[22] However, limited by small sample size, the results were less likely to be generalized and needed further exploration.

Given the clinical evidence, this study aimed to evaluate the prognostic performance of BAR in predicting the poor prognosis in critically ill patients with COPD. This retrospective cohort study assessed the association between BAR and all-cause mortality in COPD, which could shed new light on COPD management in ICU.

Methods

Data Sources and Ethical Considerations

All data of this retrospective cohort study were extracted from the eICU Collaborative Research Database (eICU-CRD, version 2.0), which was a publicly available multi-center ICU database with high granularity data for more than 200,000 electronic medical records from 208 hospitals across the United States between 2014 and 2015.[23] The documents in eICU-CRD contained records of demographic characteristics, diagnosis information, laboratory tests and physiological readings in detail. One author (Jili Li) obtained the access (record ID: 44589323) and was responsible for data extraction. The Massachusetts Institute of Technology has approved the use of this database. The study was conducted in accordance with the Helsinki Declaration. The retrospective design of this study and all anonymized patient data led the Ethics Review Board of the West China Hospital of Sichuan University to waive the requirement for ethical review and informed consent.

Study Population

We included all patients admitted to the ICU in eICU-CRD. Patients with COPD were enrolled according to the International Classification of Diseases (ICD) 9th Revision codes (490, 4910, 4911, 4912, 49120, 49121, 49122, 4918, 4919, 4920, 4928, 494, 4940, 4941, 496).[24] We selected the first ICU stay for those patients admitted to ICU for more than once. Additionally, we analyzed only adult patients (aged ≥18 years). The exclusion criteria were as follows: (1) patients with missing BUN or serum albumin values on the first day of ICU admission; (2) less than 24 hours of ICU stay; (3) patients with more than 30% missing data. Finally, the included COPD patients were divided into three groups stratified by BAR tertiles.[25]

Variable Extraction

Patient data from the eICU-CRD were extracted using Structured Query Language (SQL) with MySQL (version 5.7.33). All variables were collected within the first 24 hours after the ICU admission except for the demographic information, which was reported at the time of hospital admission. The demographic characteristic data included age, gender, ethnicity and body mass index (BMI). The BMI is defined as weight (kg) divided by the square of body height (m2). Vital signs

included heart rate, respiratory rate, percutaneous oxygen saturation, temperature, systolic blood pressure, diastolic blood pressure and mean blood pressure. Comorbidities included liver failure, diabetes mellitus, congestive heart failure, hypertension, coronary heart disease, renal failure, arrhythmias and atrial fibrillation according to ICD codes. Laboratory findings included total bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT), creatinine, PaO2/FiO2, anion gap, glucose, serum potassium, serum sodium, serum calcium, platelet, white blood cell, RBC, RDW, hemoglobin, MCHC, hematocrit, BUN and serum albumin. Additionally, we extracted whether the patient received oxygen therapy or mechanical ventilation during hospitalization. If vital signs or laboratory tests were measured multiple times, the average value was extracted for the subsequent analyses. The Acute Physiology and Chronic Health Evaluation IVa (APACHE IVa) was also included.[26] The BAR (mg/g) was calculated as blood urea nitrogen (mg/dL) divided by serum albumin (g/dL).

Imputing Missing Data

Missing data are a common problem in eICU-CRD. Simple methods like complete case analysis have the potential to bias the true estimates of the association investigated.[27] Thus, we imputed missing data for included variables using a machine learning algorithm called random forest imputation implemented in the R package "missForest",[28] which was widely used in medical research.[29,30] All included variables contained less than 30% missing values.

Primary and Secondary Outcomes

The primary outcome of our study was all-cause in-hospital mortality, defined as patient's survival status upon leaving the hospital. We selected ICU mortality as secondary outcome.

Statistical Analysis

Outlying values from vital signs were handled using the winsorization method with 1% and 99% as the cut-off points. To avoid overfitting, the variance inflation factor (VIF) was used to measure the severity of multicollinearity between variables. When adjusting for covariates, we excluded variables with VIF ≥ 5. Categorical variables were presented as percentages, and the chi-square test is used to evaluate the differences among BAR tertiles. Continuous variables were expressed as mean ± standard deviation (SD), and analysis of variance (ANOVA) is employed when comparing the BAR tertiles.

Multivariate logistic regression and Cox proportional hazards models were used to examine the association between BAR and all-cause in-hospital and ICU mortality, respectively. Kaplan–Meier curves were used to evaluate survival differences among groups based on different levels of BAR and discrepancies were compared with Log rank test. In addition, sensitivity analyses were conducted among the subgroups with the forest plots. The predictive value of APACHE IVa combined with BAR was compared with the APACHE IVa alone by calculating the area under the curve (AUC), which was estimated using DeLong's test. The optimal cut-off value was calculated by the Youden index (sensitivity+ specificity-1).[31] All statistical analyses were performed using R software (version 4.1.0; R foundation for Statistical Computing). All significance was set at two-sided $P < 0.05$.

Results

Baseline Characteristics of Patients

Among 14,014 patients with COPD in eICU-CRD, a total of 4037 adult patients were enrolled in the final analysis for this study (Figure 1). The included COPD patients were divided into three groups stratified by BAR tertiles (T1: <6.143; T2: 6.143–11.667; T3: >11.667). The baseline characteristics of patients are presented in Table 1. Patients with higher BAR were generally older, with higher APACHE scores on admission and higher prevalence of comorbidities, including diabetes mellitus, congestive heart failure, coronary heart disease, renal failure, arrhythmias and atrial fibrillation. With increasing BAR, hospital length of stay (8.28 vs 9.57 vs 12.04, $P < 0.001$), ICU length of stay (3.99 vs 4.58 vs 5.41, $P < 0.001$), in-hospital mortality (4.38% vs 11.44% vs 19.55%, $P < 0.001$), and ICU mortality (2.30% vs 6.09% vs 11.15%, $P < 0.001$) increased gradually.

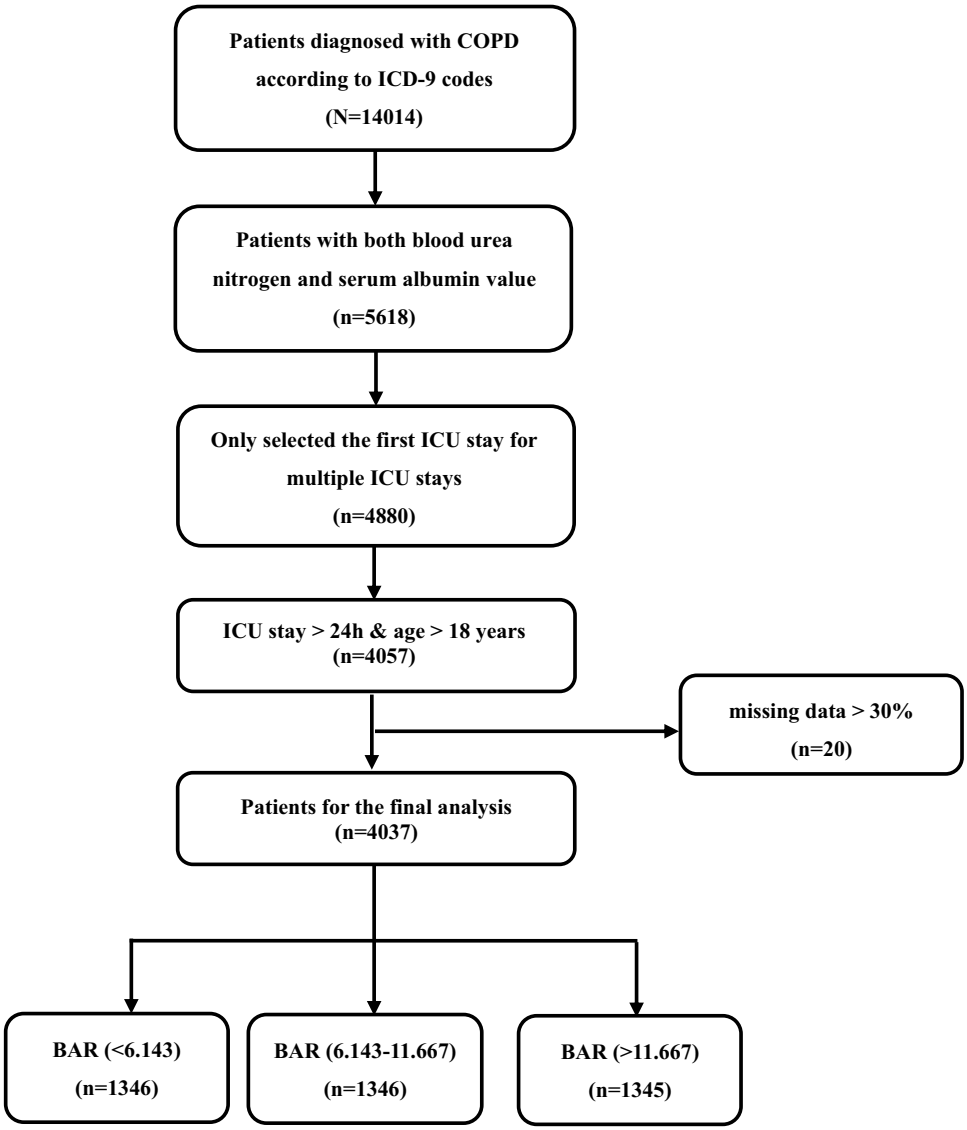

Figure 1 Flowchart of patient selection.
Abbreviations: ICD, International Classification of Diseases; BAR, blood urea nitrogen to serum albumin ratio; ICU, intensive care unit.

Association Between BAR and All-Cause Mortality

The logistic regression analysis showed a significant positive association between BAR and in-hospital mortality both in unadjusted model (OR: 1.051, 95% CI: 1.042–1.060, $P < 0.001$, Table 2) and fully adjusted model (OR: 1.039, 95% CI: 1.026–1.052, $P < 0.001$, Table 2). Furthermore, BAR was also significantly associated with ICU mortality both in unadjusted model (OR: 1.044, 95% CI: 1.034–1.054, $P < 0.001$) and fully adjusted model (OR: 1.030, 95% CI: 1.015–1.045, $P < 0.001$). The risk of in-hospital and ICU mortality of BAR T2 and T3 was higher than BAR T1, which showed a tendency of increasing with BAR (P for trend <0.001).

The Cox proportional hazards models revealed that continuous BAR was associated with an increased risk of in-hospital mortality and ICU mortality in fully adjusted model. In addition, patients in the highest BAR tertile were significantly associated with higher risk of in-hospital mortality (HR: 1.983, 95% CI: 1.419–2.772, $P < 0.001$, Table 3) and ICU mortality (HR: 2.166, 95% CI: 1.373–3.418, $P < 0.001$, Table 3).

The Kaplan–Meier survival analysis curves were plotted to assess the incidence of in-hospital and ICU mortality among three BAR levels. The difference of in-hospital mortality was statistically significant in three tertile groups (T1:

Table 1 Baseline Characteristics of Patients Stratified by BAR Tertiles

Categories	Overall	BAR Tertile 1 (<6.143)	BAR Tertile 2 (6.143–11.667)	BAR Tertile 3 (>11.667)	P-value
Number of patients	4037	1346	1346	1345	-
BAR	11.24 (9.36)	4.17 (1.23)	8.61 (1.59)	20.93 (10.40)	<0.001
Demographic					
Age(years), mean(SD)	67.88 (11.64)	63.54 (11.88)	69.33 (10.73)	70.78 (11.01)	<0.001
Gender(male), n(%)	2042 (50.58)	622 (46.21)	678 (50.37)	742 (55.17)	<0.001
Ethnicity, n(%)					
African American	335 (8.30)	114 (8.47)	121 (8.99)	100 (7.43)	0.299
Asian	27 (0.67)	11 (0.82)	8 (0.59)	8 (0.59)	
Caucasian	3396 (84.12)	1137 (84.47)	1117 (82.99)	1142 (84.91)	
Hispanic	137 (3.39)	35 (2.60)	53 (3.94)	49 (3.64)	
Native American	14 (0.35)	7 (0.52)	1 (0.07)	6 (0.45)	
Others	128 (3.17)	42 (3.12)	46 (3.42)	40 (2.97)	
BMI (kg/m^2), mean(SD)	30.24 (10.31)	29.66 (10.22)	30.12 (10.13)	30.93 (10.54)	0.005
Vital signs, mean(SD)					
Heart rate	88.09 (15.03)	88.33 (14.67)	88.00 (14.49)	87.95 (15.91)	0.777
Respiratory rate	20.47 (4.14)	20.35 (4.22)	20.49 (4.01)	20.58 (4.19)	0.373
SpO2, %	96.22 (2.09)	96.06 (2.07)	96.27 (2.12)	96.35 (2.06)	0.001
NIBP_systolic, mmHg	119.27 (17.41)	122.35 (16.99)	119.45 (16.86)	116.01 (17.81)	<0.001
NIBP_diastolic, mmHg	64.78 (10.54)	67.99 (10.29)	64.85 (10.08)	61.51 (10.24)	<0.001
NIBP_mean, mmHg	79.81 (11.81)	83.16 (11.77)	79.90 (11.28)	76.35 (11.38)	<0.001
Temperature, °C	36.85 (0.54)	36.88 (0.47)	36.86 (0.56)	36.81 (0.60)	0.005
Comorbidities, n(%)					
Liver failure	15 (0.37)	1 (0.07)	6 (0.45)	8 (0.59)	0.073
Diabetes	980(24.28)	217(16.12)	337(25.04)	426(31.65)	<0.001
Congestive heart failure	1011(25.04)	212(15.75)	372(27.64)	427(31.75)	<0.001
Hypertension	936(23.19)	313(23.25)	326(24.22)	297(22.08)	0.421
Coronary heart disease	670(16.60)	183(13.60)	222(16.49)	265(19.70)	<0.001
Renal failure	824(20.41)	68(5.05)	212(15.75)	544(40.45)	<0.001
Arrhythmias	1002(24.82)	230(17.09)	356(26.45)	416(30.93)	<0.001
Atrial fibrillation	722(17.88)	134(9.96)	269(19.99)	319(23.72)	<0.001
Laboratory tests, mean(SD)					
Total bilirubin, mg/dL	0.85 (1.37)	0.70 (0.96)	0.82 (1.33)	1.04 (1.69)	<0.001
AST, U/L	126.12 (611.50)	49.95 (133.04)	100.40 (470.61)	228.07 (930.96)	<0.001
ALT, U/L	90.64 (379.53)	40.54 (60.77)	76.69 (301.36)	154.73 (575.46)	<0.001
Anion gap, mg/dL	10.54 (3.98)	9.75 (3.47)	9.91 (3.57)	11.97 (4.44)	<0.001
Creatinine, mg/dL	1.53 (1.47)	0.82 (0.44)	1.27 (1.07)	2.52 (1.89)	<0.001
Glucose, mg/dL	155.89 (62.27)	149.13 (53.65)	160.00 (63.70)	158.53 (68.08)	<0.001
Serum potassium, mg/dL	4.22 (0.63)	4.04 (0.51)	4.18 (0.57)	4.45 (0.71)	<0.001
Serum sodium, mg/dL	138.23 (5.05)	137.68 (4.92)	138.42 (4.50)	138.61 (5.63)	<0.001
Serum calcium, mg/dL	8.42 (2.26)	8.62 (3.75)	8.41 (0.75)	8.24 (0.82)	<0.001
Platelet, K/μL	209.95 (92.32)	218.04 (88.38)	211.57 (90.34)	200.22 (97.19)	<0.001
White blood cell, K/μL	12.30 (7.64)	11.27 (7.17)	12.47 (7.95)	13.17 (7.64)	<0.001
RBC, m/μL	3.79 (0.74)	3.99 (0.69)	3.81 (0.73)	3.58 (0.75)	<0.001
RDW, %	15.76 (2.31)	15.20 (2.21)	15.69 (2.24)	16.39 (2.31)	<0.001
Hemoglobin, g/dL	11.16 (2.19)	11.89 (2.06)	11.19 (2.16)	10.40 (2.08)	<0.001
MCHC, g/dL	32.31 (1.51)	32.59 (1.52)	32.21 (1.47)	32.13 (1.51)	<0.001
Hematocrit, %	34.50 (6.70)	36.47 (6.28)	34.66 (6.64)	32.38 (6.53)	<0.001
BUN, mg/dL	30.32(21.74)	13.22(4.40)	24.76(6.22)	53.00(22.86)	<0.001
Albumin, g/dL	2.90(0.61)	3.18(0.55)	2.89(0.56)	2.62(0.59)	<0.001
PaO2/FiO2, mmHg	240.29 (99.61)	245.16 (105.03)	241.75 (106.59)	233.95 (85.57)	0.011

(*Continued*)

Table 1 (Continued).

Categories	Overall	BAR Tertile 1 (<6.143)	BAR Tertile 2 (6.143–11.667)	BAR Tertile 3 (>11.667)	P-value
APACHE IVa	63.83 (23.43)	51.22 (19.37)	64.40 (20.77)	75.86 (23.17)	<0.001
Oxygen therapy, n(%)	1561(38.67)	549(40.79)	543(40.34)	469(34.87)	0.002
Mechanical ventilation, n(%)	1398(34.63)	429(31.87)	489(36.33)	480(35.69)	0.032
Events, mean(SD)					
LOS hospital, days	9.96 (14.83)	8.28 (6.85)	9.57 (8.08)	12.04 (23.25)	<0.001
LOS ICU, days	4.66 (5.34)	3.99 (4.28)	4.58 (5.05)	5.41 (6.40)	<0.001
ICU mortality, n(%)	263(6.51)	31(2.30)	82(6.09)	150(11.15)	<0.001
In-hospital mortality, n(%)	476(11.79)	59(4.38)	154(11.44)	263(19.55)	<0.001

Abbreviations: BAR, blood urea nitrogen to serum albumin ratio; NIBP, non-invasive blood pressure; RBC, red blood cell; RDW, red blood cell distribution width; MCHC, mean corpuscular hemoglobin concentration; BUN, blood urea nitrogen; APACHE, Acute Physiology and Chronic Health Evaluation; LOS, length of stay.

Table 2 Association Between BAR and Mortality of Critically Ill COPD Patients With Logistic Regression Model

Categories	Events (%)	Model 1		Model 2		Model 3	
		OR[a] (95% CI[b])	P value	OR (95% CI)	P value	OR (95% CI)	P value
In-hospital mortality							
Continuous variable per 1 unit		1.051(1.042,1.060)	<0.001	1.051(1.041,1.060)	<0.001	1.039(1.026,1.052)	<0.001
Tertile groups[c]	476(11.79)						
T1 (n=1346)	59(4.38)	1.000(Ref)		1.000(Ref)		1.000(Ref)	
T2 (n=1346)	154(11.44)	2.818(2.078,3.870)	<0.001	2.669(1.957,3.683)	<0.001	1.993(1.436,2.795)	<0.001
T3 (n=1345)	263(19.55)	5.302(3.982,7.172)	<0.001	4.996(3.716,6.816)	<0.001	2.824(1.974,4.079)	<0.001
P for trend			<0.001		<0.001		<0.001
ICU mortality							
Continuous variable per 1 unit		1.044(1.034,1.054)	<0.001	1.046(1.036,1.057)	<0.001	1.030(1.015,1.045)	<0.001
Tertile groups	263(6.51)						
T1 (n=1346)	31(2.30)	1.000(Ref)		1.000(Ref)		1.000(Ref)	
T2 (n=1346)	82(6.09)	2.752(1.827,4.249)	<0.001	2.811(1.854,4.367)	<0.001	2.012(1.295,3.192)	0.002
T3 (n=1345)	150(11.15)	5.325(3.641,8.037)	<0.001	5.511(3.720,8.414)	<0.001	2.915(1.811,4.783)	<0.001
P for trend			<0.001		<0.001		<0.001

Notes: Model 1: unadjusted; Model 2: age, gender, ethnicity and BMI were adjusted; Model 3: age, gender, ethnicity, BMI, heart rate, respiratory rate, SPO2, systolic blood pressure, temperature, liver failure, diabetes mellitus, congestive heart failure, hypertension, coronary heart disease, renal failure, arrhythmias, atrial fibrillation, total bilirubin, AST, ALT, anion gap, glucose, creatinine, potassium, sodium, calcium, platelet, WBC, RDW, MCHC, PaO2/FiO2, oxygen therapy, and mechanical ventilation were adjusted.[a] Odds ratio [b] Confidence interval [c] BAR tertile groups: T1(<6.143), T2(6.143–11.667), T3(>11.667).

4.38% vs T2: 11.44% vs T3: 19.55%, log-rank $P < 0.0001$, Figure 2A). Besides, the curve showed similar results of ICU mortality (T1: 2.30% vs T2: 6.09% vs T3: 11.15%, log-rank $P < 0.0001$, Figure 2B).

Subgroup Analysis

We also conducted subgroup analyses of the relationship between BAR and all-cause in-hospital mortality stratified by age, gender, BMI, diabetes, hypertension, congestive heart failure, renal failure, atrial fibrillation with fully adjusted model (Figure 3). This association was similar among patients more than 65 years (OR: 1.036, 95% CI: 1.021–1.052, $P < 0.001$) and patients less than 65 years (OR: 1.049, 95% CI: 1.023–1.076, $P < 0.001$). Interestingly, statistically significant OR was only found in patients without hypertension (OR: 1.048, 95% CI: 1.033–1.064, $P < 0.001$). Besides, the predictive performance of BAR seemed to be more prominent in patients without diabetes (OR: 1.049, 95% CI: 1.032–1.067, $P < 0.001$) than those with diabetes (OR: 1.025, 95% CI: 1.003–1.048, $P = 0.023$, P for interaction = 0.045).

Table 3 Association Between BAR and Mortality of Critically Ill COPD Patients With Cox Proportional Hazards Model

Exposure	Model 1		Model 2		Model 3	
	HR[a] (95% CI[b])	P value	HR (95% CI)	P value	HR (95% CI)	P value
In-hospital mortality						
Continuous variable per 1 unit	1.022(1.016,1.028)	<0.001	1.025(1.018,1.031)	<0.001	1.017(1.008,1.026)	<0.001
Tertile groups[c]						
T1 (n=1346)	1.000(Ref)		1.000(Ref)		1.000(Ref)	
T2 (n=1346)	2.222(1.646,3.000)	<0.001	2.045(1.510,2.772)	<0.001	1.717(1.258,2.344)	<0.001
T3 (n=1345)	3.092(2.328,4.108)	<0.001	2.804(2.096,3.750)	<0.001	1.983(1.419,2.772)	<0.001
P for trend		<0.001		<0.001		<0.001
ICU mortality						
Continuous variable per 1 unit	1.020(1.012,1.027)	<0.001	1.025(1.017,1.034)	<0.001	1.016(1.004,1.028)	0.010
Tertile groups						
T1 (n=1346)	1.000(Ref)		1.000(Ref)		1.000(Ref)	
T2 (n=1346)	2.248(1.487,3.400)	<0.001	2.160(1.421,3.284)	<0.001	1.710(1.111,2.632)	0.015
T3 (n=1345)	3.328(2.257,4.905)	<0.001	3.243(2.179,4.826)	<0.001	2.166(1.373,3.418)	<0.001
P for trend		<0.001		<0.001		0.003

Notes: Model 1: unadjusted; Model 2: age, gender, ethnicity and BMI were adjusted; Model 3: age, gender, ethnicity, BMI, heart rate, respiratory rate, SPO2, systolic blood pressure, temperature, liver failure, diabetes mellitus, congestive heart failure, hypertension, coronary heart disease, renal failure, arrhythmias, atrial fibrillation, total bilirubin, AST, ALT, anion gap, glucose, creatinine, potassium, sodium, calcium, platelet, WBC, RDW, MCHC, PaO2/FiO2, oxygen therapy, and mechanical ventilation were adjusted.[a] Hazard ratio [b] Confidence interval [c] BAR tertile groups: T1(<6.143), T2(6.143–11.667), T3(>11.667).

ROC Curve Analysis

The ROC curves for APACHE IVa and APACHE IVa combined with BAR to predict in-hospital mortality were presented (Figure 4). The BAR had an incremental effect on the AUC of APACHE IVa to predict all-cause in-hospital mortality and the difference was statistically significant with the DeLong's test (Table 4). The optimal cut-off value of BAR to predict in-hospital mortality was 8.86 mg/g by the Youden index.

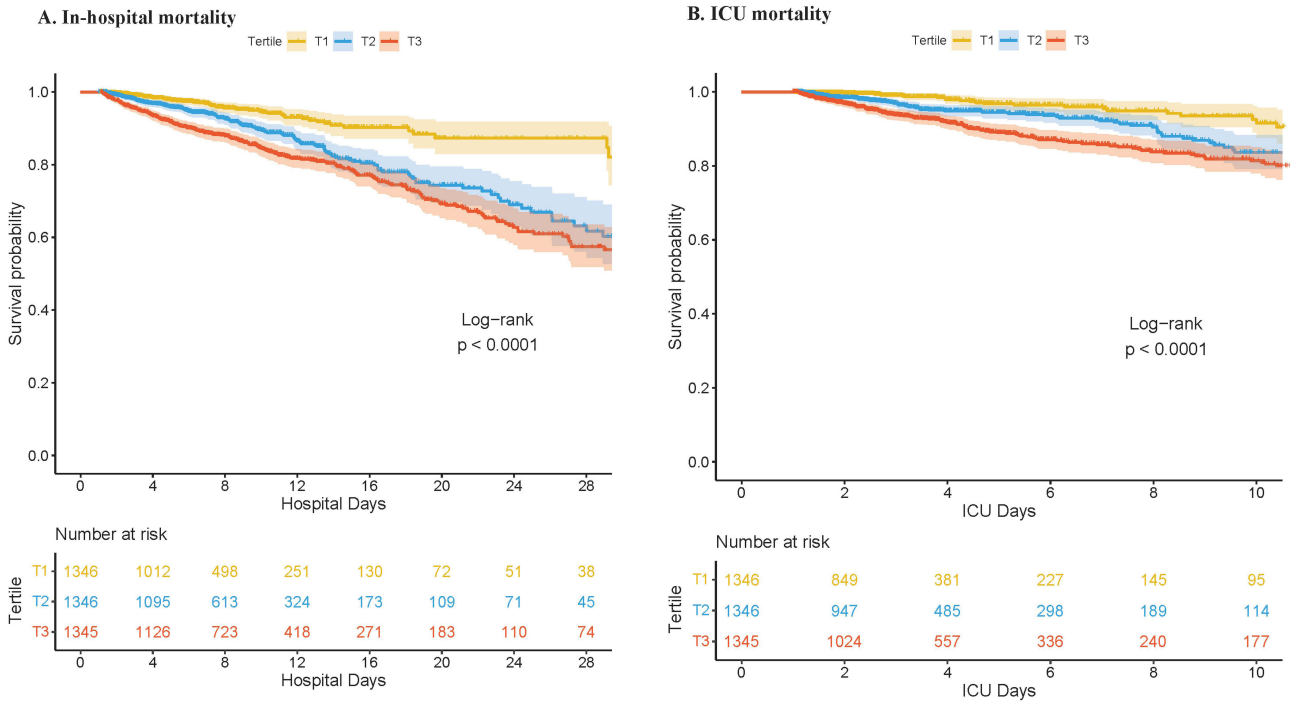

Figure 2 Kaplan–Meier curves of the tertile of BAR for in-hospital mortality **(A)** and ICU mortality **(B)**.
Abbreviations: BAR, blood urea nitrogen to serum albumin ratio; ICU, intensive care unit.

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Subgroup	No. of patients	P for interaction	OR(95% CIs), P value
Age			
<65	1537	0.317	1.049 (1.023, 1.076) <0.001
>=65	2500		1.036 (1.021, 1.052) <0.001
Gender			
Male	2042	0.637	1.041 (1.024, 1.059) <0.001
Female	1995		1.036 (1.016, 1.058) <0.001
BMI			
<30	2352	0.546	1.040 (1.023, 1.058) <0.001
>=30	1685		1.040 (1.020, 1.062) <0.001
Diabetes			
Yes	980	0.045	1.025 (1.003, 1.048) 0.023
No	3057		1.049 (1.032, 1.067) <0.001
Hypertension			
Yes	936	0.085	1.008 (0.978, 1.037) 0.596
No	3101		1.048 (1.033, 1.064) <0.001
Congestive heart failure			
Yes	1011	0.183	1.048 (1.021, 1.078) <0.001
No	3026		1.037 (1.022, 1.053) <0.001
Renal failure			
Yes	824	0.007	1.027 (1.009, 1.046) 0.004
No	3213		1.052 (1.033, 1.071) <0.001
Atrial fibrillation			
Yes	722	0.090	1.025 (1.001, 1.050) 0.043
No	3315		1.048 (1.032, 1.064) <0.001

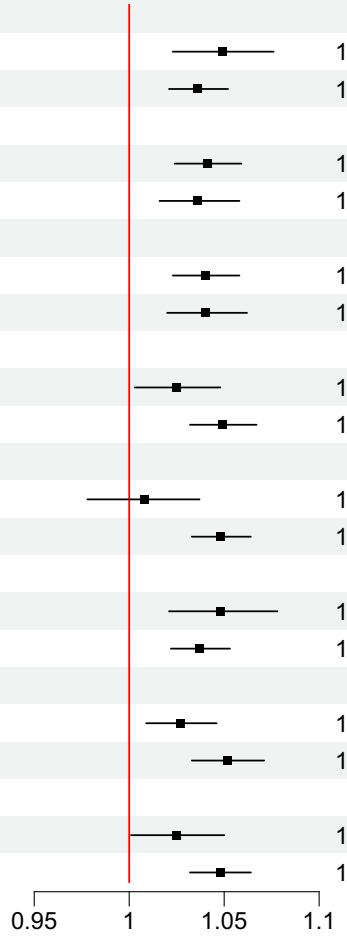

Figure 3 Subgroup analysis of associations between BAR and in-hospital mortality.
Abbreviations: BAR, blood urea nitrogen to serum albumin ratio; OR, Odds ratio.

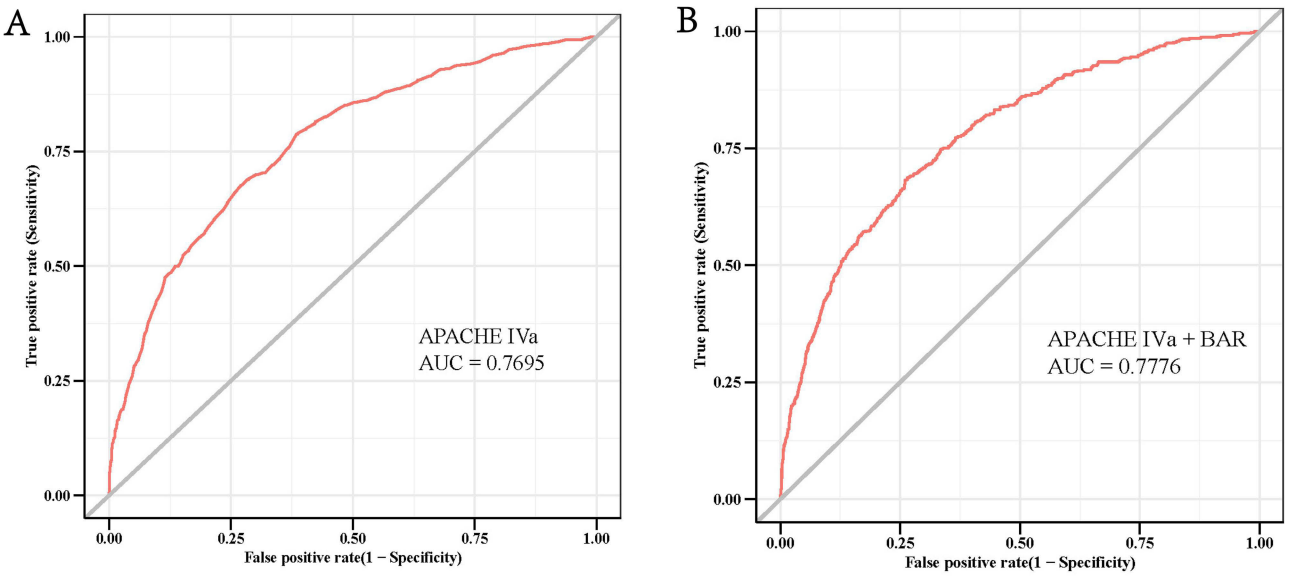

Figure 4 ROC curves of APACHE IVa **(A)** and APACHE IVa + BAR **(B)** to predict in-hospital mortality.
Abbreviations: BAR, blood urea nitrogen to serum albumin ratio; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 4 ROC Curve for All-Cause in-Hospital Mortality

Model	AUC	95% CI	P
APACHE IVa	0.7695	0.7467–0.7922	
APACHE IVa + BAR	0.7776	0.7553–0.7999	<0.001

Discussion

Timely identification of patients with high risk is essential in clinical work. The BAR is a composite biomarker that incorporates both blood urea nitrogen and serum albumin. Serving as an innovative risk factor for patients in ICU, the BAR is not only readily identifiable but also easily accessible. In the present study, we demonstrated that higher BAR was positively associated with all-cause mortality in critically ill patients with COPD. This association remained statistically significant even after we adjusted for a wide variety of covariates, including demographics, laboratory tests, vital signs and comorbidities. Correlated subgroup analyses showed that BAR was still positively associated with all-cause in-hospital mortality among males or females, people more than 65 years old or not, obese people or not. At the same time, the relationship was not noted for ICU patients with hypertension, which indicates that this positive association may vary in certain population settings. But most importantly, our study provides an efficient, easily accessible and inexpensive biomarker for the early detection of high mortality in critically ill patients with COPD.

Blood urea nitrogen is affected by protein intake and consumption, catabolic state, reabsorption in renal tubes and other factors. Although some studies have demonstrated that BUN was a powerful predictor of poor prognosis in COPD, the underlying mechanism remains unclear.[19,32] Emerging evidence has shown that patients with COPD often experience elevated levels of inflammation biomarkers and carbon dioxide retention, which may affect neurohormonal activation and cardiorenal functions. Besides, previous studies have shown that COPD is independently associated with increasing prevalence of cardiovascular disease as comorbidities,[33,34] which can increase the activity of sympathetic nervous systems and the renin-angiotensin-aldosterone system and then reduce the renal perfusion,[35] ultimately leading to an increased BUN.

Hypoalbuminemia is highly correlated with elevated parameters of inflammation and increased risk of malnutrition.[36] From the perspective of pathophysiology, the inflammation response increases capillary permeability and causes the escape of albumin, resulting in expansion of interstitial space, which may be involved in the pathogenesis of many chronic diseases.[37,38] Our study has also shown that with the increase of BAR, the level of white blood cell seems to have an increasing trend. Furthermore, malnutrition is independently associated with poor clinical outcomes among critically ill patients,[39] so hypoalbuminemia might be the poor prognostic biomarker in critically ill patients with COPD due to mechanisms characterized by inflammation and malnutrition.

As an innovative biomarker, BAR serves as a prognostic factor for ICU patients not only with COPD but also with multiple pulmonary diseases such as acute pulmonary embolism and aspiration pneumonia.[40,41] This mechanism may be linked to the pathophysiological mechanism of serum albumin, mirroring the prognostic prediction of COPD. In addition, researchers have found that BAR can accurately predict the severity of community-acquired pneumonia.[42] Concurrently, it can also be used to predict the prognosis of ICU patients with heart and kidney diseases. A study conducted by Liu S et al has demonstrated a correlation between BAR and a lower 90-day survival rate in type 2 diabetes mellitus patients with chronic kidney disease in the ICU.[43]

The latest version of the APACHE scoring system, APACHE IVa, was developed using the worst values of 142 patient variables within the first 24 hours of each ICU admission based on multivariable logistic regression.[26] Its application in predicting in-hospital and ICU mortality has gained considerable favor globally and is also effective in patients with COPD.[44] However, it remains uncertain whether the addition of BAR could improve the accuracy at the basis of this severity score system in critically ill patients with COPD. The present study revealed BAR had an incremental effect on APACHE IVa to predict all-cause in-hospital mortality, which could facilitate decision making based on this severity score in critically ill patients with COPD.

However, our study should be interpreted in the context of some limitations. First, our models were based on data within 24 hours of each ICU admission, so the dynamic changes of BAR were neglected, which could not reflect the time dimension and may cause some confounders. Second, the eICU-CRD did not contain long-term follow-up data and we could not evaluate the relationship between BAR and long-term follow-up death. Third, we did not include more important predictor variables that may affect the prognosis (such as lactate) due to the large proportion of missing values. Fourth, due to the retrospective nature of this study, there may be potential covariate imbalance and selection bias. Although eICU-CRD is a multicenter ICU database and multivariate regression models have been applied in our study, more high-quality clinical research is still needed to demonstrate its value in clinical practice.

Conclusion

Our study shows that high level of BAR is associated with increasing all-cause in-hospital and ICU mortality in critically ill patients with COPD. Our findings indicate that this innovative and promising biomarker may help physicians identify patients with COPD who are of high risk and guide timely appropriate treatments. Further prospective studies with larger sample size are required to confirm our conclusions.

Abbreviations

BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; BAR, blood urea nitrogen to serum albumin ratio; ICU, intensive care unit; eICU-CRD, eICU Collaborative Research Database; SQL, Structured Query Language; ICD, International Classification of Diseases; BMI, body mass index; APACHE IVa, Acute Physiology and Chronic Health Evaluation IVa; LOS, length of stay; SD, standard deviation; ANOVA, analysis of variance; VIF, variance inflation factor; OR, Odds ratio; HR, Hazard ratio; AUC, area under the curve; NIBP, non-invasive blood pressure; RBC, red blood cell; RDW, red blood cell distribution width; MCHC, mean corpuscular hemoglobin concentration.

Data Sharing Statement

The datasets are available in the website of eICU-CRD: https://eicu-crd.mit.edu/. The abovementioned link is the direct persistent link to the dataset and researchers need to complete the course Protecting Human Research Participants on the website of National Institutes of Health and obtain the certification prior to accession.

Ethics Approval and Consent to Participate

All data of this retrospective study were extracted from the eICU Collaborative Research Database. One author (Jili Li) has obtained the access (record ID: 44589323) and was responsible for data extraction. The retrospective design of this study and all anonymized patient data led the Ethics Review Board of the West China Hospital of Sichuan University to waive the requirement for ethical review and informed consent.

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The datasets analyzed in the present study are available in the eICU Collaborative Research Database v2.0 (https://physionet.org/content/eicu-crd/2.0/). Thanks to the researchers at the Philips Healthcare and MIT Laboratory for Computational Physiology.

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Disclosure

All authors declare that they have no conflicts of interests.

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