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Blood urea nitrogen to serum albumin ratio as a new prognostic indicator in critical patients with chronic heart failure

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Abstract

Aims   Chronic heart failure (CHF) is often a common comorbidity in critically ill patients admitted to the intensive care unit (ICU) and carries an extremely poor prognosis. The study aimed to investigate the relationship between the blood urea nitrogen to serum albumin ratio (BAR) and the prognosis of patients with CHF admitted to the ICU.
Methods and results   This retrospective cohort study included 1545 critically ill patients with CHF as a diagnosed comorbidity admitted to the ICU deposited in the MIMIC-III database, of whom 90 day all-cause mortality was 27.6% (n = 427) and in-hospital mortality was 17.3% (n = 267). The results of multiple logistic regression analysis indicated that BAR is an independent risk factor for in-hospital mortality in critically ill patients with CHF [compared with BAR $\leq$ 0.83; $0.83 <$ BAR ≤ 1.24: odds ratio (OR) 2.647, 95% confidence interval (CI) 1.797–3.900, $P < 0.001$; BAR ≥ 1.24: OR 3.628, 95% CI 2.604–5.057, $P < 0.001$]. Multiple *COX* regression analysis found a relationship between BAR and all-cause mortality at 90 day follow-up ($0.83 <$ BAR ≤ 1.24: OR 1.948, 95% CI 1.259–3.014, $P < 0.003$; BAR ≥ 1.24: OR 1.807, 95% CI 1.154–2.830, $P < 0.01$; BAR ≤ 0.83 as a reference). Kaplan–Meier curves also showed similar results as well ($P < 0.001$). The areas under the receiver operating characteristic curves for predicting in-hospital mortality and 90 day all-cause mortality were 0.622 and 0.647, respectively.
Conclusions   BAR is an independent risk factor for in-hospital mortality and 90 day mortality in critically ill patients with CHF admitted to the ICU.

Introduction

Heart failure is a clinical syndrome that is the end-stage manifestation of a variety of cardiac diseases. Worldwide, the burden of heart failure has increased to approximately 23 million people, and we have reason to assume that this number is still increasing.[1]

The difference between chronic heart failure and acute heart failure is that the condition of chronic heart failure is prolonged and has long-term damage to the body, which is more prone to make patients appear debilitated and can suddenly aggravate under the action of a certain

inducement and endanger life. Decreased effective circulating blood volume and hypoperfusion of organs are pathophysiological mechanisms of persistent damage to the body from chronic heart failure. This situation is particularly prominent in the kidney. Although blood urea nitrogen (BUN) is less sensitive to renal dysfunction than serum creatinine, previous studies have confirmed that the increase of BUN is associated with poor prognosis in patients with heart failure.[2–5] In addition, hypoalbuminaemia, which is thought to be mainly caused by cachexia, renal dysfunction, liver dysfunction, and inflammation, has now emerged as an independent risk factor for several cardiovascular

diseases.[6] Studies have shown that hypoalbuminaemia is an independent predictor of poor outcomes regardless of acute or chronic heart failure.[7–9]

Blood urea nitrogen to serum albumin ratio (BAR) is a novel prognostic biomarker discovered in recent years, which combines two important predictors—urea nitrogen and albumin, and this biomarker shows a good predictive effect in the mortality of patients with pneumonia or acute pulmonary embolism.[10–14] Most critically ill patients admitted to the intensive care unit (ICU) have multiple organ damages. Chronic heart failure is a common comorbidity, which makes the mortality rate of these patients higher. To seek simple and easily available biomarkers to judge the prognosis of such patients, the BAR was considered. At present, the relationship between BAR and the prognosis of critically ill patients with chronic heart failure as comorbidity is unclear. To predict the prognosis of these patients simply and effectively remains to be explored.

Material and method

Data source

Data were obtained from the Medical Information Mart for the Intensive Care III database (Version 1.4) (https://doi.org/10.13026/C2XW26), an open access, single-centre critical care clinical database, which includes health data for more than 40 000 patients hospitalized in the ICU of Beth Israel Deaconess Medical Center from 2001 to 2012.[15] The database was approved by the institutional review boards of the Massachusetts Institute of Technology (Cambridge, Massachusetts) and the Beth Israel Deaconess Medical Center (Boston, Massachusetts). The data of this study were obtained by the first author (Lin), finished the online training for the Collaborative Institutional Training Initiative (CITI) programme of the National Institutes of Health (NIH) (Record ID 40923254).

Study design and population

The PostgreSQL tools (Version 9.6.18) was used to construct the data management platform and extract the data required for the study. Enrolled patients were defined as critically ill patients with chronic heart failure as a diagnosed comorbidity admitted to the ICU. The study population was selected according to the International Classification of Diseases (ICD-9) (4280 = congestive heart failure, 4281 = left heart failure, 42 820 = systolic heart failure, 42 822 = chronic systolic heart failure, 42 830 = diastolic heart failure, 42 832 = chronic diastolic heart failure, 42 840 = diastolic heart failure combined with systolic heart failure, 4289 = heart failure). Exclusion criteria were as follows: (1) <18 or ≥90 years; (2) acute heart failure; (3) patients with malignancies, including solid tumours but also haematologic malignancies; (4) missing baseline values of BUN and albumin at ICU admission; and (5) missing left ventricular ejection fraction values or ranges reported by echocardiography.

Primary and secondary outcomes

The survival information of patients comes from Social Security Death Index Records. The primary outcome was defined as all-cause death within 90 days of ICU admission, whereas the secondary outcome was defined as in-hospital all-cause death after ICU admission.

Statistical analysis

BAR (mg/g) was calculated from BUN (mg/L) and albumin (g/L). Variables with more than 80% missing values are deleted. The missing values are interpolated by random forest interpolation using missForest package.[16] Outliers from laboratory results were handled by the winsorize method, which was implemented with the STATA winsor2 command, with 1% and 99% as the cut-off points. Kolmogorov–Smirnov test is used to evaluate the normality of continuous variables. Normally distributed variable was presented as mean ± standard deviation. Non-normally distributed continuous variable was presented as median [25th–75th percentile]. Pearson's χ^2 test was used for categorical variables, and the Mann–Whitney U test was used for non-normally distributed continuous variables. Student's t-test was used for variables with normal distribution. Cox regression model with restricted cubic spline was used to evaluate the relationship between baseline BAR value (continuous variable) and the risk of 90 day all-cause mortality. The optimal cut-off value of the BAR for 90 day all-cause mortality was determined by X-tile (Version 3.6.1, Yale University School of Medicine) software.[17] Univariate and multivariate logistic regression analyses were used to identify independent risk factors for in-hospital mortality. Univariate and multivariate Cox regression analyses were used to assess the hazard ratio (HR) of BAR within 90 day mortality. Survival curves were estimated using the Kaplan–Meier method and compared by the log-rank test. Receiver operating characteristic (ROC) curves were constructed, as well as the area under the curve (AUC). Statistical significance was set at $P < 0.05$ (two-sided). Data analysis was performed using STATA software (STATA/SE for Mac Version 15.1, Stata Corporation, College Station, TX, USA), IBM SPSS statistical software for Mac Version 26.0 (Chicago, IL, USA), and R language (R for Mac Version 4.0.3, R Foundation for Statistical Computing, Vienna).

Results

Characteristics of patients

The patient selection process is shown in *Figure 1*. A total of 1545 patients were finally included in the study. Since admission to ICU, the in-hospital mortality was 17.3% (*n* = 267), and the all-cause mortality within 90 days was 27.6% (*n* = 427). Patients were divided into survivor and non-survivor groups according to whether they died within 90 days. Non-survivors had substantial differences at baseline compared with survivors. Most of non-survivors were older women with lower pH, PO₂, SO₂, and blood pressure, while Sequential Organ Failure Assessment (SOFA) scores were higher. In terms of medical history, non-survivors had a higher prevalence of atrial fibrillation, renal dysfunction, and pyohaemia but a lower prevalence of coronary heart disease and hypertension. In terms of medication use, the survivors' utilization of aspirin, dihydropyridines calcium channel blocker (DHPs CCB), angiotensin-converting enzyme inhibitors (ACEI), furosemide, and beta-blocker was less frequently used, whereas warfarin and digoxin were more frequently used. In addition, in terms of laboratory data, survivors had lower red blood cell (RBC), lymphocytes, haemoglobin, and albumin compared with non-survivors. However, survivors had significantly higher white blood cell (WBC), red blood cell distribution width (RDW), neutrophilic granulocyte (NEU), serum creatinine, BUN, lactate dehydrogenase (LDH), lactic, aspartate aminotransferase (ALT), activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), N-terminal pro-brain natriuretic peptide (NT-proBNP), and BAR. Specific baseline characteristics of the patients are shown in *Table*

1. We further examined the correlation between BAR and laboratory data and found that BAR had a significant negative correlation with RBC, lymphocytes, haemoglobin, haematocrit, and pH, while a significant positive correlation with WBC, RDW, NEU, serum creatinine, glucose, potassium, APTT, PT, INR, NT-proBNP, and body mass index, as shown in *Table 2*.

Association between BAR and in-hospital mortality

Before exploring the prognostic correlation between BAR and patients with critical chronic heart failure, we had defined BAR as a continuous variable, with the median (0.96) as the reference point, and used restricted cubic spline regression to fit the unadjusted *COX* proportional hazards model. Unadjusted spline plots showed a non-linear association between BAR and HR for all-cause mortality within 90 days, as shown in *Figure 2*. Given such results, we further stratified BAR using X-tile software and finally selected cut-off points of 0.83 and 1.24. According to the cut-off points, BAR was stratified into three levels (BAR ≤ 0.83, 0.83 < BAR ≤ 1.24, and BAR > 1.24).

Variables with significant differences (*P* < 0.05) in baseline table were included in univariate logistic regression analysis. BAR was predictive of in-hospital mortality when used as the only explanatory variable in a logistic regression model [compared with BAR ≤ 0.83; 0.83 < BAR ≤ 1.24: odds ratio (OR) 2.647, 95% confidence interval (CI) 1.797–3.900, *P* < 0.001; BAR ≥ 1.24: OR 3.628, 95% CI 2.604–5.057, *P* < 0.001]. Except for BUN and albumin, variables with *P* < 0.10 in univariate logistic regression considered potential confounders entered multivariate logistic regression

Figure 1 Study flow diagram depicting exclusion criteria and outcomes. BUN, blood urea nitrogen; ICD-9, International Classification of Diseases; LVEF, left ventricular ejection fraction.
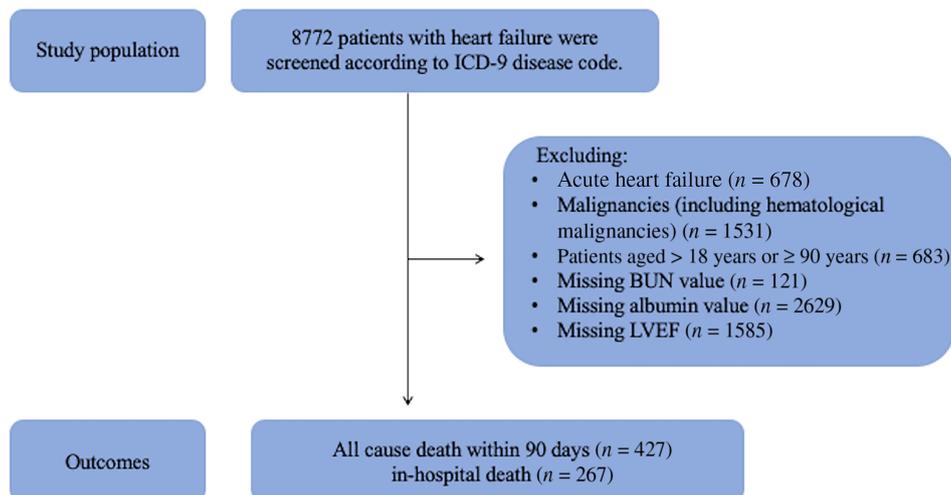
Table 1 Baseline characteristics of study population

Overall population	Survivors N = 1545	Non-survivors N = 1118	P-value	N = 427
Age (years)	72.3 [60.9–80.8]	70.2 [59.4–79.6]	77.0 [66.4–83.0]	<0.001
Male, n (%)	799 (51.7)	560 (50.1)	239 (56.0)	0.039*
Ethnicity, n (%)				
White	1121 (72.6)	818 (73.2)	303 (71.0)	
Black	127 (8.2)	97 (8.7)	30 (7.0)	
Other	297 (19.2)	203 (18.2)	94 (22.0)	
Height (cm)	167.9 [161.0–174.0]	167.6 [160.8–174.6]	168.0 [161.4–173.6]	0.563
Body weight (kg)	80.0 [68.0–96.0]	81.0 [69.0–97.0]	79.0 [67.0–96.0]	0.152
BMI (kg/m^2)	28.8 [24.7–33.6]	29.0 [25.0–33.8]	24.3 [21.6–28.1]	0.085
pH	7.37 [1.32–7.42]	7.38 [7.32–7.42]	7.36 [7.31–7.42]	0.021*
PO$_2$ (mmHg)	91.3 [72.2–103.1]	92.2 [73.0–104.0]	88.7 [70.0–100.3]	0.001*
PCO$_2$ (mmHg)	42.0 [38.0–48.0]	42.0 [38.1–48.0]	41.8 [36.9–48.0]	0.128
SO$_2$ (%)	89.7 [80.4–94.7]	90.5 [81.3–94.8]	87.9 [76.9–74.1]	0.002*
SBP (mmHg)	98.0 [76.2–119.1]	103.6 [76.4–120.9]	90.9 [76.0–115.0]	0.010*
DBP (mmHg)	55.6 [49.6–61.4]	56.8 [50.6–62.0]	53.1 [48.1–58.3]	<0.001
Heart ratio (b.p.m.)	73.6 [62.6–81.8]	73.6 [62.1–81.5]	73.7 [63.0–83.3]	0.351
LVEF, n (%)				
≥50%	1099 (71.1)	793 (70.9)	306 (71.7)	0.776
40–50%	103 (6.7)	81 (7.2)	22 (5.2)	0.140
30–40%	135 (8.7)	102 (9.1)	33 (7.7)	0.385
20–30%	147 (9.5)	101 (9.0)	46 (10.8)	0.298
<20%	61 (3.9)	41 (3.7)	20 (4.7)	0.359
SOFA	5 (4)	5 [3–7]	6 [4–9]	<0.001
Medical history				
Atrial fibrillation, n (%)	709 (45.9)	458 (43.4)	224 (52.5)	0.001*
Coronary heart disease, n (%)	549 (35.5)	428 (38.3)	121 (28.3)	<0.001
COPD, n (%)	86 (5.6)	57 (5.1)	29 (6.8)	0.194
Hypertension, n (%)	984 (36.3)	433 (38.7)	128 (30.0)	0.001*
Diabetes mellitus, n (%)	593 (38.4)	438 (39.2)	155 (36.2)	0.298
PAD, n (%)	128 (8.3)	86 (7.7)	42 (9.8)	0.172
Stroke/TIA, n (%)	116 (7.5)	87 (7.8)	29 (6.8)	0.509
Systemic embolism, n (%)	162 (10.5)	107 (6.9)	55 (3.6)	0.058
Renal insufficiency, n (%)	739 (47.8)	487 (43.6)	252 (59.0)	<0.001
Myocardial infarction, n (%)	206 (13.3)	160 (77.7)	46 (22.3)	0.067
Pyohaemia, n (%)	326 (21.1)	183 (16.4)	143 (33.5)	<0.001
Medication use				
Warfarin, n (%)	385 (24.9)	315 (28.2)	70 (16.4)	<0.001
Aspirin, n (%)	923 (59.7)	701 (62.7)	222 (52.0)	<0.001
Spironolactone, n (%)	97 (6.3)	67 (6.0)	30 (7.0)	0.454
Clopidogrel, n (%)	216 (14.0)	158 (14.1)	58 (13.6)	0.781
DHPs CCB, n (%)	219 (14.2)	175 (15.7)	44 (10.3)	0.007*
ACEI, n (%)	484 (31.3)	405 (36.2)	79 (18.5)	<0.001
Furosemide, n (%)	779 (50.4)	587 (52.5)	192 (45.0)	0.008*
Beta-blocker, n (%)	943 (61.0)	712 (63.7)	231 (54.1)	0.001*
Digoxin, n (%)	134 (8.7)	93 (8.3)	41 (9.6)	0.423
Laboratory data				
RBC (m/μL)	3.5 [3.0–4.0]	3.5 [3.0–4.0]	3.3 [3.0–3.9]	0.005*
WBC (K/μL)	11.2 [8.1–15.6]	11.0 [8.0–15.0]	12 [8.3–16.9]	0.009*
Platelets (K/μL)	200.0 [138.0–275.0]	201.0 [145–274]	198 [121–278]	0.135
RDW (%)	15.1 [14.0–16.6]	14.8 [13.9–16.3]	15.8 [14.6–19.0]	<0.001
NEU (%)	82.5 [76.1–86.6]	82.1 [75.0–86.0]	83.4 [78.1–88.7]	<0.001
Lymphocytes (%)	9.7 [6.3–13.3]	10.2 [7.2–14.3]	8.1 [4.8–11.1]	<0.001
Haemoglobin (g/dL)	10.4 [9.1–11.9]	10.5 [9.2–11.9]	10.2 [9.0–11.6]	0.035*
Haematocrit (%)	31.1 [27.4–35.4]	31.4 [27.4–35.5]	30.4 [27.2–35.0]	0.189
Serum creatinine (mg/dL)	1.2 [0.9–2.1]	1.1 [0.8–1.9]	1.5 [1.0–2.4]	<0.001
Blood urea nitrogen (mg/dL)	28.0 [18.0–45]	26.0 [17.0–41.3]	36 [23.0–57.0]	<0.001
Glucose (mg/dL)	131.0 [106–168]	130.0 [105.0–165.2]	134 [106.0–174.0]	0.168
Sodium (mEq/L)	139.0 [136.0–141]	139.0 [136.0–141.0]	139.0 [135.0–142.0]	0.191
Potassium (mEq/L)	4.1 [3.7–4.6]z	4.1 [3.7–4.6]	4.2 [3.8–4.7]	0.117
LDH (IU/L)	303.0 [234–390]	295.8 [230–372.4]	335.7 [248.0–450.0]	<0.001
Lactic (mmol/L)	1.8 [1.3–2.5]	1.8 [1.3–2.4]	2.0 [1.4–2.7]	<0.001
AST (IU/L)	42.0 [26.0–80.0]	40.0 [25.0–71.0]	50.0 [28.0–104.0]	<0.001
ALT (IU/L)	29.0 [17.0–57.0]	29.0 [17.0–51.9]	34.0 [18.0–70.31]	0.005*
Albumin (g/L)	30.0 [26.0–34.0]	30.0 [26.0–34.0]	29.0 [24.0–33.0]	<0.001
APTT (s)	33.2 [28.0–42,3]	32.4 [27.7–41.4]	35.5 [29.4–45.4]	<0.001

(Continues)

Table 1 (continued)

Overall population	Survivors N = 1545	Non-survivors N = 1118	P-value	N = 427
PT (s)	15.10 (4.20)	14.7 [13.4–17.4]	15.7 [14.2–19.0]	<0.001
INR	1.4 [1.2–1.7]	1.3 [1.2–1.7]	1.5 [1.3–1.8]	<0.001
NT-proBNP (pg/mL)	8064.7 [5138.0–13 075.3]	7252.1 [4783.4–11 150.5]	11 522.0 [7280.0–16 656.4]	<0.001
BAR	0.96 [0.58–1.6]	0.84 [0.53–1.46]	1.35 [0.84–2.10]	<0.001

ACEI, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BAR, blood urea nitrogen to serum albumin ratio; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DHPs CCB, dihydropyridines calcium channel blocker; INR, international normalized ratio; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; NEU, neutrophilic granulocyte percentage; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAD, peripheral artery disease; PT, prothrombin time; RBC, red blood cell; RDW, red blood cell distribution width; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; TIA, transient ischaemic attack; WBC, white blood cell.
Data are *n/N* (%) or mean ± standard deviation or median [25th–75th percentile].
*$P < 0.05$.

Table 2 Spearman correlation analysis between BAR and other variable

Variable	Correlation coefficient (r_s)	P-value
RBC (m/μL)	−0.018	<0.001
WBC (K/μL)	0.102	<0.001
Platelets (K/μL)	0.013	0.606
RDW (%)	0.314	<0.001
NEU (%)	0.144	<0.001
Lymphocytes (%)	−0.211	<0.001
Haemoglobin (g/dL)	−0.209	<0.001
Haematocrit (%)	−0.167	<0.001
Serum creatinine (mg/dL)	0.731	<0.001
Glucose (mg/dL)	0.083	0.001*
Sodium (mEq/L)	0.003	0.902
Potassium (mEq/L)	0.286	<0.001
LDH (IU/L)	0.028	0.265
Lactic (mmol/L)	0.048	0.061
AST (IU/L)	−0.008	0.871
ALT (IU/L)	−0.004	0.871
APTT (s)	0.058	0.022*
PT (s)	0.129	<0.001
INR	0.139	<0.001
NT-proBNP (pg/mL)	0.595	<0.001
BMI	0.085	0.001
pH	−0.197	<0.001

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BAR, blood urea nitrogen to serum albumin ratio; BMI, body mass index; INR, international normalized ratio; LDH, lactate dehydrogenase; NEU, neutrophilic granulocyte percentage; NT-proBNP, N-terminal pro-brain natriuretic peptide; PT, prothrombin time; RBC, red blood cell; RDW, red blood cell distribution width; WBC, white blood cell.
*$P < 0.05$.

Figure 2 Hazard ratios of 90 day all-cause mortality as a function of baseline BAR (BAR as a continuous variable fitted an unadjusted *COX* regression model using restricted cubic spline regression). BAR, blood urea nitrogen to serum albumin ratio; CI, confidence interval; HR, hazard ratio; RCS, restricted cubic spline.
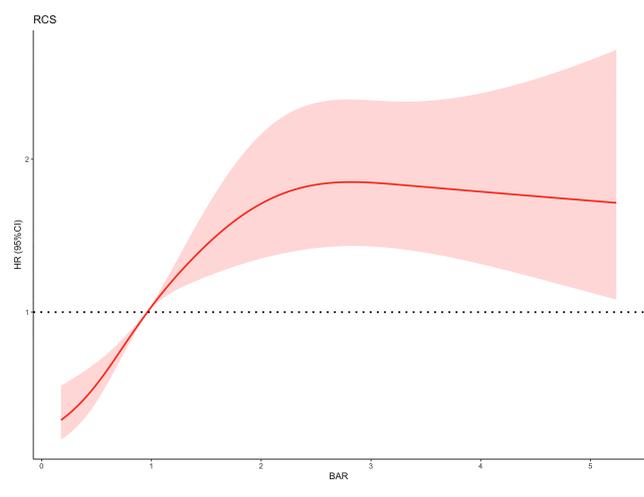
ence). The logistic regression results are shown in *Table 3*. We further used an ROC curve to compare the predictive ability of BAR and SOFA score in in-hospital mortality. The results showed no significant differences in the AUCs between BAR and SOFA score (BAR: AUC = 0.622, 95% CI 0.610–0.674; SOFA score: AUC = 0.680, 95% CI 0.644–0.716, DeLong's test $P = 0.082$), as shown in *Figure 3A*.

Association between BAR and 90 day mortality

Variables with significant differences ($P < 0.05$) in *Table 1* were included in univariate *COX* regression analysis. The results showed that unadjusted BAR was significantly associated with all-cause mortality within 90 days (0.83 < BAR ≤ 1.24: HR 2.063, 95% CI 1.558–2.733, $P < 0.001$; BAR > 1.24: HR 3.035, 95% CI 2.404–3.831, $P < 0.001$). Variables with $P < 0.10$ in the

model, and we used backward regression and excluded variables with a likelihood ratio test *P*-value of at least 0.05. In the logistic regression model finally adjusted for age, SO₂, diastolic blood pressure (DBP), SOFA, coronary heart disease, pyohaemia, warfarin, ACEI, aspirin, beta-blocker, RDW, serum creatinine, INR, and lactic, BAR still has significant predictive value for in-hospital mortality (0.83 < BAR ≤ 1.24: OR 1.948, 95% CI 1.259–3.014, $P < 0.003$; BAR ≥ 1.24: OR 1.807, 95% CI 1.154–2.830, $P < 0.01$; BAR ≤ 0.83 as a refer-

Table 3 Results of univariate and multivariate logistic regression analysis

Variable	Univariable LR			Multivariable LR		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.013	1.002–1.023	0.016*	1.017	1.005–1.030	0.005*
Sex (male)	1.129	0.988–1.682	0.061			
pH	0.043	0.010–0.182	<0.001			
PO$_2$	0.992	0.986–0.999	0.016*			
SO$_2$	0.985	0.976–0.995	0.003*	1.012	0.999–1.026	0.074
SBP	0.996	0.992–0.999	0.015*			
DBP	0.985	0.977–0.993	<0.001	0.983	0.973–0.993	0.001*
SOFA	1.209	1.163–1.256	<0.001	1.112	1.058–1.170	<0.001
Atrial fibrillation	1.167	0.896–1.519	0.253			
Coronary heart disease	0.528	0.390–0.714	<0.001	0.573	0.395–0.830	0.003*
Hypertension	0.724	0.545–0.962	0.026*			
Renal insufficiency	1.614	1.237–2.108	<0.001			
Pyohaemia	3.035	2.281–4.037	<0.001	1.891	1.347–2.656	<0.001
Warfarin	0.302	0.201–0.455	<0.001	0.307	0.191–0.493	<0.001
ACEI	0.331	0.232–0.472	<0.001	0.613	0.412–0.912	0.016*
Aspirin	0.440	0.337–0.575	<0.001	0.623	0.444–0.873	0.006*
DHPs	0.493	0.310–0.782	0.003*			
Furosemide	0.570	0.435–0.746	<0.001			
Beta-blocker	0.486	0.327–0.634	<0.001	0.710	0.516–0.976	0.035*
RBC	0.793	0.655–0.959	0.017*			
WBC	1.014	1.002–1.026	0.020*			
RDW	1.184	1.119–1.254	<0.001	1.079	1.008–1.154	0.028*
NEU	0.999	0.988–1.011	0.929			
Lymphocytes	0.963	0.942–0.985	0.001*			
Haemoglobin	0.944	0.884–1.008	0.087			
Serum creatinine	1.074	1.001–1.152	0.048*	0.768	0.675–0.873	<0.001
Blood urea nitrogen	1.014	1.009–1.018	<0.001			
PT	1.023	1.009–1.037	0.001*			
INR	1.244	1.115–1.388	<0.001	1.184	1.038–1.351	0.012*
Lactic	1.186	1.111–1.265	<0.001	1.096	1.015–1.184	0.019*
AST	1.000	1.000–1.000	0.019*			
ALT	1.000	1.000–1.001	0.079			
APTT	1.005	1.001–1.010	0.029*			
LDH	1.000	1.000–1.001	0.002*			
NT-proBNP	1.000	1.000–1.000	<0.001	1.000	1.000–1.000	<0.001
Albumin	0.560	0.447–0.700	<0.001			
BAR ≤ 0.83	1			1		
0.83 < BAR ≤ 1.24	2.647	1.797–3.900	<0.001	1.948	1.259–3.014	0.003*
BAR > 1.24	3.628	2.604–5.057	<0.001	1.807	1.154–2.830	0.010*

ACEI, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BAR, blood urea nitrogen to serum albumin ratio; CI, confidence interval; DBP, diastolic blood pressure; DHPs, dihydropyridine calcium antagonist; INR, international normalized ratio; LDH, lactate dehydrogenase; LR, logistic regression; NEU, neutrophilic granulocyte percentage; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio; PT, prothrombin time; RBC, red blood cell; RDW, red blood cell distribution width; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.
*$P < 0.05$.

univariate *COX* analysis were entered in the univariate *COX* regression analysis. Except for NEU and ALT, other candidate variables showed a $P < 0.10$. Then, they entered into backward multivariable *COX* regression analysis and excluded variables with a likelihood ratio test *P*-value of at least 0.05. In the final Cox regression model [including age, sex (male), DBP, SOFA, atrial fibrillation, coronary heart disease, renal insufficiency, pyohaemia, warfarin, aspirin, ACEI, beta-blocker, WBC, LDH, INR, NT-proBNP, and BAR], BAR was an independent risk factor for all-cause mortality within 90 days in patients with severe chronic heart failure (0.83 < BAR ≤ 1.24: HR 1.455, 95% CI 1.082–1.956, $P = 0.013$; BAR > 1.24: HR 1.629, 95% CI 1.205–2.202, $P = 0.002$). Univariate and multivariate Cox regression analyses are summarized in *Table 4*.

To evaluate the ability of BAR and SOFA score to predict all-cause death within 90 days, the AUCs of ROC curve were 0.647 (95% CI 0.619–0.675) and 0.647 (95% CI 0.616–0.677), respectively. There was no significant difference between the AUCs of BAR and SOFA score (DeLong's test $P = 0.992$), as shown in *Figure 3B*.

Survival curves were plotted using the Kaplan–Meier method for the three different BAR levels. The mortality rates of the three BAR levels were 15.7%, 29.1%, and 40.3%, respectively (log-rank test $P < 0.0001$). The differences among the three survival curves were statistically significant (0.83 < BAR ≤ 1.24 vs. BAR < 0.83, $P_{adjusted} < 0.0001$; 0.83 < BAR ≤ 1.24 vs. BAR ≥ 1.24, $P_{adjusted} = 0.002$; BAR ≥ 1.24 vs. BAR < 0.83, $P_{adjusted} < 0.0001$; log-rank test

Figure 3 The ROC curve of all-cause mortality, (A) ROC curves for in-hospital mortality comparing BAR with SOFA score; (B) ROC curves for 90 day all-cause mortality comparing BAR with SOFA score. BAR, blood urea nitrogen to serum albumin ratio; ROC, receiver operating characteristic; SOFA, Sequential Organ Failure Assessment.
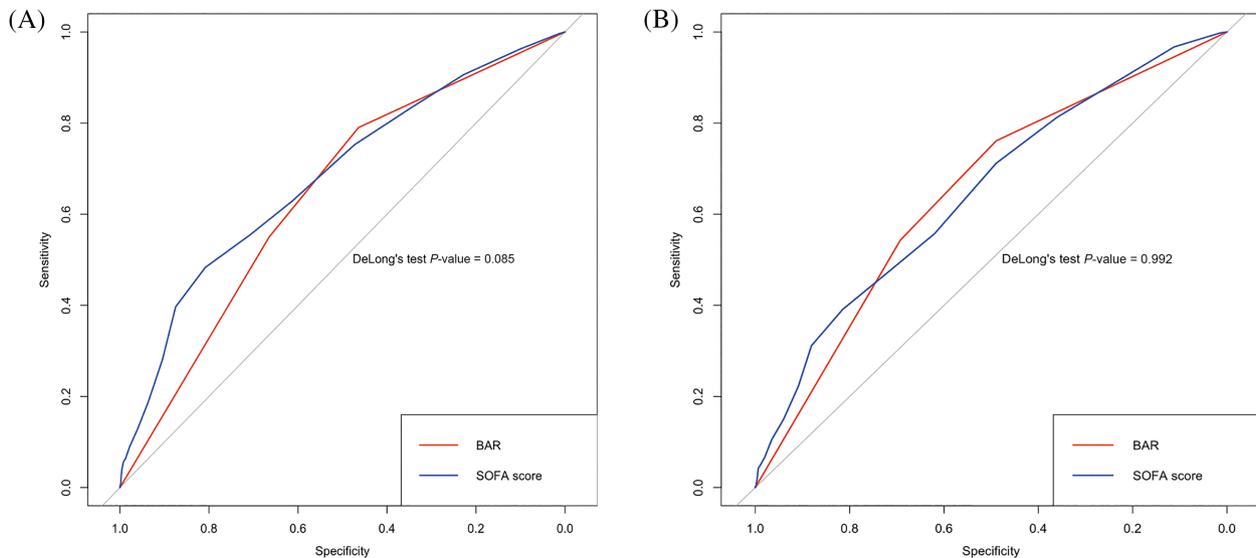
P-value adjustment method: Benjamini–Hochberg method), as shown in *Figure 4*.

Discussion

Timely identification of high risk is an important link in our clinical work. This study found that BAR is an independent predictor of all-cause mortality in patients with critical chronic heart failure. We were not surprised by such results. This is because BAR is an indicator that combines BUN and serum albumin, and previous studies have shown that increased BUN levels and hypoalbuminaemia are independent risk factors in patients with heart failure.[9,18] Different from previous studies, BAR makes up for the lack of prediction performance of albumin or BUN alone.

Several key points of our study need to be illustrated. First, to our knowledge, data related to BAR are lacking, and this study may be the first study on the BAR and the prognosis of critically ill patients with chronic heart failure. The mechanisms between BAR and poor prognosis are not unequivocal, so the possible mechanisms can only be explained starting from the aspects of BUN and albumin.

Blood urea nitrogen is an important indicator of renal function, but its sensitivity is not higher than glomerular filtration rate (GFR) and creatinine. In addition, BUN is also affected by age, protein intake, bleeding, catabolic state, and other factors. Therefore, although many studies have found BUN to be a powerful predictor of heart failure, perhaps even beyond GFR and serum creatinine, the mechanism behind it is

not so clear that it is difficult to make a bold statement about the clinical application of BUN.[3,19–21] Kazory summarizes previous studies and suggests a new concept that BUN may serve as a biomarker of neurohormonal activation in heart failure.[22] Based on this concept, Jeffrey M. Testani *et al.* found that high doses of loop diuretics are protective in a population with chronic heart failure with non-elevated BUN, which may illustrate that BUN is a biomarker that parallels neurohormonal activation in the kidney and can identify a patient population at risk of adverse neurohormonal effects from high doses of loop diuretics.[23] In patients with chronic heart failure, the compensatory effect of the kidney may keep the BUN at a low level, but with the aggravation of heart failure, the effective circulating blood volume gradually becomes insufficient so that multiple neurohormones are secreted, leading to further reduction in renal perfusion, at which point high levels of BUN may herald more severe heart failure. This may also be one of the reasons why BUN can be an independent risk factor for heart failure patients.

Albumin is another important component of BAR, and it has been previously reported that low albumin is highly correlated with poor prognosis in a variety of cardiovascular disease.[6,24] Heart failure may not directly cause hypoalbuminaemia, but prolonged chronic heart failure is often complicated by infections, malnutrition, hepatic dysfunction, and renal disease that drive further albumin loss that disrupts the body's fluid balance.[25,26] It is well known that heart failure itself is a disease of relative organ hypoperfusion due to cardiac overload, and when hypoalbuminaemia occurs, body fluids in the circulatory system are further lost, forming a vicious circle causing adverse prognosis.

Table 4 Results of univariate and multivariate Cox regression analyses

| Variable	Univariable COX			Multivariable COX		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.025	1.017–1.033	<0.001	1.024	1.015–1.033	<0.001
Sex (male)	1.212	1.001–1.467	0.049*	1.352	1.106–1.654	0.003*
pH	0.177	0.063–0.494	0.001*			
PO$_2$	0.993	0.998–0.997	0.002*			
SO$_2$	0.988	0.982–0.995	<0.001			
SBP	0.997	0.997–1.000	0.029*			
DBP	0.989	0.984–0.995	<0.001	0.989	0.983–0.995	<0.001
SOFA	1.133	1.106–1.160	<0.001	1.076	1.045–1.108	<0.001
Atrial fibrillation	1.349	1.115–1.631	0.002*	1.244	1.005–1.539	0.045*
Hypertension	0.734	0.597–0.903	0.003*			
Coronary heart disease	0.680	0.551–0.839	<0.001	0.650	0.516–0.819	<0.001
Renal insufficiency	1.683	1.388–2.042	<0.001	1.292	1.037–1.608	0.022*
Pyohaemia	2.146	1.755–2.624	<0.001	1.342	1.075–1.674	0.009*
Warfarin	0.529	0.409–0.683	<0.001	0.506	0.383–0.668	<0.001
Aspirin	1.501	1.242–1.815	<0.001	0.822	0.664–1.016	0.070
ACEI	0.441	0.346–0.564	<0.001	0.606	0.470–0.783	<0.001
Furosemide	0.743	0.614–0.899	0.002*			
DHPs	0.647	0.474–0.884	0.006*			
Beta-blocker	0.681	0.563–0.824	<0.001	0.748	0.610–0.917	0.005*
RBC	0.858	0.747–0.985	0.030*			
WBC	1.010	1.005–1.016	<0.001	1.007	1.000–1.015	0.062
RDW	1.156	1.117–1.195	<0.001			
NEU	1.005	0.996–1.015	0.272			
Lymphocytes	0.965	0.949–0.981	<0.001			
Haemoglobin	0.953	0.909–1.000	0.051			
Serum creatinine	1.060	1.014–1.109	0.011*			
Blood urea nitrogen	1.011	1.008–1.014	<0.001			
AST	1.000	1.000–1.000	0.014*			
ALT	1.000	1.000–1.000	0.159			
APTT	1.005	1.002–1.008	0.001*			
LDH	1.000	1.000–1.000	<0.001	1.000	1.000–1.000	0.015*
PT	1.015	1.006–1.023	0.001*			
INR	1.144	1.071–1.223	<0.001	1.092	1.015–1.175	0.018*
Lactic	1.110	1.069–1.153	<0.001			
NT-proBNP	1.000	1.000–1.000	<0.001	1.000	1.000–1.000	<0.001
Albumin	0.631	0.538–0.741	<0.001			
BAR ≤ 0.83	1			1		
0.83 < BAR ≤ 1.24	2.063	1.558–2.733	<0.001	1.455	1.082–1.956	0.013*
BAR > 1.24	3.035	2.404–3.831	<0.001	1.629	1.205–2.202	0.002*

ACEI, angiotensin-converting enzyme inhibitors; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BAR, blood urea nitrogen to serum albumin ratio; CI, confidence interval; DBP, diastolic blood pressure; DHPs, dihydropyridine calcium antagonist; HR, hazard ratio; INR, international normalized ratio; LDH, lactate dehydrogenase; NEU, neutrophilic granulocyte percentage; NT-proBNP, N-terminal pro-brain natriuretic peptide; PT, prothrombin time; RBC, red blood cell; RDW, red blood cell distribution width; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; WBC, white blood cell.
*$P < 0.05$.

Previous studies[27,28] have found that hepatic and renal impairment is a prevalent condition in patients with acute heart failure and that mortality is highly correlated with the MELD-XI score, which consists of creatinine and bilirubin. BUN and albumin can be used as a marker for liver and kidney dysfunction. Therefore, there are some similarities between BAR and MELD-XI score. But whether BAR can be used to evaluate the degree of hepatic and renal dysfunction in patients with heart failure also needs to be further explored. Furthermore, given the role of albumin and BUN in the progression of chronic heart failure, BAR also seems to be an index reflecting the effective circulating blood volume; that is, the increase of BAR value indicates the relative shortage of circulating blood volume. Therefore, whether BAR can be used to evaluate the effective circulating blood volume of patients and guide the volume management of patients with heart failure needs more research.

Secondly, another critical point needs to be illustrated. SOFA score is an important score for ICU patients, which has a good predictive effect on the mortality of critically ill patients.[29] But there is no significant difference in the AUC between BAR and SOFA score in our study (in-hospital mortality: AUC$_{BAR}$ = 0.622 vs. AUC$_{SOFA score}$ = 0.680, P = 0.082; 90 day mortality: AUC$_{BAR}$ = 0.647 vs. AUC$_{SOFA score}$ = 0.647, P = 0.992). Therefore, we suggest that BAR may be a convenient predictor for the short-term prognosis of critically ill patients with chronic heart failure and may replace SOFA score. However, this need to be confirmed by further research, because this study only compared the relationship between BAR and SOFA scores and mortality when admitted to the

Figure 4 Kaplan–Meier survival analysis plot for 90 day overall survival for three different BAR levels. BAR, blood urea nitrogen to serum albumin ratio.
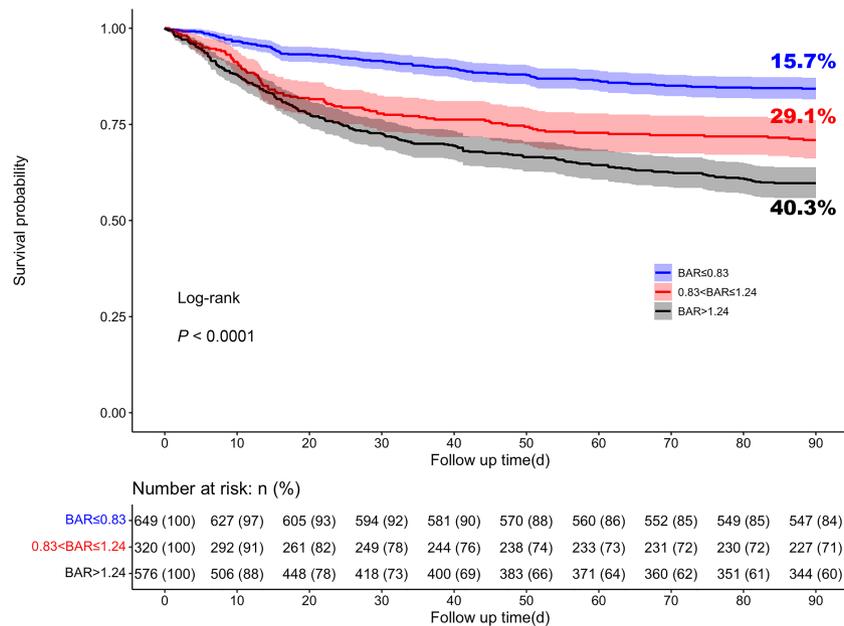
ICU and did not consider the possible risk change caused by the continuous evaluation of changes in SOFA and BAR.

Finally, we found that coronary heart disease and serum creatinine seem to be protective factors in our data, but this is obviously unreasonable. We carefully reviewed these patients and found that survivors had a higher prevalence of coronary heart disease or myocardial infarction. This is because MIMIC-III database also include those patients admitted to the cardiac intensive care unit (CCU) who may have been treated with percutaneous coronary intervention or timely treatment prior to admission to the CCU, and most patients have a favourable prognosis after spending a critical period. For serum creatinine, although there were significant differences in creatinine levels between survivors and non-survivors in the two groups, the total creatinine levels of patients in the two groups can only be described as a slight or moderate increase in the real world. We included it in multiple regression analysis as a continuous variable, which may ignore the relationship between normal level and elevated level, and the collinearity between variables is likely to cause abnormal results of serum creatinine.

Limitation

There are some limitations of our study that cannot be ignored. First, the limitations of observational studies themselves are inevitable. Despite efforts to minimize confounding by confounders, there are potential confounders that remain unidentified. Secondly, the process of extracting data from the database is cumbersome and difficult, and many variables have to be discarded due to serious lack. Third, we have identified the required population through the coding of ICD-9. Therefore, it is difficult to determine whether these patients are hospitalized due to chronic heart failure. Last but not least, in our study, although we found that the level of BAR was associated with poor prognosis, we may not have determined the optimal level division. From the Cox regression model with restricted cubic splines, the HRs tended to be stable at higher BAR levels, but the CIs were wide, which illustrates that patients with high levels of BAR are less and more samples may still be needed.

Summary

High levels of BAR are an independent risk factor for in-hospital mortality and mortality within 90 days in critically ill patients with chronic heart failure. Therefore, BAR is likely to be a convenient and effective prognostic indicator, but its mechanism and clinical usefulness of treatment for BAR still require further investigation.

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Conflict of interest

None declared.

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