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ORIGINAL RESEARCH

Predictive Value of Blood Urea Nitrogen to Albumin Ratio in Long-Term Mortality in Intensive Care Unit Patients with Acute Myocardial Infarction: A Propensity Score Matching Analysis

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Background: Blood urea nitrogen to albumin ratio (BAR) has been implicated in predicting outcomes of various inflammatory-related diseases. However, the predictive value of BAR in long-term mortality in patients with acute myocardial infarction (AMI) has not yet been evaluated.

Methods: In this retrospective cohort study, the patients were recruited from the Medical Information Mart for Intensive Care III (MIMIC III) database and categorized into two groups by a cutoff value of BAR. Kaplan–Meier (K-M) analysis and Cox proportional hazard model were performed to determine the predictive value of BAR in long-term mortality following AMI. In order to adjust the baseline differences, a 1:1 propensity score matching (PSM) was carried out and the results were further validated.

Results: A total of 1827 eligible patients were enrolled. The optimal cutoff value of BAR for four-year mortality was 7.83 mg/g. Patients in the high BAR group tended to have a longer intensive care unit (ICU) stay and a higher rate of one-, two-, three- and four-year mortality (all $p<0.001$) compared with those in the low BAR group. K-M curves indicated a significant difference in four-year survival ($p<0.001$) between low and high BAR groups. The Cox proportional hazards model showed that higher BAR (>7.83) was independently associated with increased four-year mortality in the entire cohort, with a hazard ratio (HR) of 1.478 [95% CI (1.254–1.740), $p<0.001$]. After PSM, the baseline characteristics of 312 pairs of patients in the high and low BAR groups were well balanced, and similar results were observed in K-M curve ($p=0.003$).

Conclusion: A higher BAR (>7.83) was associated with four-year mortality in patients with AMI. As an easily available biomarker, BAR can predict the long-term mortality in AMI patients independently.

Keywords: acute myocardial infarction, blood urea nitrogen, albumin, long-term mortality, MIMIC III database

Introduction

Acute myocardial infarction (AMI) is caused by acute obstruction of the coronary arteries, leading to an acute, persistent ischemia and hypoxia and eventually resulting in myocardial necrosis.[1,2] Despite the advancements of emergency revascularization that has markedly reduced the mortality following AMI, ischemic heart disease remains one of the leading causes of death all over the world and imposes a huge financial burden on public health.[3–5] It is reported that in the United States an AMI event occurs every 43 seconds and a cardiovascular disease (CVD)-related death occurs every 40 seconds.[6] Notably, the long-term prognosis of AMI is relatively poor, with a 5-year survival rate being only ~50%.[7,8]

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Therefore, validating biomarkers with predictive value of long-term mortality in AMI patients has become increasingly important for identification of high-risk individuals.

Renal insufficiency has long been associated with poor outcomes in cardiovascular diseases.[9–11] In patients with AMI, blood urea nitrogen (BUN) reflects not only renal function but also neurohormonal activation.[12] One study confirmed that high level of BUN was a powerful indicator for in-hospital mortality in patients with AMI.[13] In another study Aronson and his team found that BUN was strongly associated with long-term mortality in ST-elevation MI.[14] Albumin, a main component of plasma proteins, plays a key role in maintaining vascular osmotic pressure, transporting endogenous and exogenous compounds, and regulating pharmacokinetics of drugs.[15] Hypoalbuminemia predicts a poorer outcome in heart failure (HF), stroke, and coronary artery disease (CAD).[16,17] Plakht et al found that a decrease in albumin at admission might be an independent predictor of long-term mortality in discharged patients with AMI.[15] In the present study, we aimed to explore the prognostic value of blood urea nitrogen to albumin ratio (BAR) in predicting the long-term mortality of patients with AMI.

Materials and Methods

Data Source

All data analyzed in this retrospective study were obtained from the Medical Information Mart for Intensive Care III (MIMIC III) database. This large and freely-available database recorded medical information of > 40,000 patients in critical care units of the Beth Israel Deaconess Medical Center (BIDMC) between 2001 and 2012.[18] Since all subjects in the database were anonymous, informed consent and ethical approval were not required. One author (Zhao DM) was approved to extract data from the database after finishing the online training for the Collaborative Institutional Training Initiative (CITI) program of the National Institutes of Health (NIH) (Record ID: 36309330).

Patient Selection

According to the Ninth Revision of International Classification of Disease (ICD-9) diagnosis codes (410.00–410.92), all intensive care unit (ICU) patients in the database diagnosed with AMI were included. And patients were excluded according to: (1) patients with repeated ICU admissions (n=892); (2) either BUN or albumin values missing at admission (n=2152); (3) less than 24 hours of ICU stay (n=182); (4) patients in the metavision system (n=861). Finally, a total of 1827 patients were included in the study and these patients were followed-up for at least four years.

Data Collection and Outcomes

Structured Query Language (SQL) was used to extract the clinical data of all eligible patients and pgAdmin4 was employed as the administrative platform. Demographics included age and gender. Vital signs included heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate, temperature and saturation of percutaneous oxygen (SpO2). Comorbidities included hypertension, chronic obstructive pulmonary disease (COPD), diabetes, HF, hyperlipidemia, chronic kidney disease (CKD) and atrial fibrillation (AF). Laboratory parameters included white blood cell (WBC), hemoglobin, hematocrit, platelet, glucose, creatinine and the BAR was calculated by dividing the BUN by the albumin. Scoring systems included sequential organ failure assessment (SOFA), acute physiology score III (APS III) and systemic inflammatory response syndrome (SIRS). Clinical interventions included vasoactive use (dopamine, epinephrine and norepinephrine), mechanical ventilation, renal replacement treatment, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). And the first recorded vital signs and laboratory parameters after admission were used for analysis. The missing values of continuous variables were all less than 5% and replaced with median values (Table S1). The primary outcome was four-year all-cause mortality, and total length of ICU stay, Hospital mortality, one-, two-, three-year mortality were also secondary outcomes.

Statistical Analysis

Patients were divided into the low BAR group and high BAR group according to the optimal cutoff value of BAR determined by X-tile software (Version 3.6.1, Yale University School of Medicine). Continuous variables were analyzed

using *t*-test or Mann–Whitney *U*-test based on the distribution of variables, and presented as mean ± standard deviation (SD) or median (interquartile range, IQR). Categorical variables were expressed as numbers (percentages) and chi-square test or Fisher's exact test were used for comparison. Propensity score matching (PSM) (1:1) was performed to balance the selection bias and potential confounding factors between the low and high BAR groups. A multivariable logistic model with a caliper width of 0.02 was conducted and the propensity score was calculated based on baseline characteristics including demographics, vital signs, comorbidities, laboratory parameters, scoring systems and clinical interventions. Finally, 312 matched pairs were generated.

In both unmatched and matched cohort, survival curves were estimated using Kaplan-Meier method, and the differences between two groups were detected using Log rank test. To further explore the association between BAR and four-year all-cause mortality, Cox proportional hazard model was employed in unmatched cohort. Variables in the univariate regression model with $p<0.1$ were selected into the multivariable regression model, and the results were presented as hazard ratio (HR) with 95% confidence interval (CI). The receiver operating characteristic (ROC) curves were constructed to evaluate the predictive value of BAR for four-year mortality of AMI patients. Subgroup analysis was conducted to further assess the role of BAR on the outcomes in subsets of participants using a stratified Cox proportional-hazards regression model.

All analysis was performed by STATA V.14.0, SPSS Statistics 25 (IBM, Chicago, IL), RStudio software (Version 1.2.5001) and GraphPad Prism 8. All tests were two-sided and a p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

The MIMIC III database contained 5914 patients with a diagnosis of AMI, and 1827 patients were finally enrolled in our study. The details of selection was shown in the Figure 1. The BAR levels in patients with AMI were statistically significant in the non-survival group compared to the survival group [non-survival vs survival, in-hospital: 11.06 (7.00–18.59) vs 7.24 (4.69–12.00), $p<0.001$; one-year: 10.95 (7.33–17.83) vs 6.48 (4.41–10.30), $p<0.001$; two-year: 10.65 (7.14–17.35) vs 6.19 (4.29–9.58), $p<0.001$; three-year: 10.51 (7.10–17.11) vs 5.94 (4.18–9.18), $p<0.001$; four-year: 10.42 (7.00–16.71) vs 5.90 (4.14–9.09), $p<0.001$, respectively] (Figure 2).

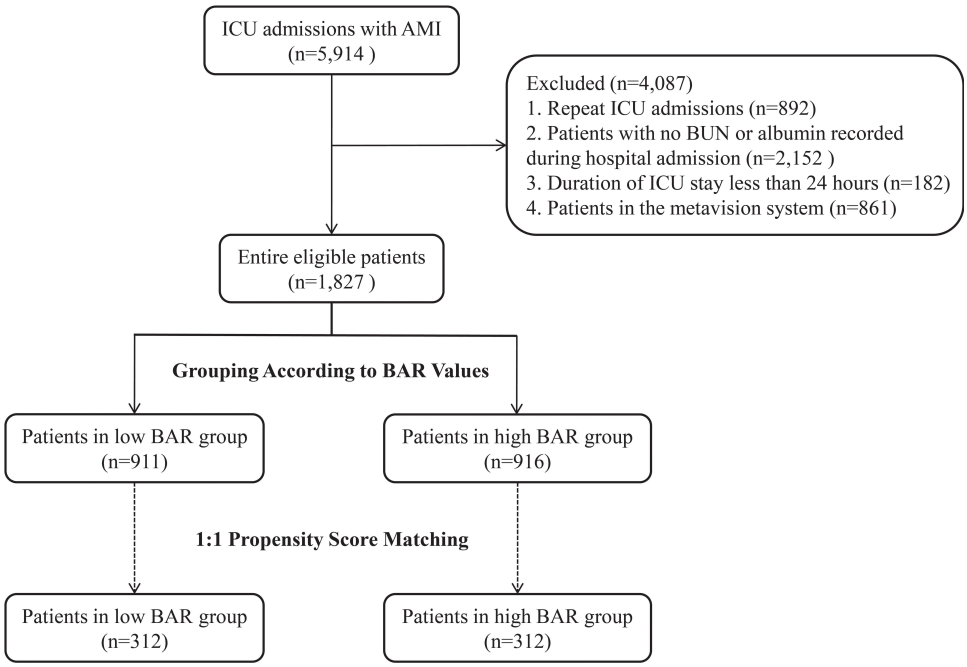

Figure 1 Research flowchart.
Abbreviations: ICU, intensive care unit; AMI, acute myocardial infarction; BUN, blood urea nitrogen; BAR, blood urea nitrogen to albumin ratio.

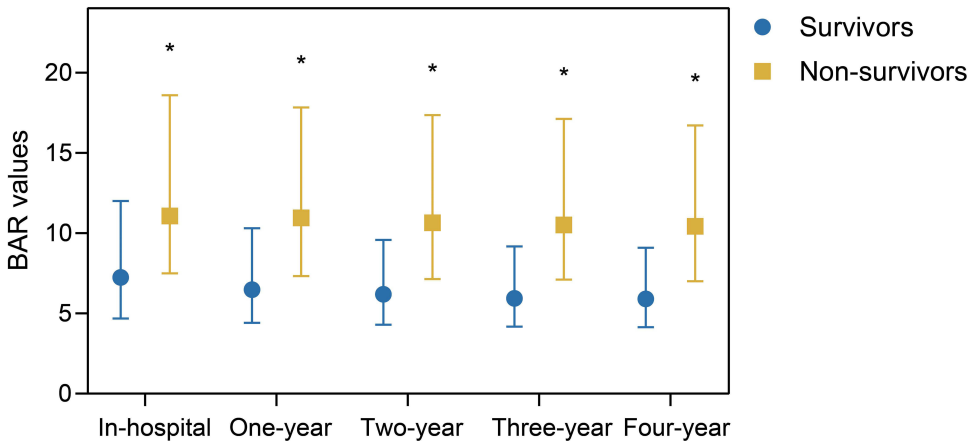

Figure 2 BAR levels in survivors and non-survivors at different follow-up times. The median (interquartile range) BAR values are statistically different between survivors and non-survivors at different follow-up times. [non-survival vs survival, In-hospital: 11.06 (7.00–18.59) vs 7.24 (4.69–12.00), p<0.001; one-year: 10.95 (7.33–17.83) vs 6.48 (4.41–10.30), p<0.001; two-year: 10.65 (7.14–17.35) vs 6.19 (4.29–9.58), p<0.001; three-year: 10.51 (7.10–17.11) vs 5.94 (4.18–9.18), p<0.001; four-year: 10.42 (7.00–16.71) vs 5.90 (4.14–9.09), p<0.001, respectively], BAR, blood urea nitrogen to albumin. *p<0.001.

With the help of X-tile software, the optimal cutoff value of BAR for four-year mortality was determined as 7.83 mg/g, and the whole cohort was then divided into a low BAR group (≤7.83, n=911) and a high BAR group (>7.83, n=916). The baseline characteristics of each group were shown in Table 1. The results revealed that compared to the low BAR group, patients in the high BAR group were at a more advanced age (p<0.001), more likely to have a history of COPD (p=0.035), diabetes (p<0.001), HF (p<0.001), CKD (p<0.001) and AF (p=0.001), and had a higher level of respiratory rate (p<0.001), glucose (p<0.020), creatinine (p<0.001), SOFA score (p<0.001) and APS III score (p<0.001). Besides, clinical interventions such as vasoactive use and renal replacement treatment were more frequent in high BAR group (both p<0.001). However, more patients in the low BAR group underwent PCI or CABG (both p<0.001).

Prognostic Role of BAR Before PSM

As shown in Table 2, patients in the high BAR group had a longer duration of ICU stay [5.35 (2.94–10.25) vs 3.48 (2.02–7.01), p<0.001] and a higher rate of in-Hospital mortality [26.09% (239/916) vs 9.55% (87/911), p<0.001], one-year mortality [51.86% (475/916) vs 21.08% (192/911), p<0.001], two-year mortality [61.24% (561/916) vs 25.91% (236/911), p<0.001], three-year mortality [67.14% (615/916) vs 29.31% (267/911), p<0.001] and four-year mortality [69.98% (641/916) vs 32.38% (295/911), p<0.001], compared to the low BAR group. The Kaplan-Meier analysis in unmatched cohort also showed a poorer survival rate in the high BAR group during a four-year follow-up (p<0.001) (Figure 3A).

After that a univariate Cox proportional hazard model was performed to screen the predictors of four-year mortality in AMI patients. Most variables except SBP, diabetes, platelet and mechanical ventilation were identified as risk factors in long-term mortality in AMI. Then variables with a p value <0.1 were selected to enter into the multivariate Cox regression analysis. The results of both univariate and multivariate analysis were presented in Table 3 and showed that BAR [HR 1.478, 95% CI (1.254–1.74), p<0.001] and other variables including age [HR 1.036, 95% CI (1.030–1.042), p<0.001], male [HR 1.203, 95% CI (1.050–1.378), p=0.008], respiratory rate [HR 1.025, 95% CI (1.008–1.043), p=0.004], hyperlipidemia [HR 0.751, 95% CI (0.634–0.891), p=0.001], AF [HR 1.218, 95% CI (1.063–1.395), p=0.004], hemoglobin [HR 0.874, 95% CI (0.810–0.944), p=0.001], hematocrit [HR 1.027, 95% CI (1.001–1.054), p=0.040], creatinine [HR 1.054, 95% CI (1.012–1.097), p=0.010], APS III scores [HR 1.009, 95% CI (1.005–1.013), p<0.001], vasoactive use [HR 1.461, 95% CI (1.273–1.676), p<0.001], PCI [HR 0.680, 95% CI (0.579–0.797), p<0.001] and CABG [HR 0.427, 95% CI (0.349–0.522), p<0.001] were independently associated with four-year mortality after AMI.

To further access the association between the preoperative BAR and four-year mortality, subgroup analysis stratified by age, gender and various comorbidities in unmatched cohort was performed and p for interaction was calculated

Table 1 Baseline Characteristics of Patients Categorized According to BAR Levels

Characteristics	Unmatched Cohort		p	Matched Cohort		p
	Low BAR Group (≤ 7.83 mg/g) (n = 911)	High BAR Group (>7.83 mg/g) (n =916)		Low BAR Group (≤ 7.83 mg/g) (n = 312)	High BAR Group (>7.83 mg/g) (n = 312)	
Demographics						
Age (years)	68.43 (58.29, 78.03)	76.19 (66.54, 83.47)	<0.001	75.42 (65.55, 82.78)	74.81 (64.39, 82.44)	0.637
Male, n (%)	556 (61.03%)	523 (57.10%)	0.087	176 (56.41%)	167 (53.53%)	0.469
Vital signs						
Heart rate (beats/min)	84.12 (73.93, 93.42)	83.03 (73.61, 94.72)	0.956	84.54 (74.39, 94.12)	83.62 (74.46, 94.18)	0.763
SBP (mmHg)	112.00 (103.73, 123.25)	112.00 (103.05, 125.38)	0.563	112.78 (103.08, 124.85)	112.22 (103.18, 124.81)	0.852
DBP (mmHg)	58.83 (53.38, 64.93)	54.89 (49.19, 61.16)	<0.001	56.63 (51.50, 62.90)	56.80 (51.47, 62.93)	0.814
Respiratory rate (beats/min)	18.17 (16.14, 20.36)	18.69 (16.38, 21.95)	<0.001	18.51 (16.29, 21.07)	18.08 (16.03, 21.40)	0.368
Temperature (°C)	36.91 (36.59, 37.28)	36.80 (36.42, 37.21)	<0.001	36.84 (36.49, 37.25)	36.86 (36.50, 37.25)	0.892
SpO_2 (%)	97.83 (96.61, 98.77)	97.68 (96.27, 98.65)	0.017	97.84 (96.40, 98.78)	97.84 (96.49, 98.66)	0.920
Comorbidities, n (%)						
Hypertension	464 (50.93%)	282 (30.79%)	<0.001	125 (40.06%)	128 (41.03%)	0.807
COPD	131 (14.38%)	165 (18.01%)	0.035	56 (17.95%)	60 (19.23%)	0.681
Diabetes	244 (26.78%)	376 (41.05%)	<0.001	105 (33.65%)	102 (32.69%)	0.799
Heart failure	428 (46.98%)	605 (66.05%)	<0.001	185 (59.29%)	184 (58.97%)	0.935
Hyperlipidemia	302 (33.15%)	186 (20.31%)	<0.001	72 (23.80%)	74 (23.72%)	0.850
Chronic kidney disease	27 (2.96%)	144 (15.72%)	<0.001	18 (5.77%)	25 (8.01%)	0.269
Atrial fibrillation	277 (30.41%)	344 (37.55%)	0.001	115 (36.86%)	117 (37.50%)	0.868
Laboratory parameters						
White blood cell (10^9 /L)	10.50 (8.00, 13.80)	11.10 (7.80, 15.28)	0.080	10.45 (7.40, 14.60)	10.75 (7.60, 14.60)	0.824
Hemoglobin (g/dL)	12.30 (10.90, 13.50)	10.80 (9.70, 12.00)	<0.001	11.50 (10.20, 12.60)	11.50 (10.30, 12.70)	0.771
Hematocrit (%)	35.70 (32.00, 38.90)	32.25 (28.80, 35.60)	<0.001	33.90 (30.53, 36.70)	33.60 (30.20, 37.60)	0.795
Platelet (10^9 /L)	232.00 (183.00, 285.00)	212.00 (160.00, 273.00)	<0.001	218.00 (169.00, 270.75)	213.50 (166.25, 287.00)	0.952
Glucose (mg/dL)	135.00 (110.00, 184.00)	145.00 (108.25, 201.00)	0.020	141.50 (113.25, 200.25)	142.50 (111.00, 206.50)	0.949
Creatinine (mg/dL)	0.90 (0.70, 1.10)	1.60 (1.20, 2.70)	<0.001	1.10 (0.90, 1.30)	1.10 (0.90, 1.40)	0.193
Scoring systems						
SOFA scores	3.00 (2.00, 5.00)	6.00 (4.00, 8.00)	<0.001	5.00 (3.00, 7.00)	5.00 (3.00, 7.00)	0.826
APS III scores	37.00 (28.00, 46.00)	54.00 (44.00, 66.75)	<0.001	45.00 (35.25, 58.00)	46.00 (37.25, 57.00)	0.316
SIRS scores	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.109	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.706
Clinical interventions						
Vasoactive use, n (%)	306 (33.59%)	426 (46.51%)	<0.001	137 (43.91%)	131 (41.99%)	0.628
Mechanical ventilation, n (%)	488 (53.57%)	490 (53.49%)	0.975	172 (55.13%)	178 (57.05%)	0.628
Renal replacement treatment, n (%)	9 (0.99%)	87 (9.50%)	<0.001	4 (1.28%)	7 (2.24%)	0.361
PCI, n (%)	317 (34.80%)	222 (24.24%)	<0.001	94 (30.13%)	101 (32.37%)	0.545
CABG, n (%)	339 (37.21%)	163 (17.79%)	<0.001	76 (24.36%)	75 (24.04%)	0.926

Notes: Normally distributed data are presented as the mean ± SD; non-normally distributed data are presented as median (IQR), and categorical variables are presented as n (%). P values were calculated based on *t*-test or Mann–Whitney *U*-test for continuous variables, and chi-square test or Fisher's exact test for categorical variables.

Abbreviations: BAR, blood urea nitrogen to albumin ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment; APS III, acute physiology score III; SIRS, systemic inflammatory response syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

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Table 2 Clinical Outcomes of Patients with AMI

	Unmatched Cohort			Matched Cohort		
	Low BAR Group (≤ 7.83 mg/g) (n = 911)	High BAR Group (>7.83 mg/g) (n = 916)	p	Low BAR Group (≤ 7.83 mg/g) (n = 312)	High BAR Group (>7.83 mg/g) (n = 312)	p
Clinical outcomes						
ICU stay, days	3.48 (2.02, 7.01)	5.35 (2.94, 10.25)	<0.001	4.22 (2.20, 9.59)	5.85 (3.09, 11.82)	0.001
Hospital mortality, n (%)	87 (9.55%)	239 (26.09%)	<0.001	53 (16.99%)	74 (23.72%)	0.037
1-year mortality, n (%)	192 (21.08%)	475 (51.86%)	<0.001	108 (34.62%)	132 (42.31%)	0.048
2-year mortality, n (%)	236 (25.91%)	561 (61.24%)	<0.001	127 (40.71%)	161 (51.60%)	0.006
3-year mortality, n (%)	267 (29.31%)	615 (67.14%)	<0.001	140 (44.87%)	180 (57.69%)	0.001
4-year mortality, n (%)	295 (32.38%)	641 (69.98%)	<0.001	156 (50.00%)	192 (61.54%)	0.004

Notes: Clinical outcomes before and after PSM were compared between the low BAR and high BAR groups.
Abbreviations: AMI, acute myocardial infarction; BAR, blood urea nitrogen to albumin ratio; ICU, intensive care unit; PSM, propensity score matching.

(Figure 4). Our results showed that the effect of BAR on four-year mortality after AMI were consistently significant in most subgroups without obvious interactions.

Prognostic Role of BAR After PSM

The baseline characteristics of the patients enrolled in the two groups were unbalanced. Therefore, a 1:1 ratio PSM was performed and 312 patients in the high BAR group and 312 patients in the low BAR group were enrolled in the matched cohort. The baseline characteristics were well balanced between the two groups, as shown in Table 1. After PSM, the difference in each outcome between the two groups was still statistically significant. Patients in the high BAR group were associated with prolonged ICU stay [5.85 (3.09–11.82) vs 4.22 (2.20–9.59), p=0.001] and a higher rate of in-hospital mortality [23.72% (74/312) vs 16.99% (53/312), p=0.037], one-year mortality [42.31% (132/312) vs 34.62% (108/312), p=0.048], two-year mortality [51.60% (161/312) vs 40.71% (127/312), p=0.006], three-year mortality [57.69% (180/312)

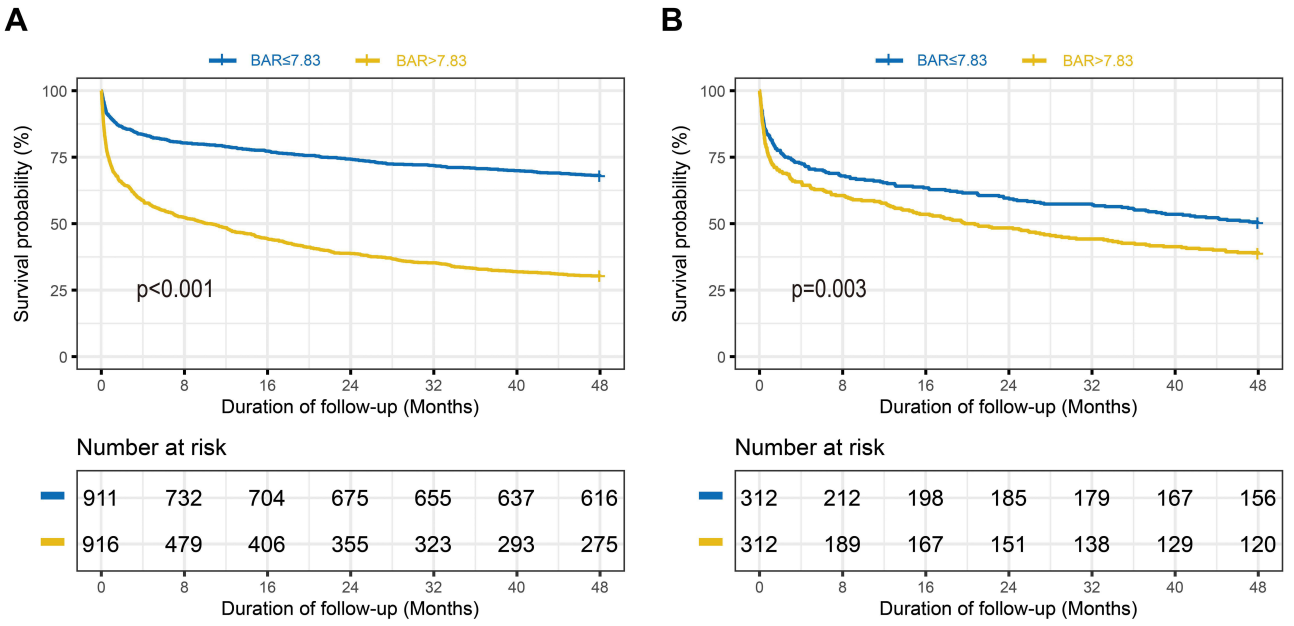

Figure 3 Kaplan-Meier survival curves for four-year overall survival. A significantly lower four-year survival probability can be identified in the higher BAR group in patients before (**A**) and after (**B**) PSM. P-value was calculated by Log rank test.
Abbreviations: BAR, blood urea nitrogen to albumin ratio; PSM, propensity score matching.

Table 3 Univariate and Multivariate Cox Regression Analyses for Four-Year All-Cause Mortality in Patients with AMI

Variables	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	p	Hazard Ratio (95% CI)	p
Demographics				
Age (years)	1.046 (1.040–1.052)	<0.001	1.036 (1.030–1.042)	<0.001
Male, n (%)	0.863 (0.758–0.982)	0.025	1.203 (1.050–1.378)	0.008
Vital signs				
Heart rate (beats/min)	1.008 (1.003–1.012)	0.001	Not selected	–
SBP (mmHg)	1.000 (0.996–1.004)	0.924	–	–
DBP (mmHg)	0.973 (0.966–0.980)	<0.001	Not selected	–
Respiratory rate (beats/min)	1.065 (1.048–1.083)	<0.001	1.025 (1.008–1.043)	0.004
Temperature (°C)	0.834 (0.745–0.933)	0.002	Not selected	–
SpO_2 (%)	0.944 (0.909–0.980)	0.003	Not selected	–
Comorbidities, n (%)				
Hypertension	0.612 (0.534–0.702)	<0.001	Not selected	–
COPD	1.428 (1.216–1.677)	<0.001	Not selected	–
Diabetes	1.017 (0.889–1.164)	0.805	–	–
Heart failure	1.769 (1.545–2.026)	<0.001	Not selected	–
Hyperlipidemia	0.506 (0.429–0.597)	<0.001	0.751 (0.634–0.891)	0.001
Chronic kidney disease	1.456 (1.194–1.775)	<0.001	Not selected	–
Atrial fibrillation	1.454 (1.276–1.658)	<0.001	1.218 (1.063–1.395)	0.004
Laboratory parameters				
White blood cell (10^9 /L)	1.012 (1.001–1.023)	0.040	Not selected	–
Hemoglobin (g/dL)	0.828 (0.801–0.855)	<0.001	0.874 (0.810–0.944)	0.001
Hematocrit (%)	0.952 (0.942–0.963)	<0.001	1.027 (1.001–1.054)	0.040
Platelet (10^9 /L)	1.000 (0.999–1.001)	0.681	–	–
Glucose (mg/dL)	1.001 (1.000–1.002)	0.026	Not selected	–
Creatinine (mg/dL)	1.158 (1.125–1.193)	<0.001	1.054 (1.012–1.097)	0.010
Scoring systems				
SOFA scores	1.121 (1.100–1.143)	<0.001	Not selected	–
APS III scores	1.024 (1.021–1.027)	<0.001	1.009 (1.005–1.013)	<0.001
SIRS scores	1.140 (1.069–1.216)	<0.001	Not selected	–
Clinical interventions				
Vasoactive use, n (%)	1.539 (1.353–1.750)	<0.001	1.461 (1.273–1.676)	<0.001
Mechanical ventilation, n (%)	1.063 (0.934–1.208)	0.354	–	–
Renal replacement treatment, n (%)	1.902 (1.497–2.417)	<0.001	Not selected	–
PCI, n (%)	0.676 (0.582–0.785)	<0.001	0.680 (0.579–0.797)	<0.001
CABG, n (%)	0.348 (0.291–0.417)	<0.001	0.427 (0.349–0.522)	<0.001
BAR > 7.83 mg/g	3.076 (2.677–3.533)	<0.001	1.478 (1.254–1.740)	<0.001

Notes: Univariate Cox proportional hazard model was performed and variables with a p value <0.1 were selected to enter into the multivariate Cox regression analysis.
Abbreviations: AMI, acute myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment; APS III, acute physiology score III; SIRS, systemic inflammatory response syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

vs 44.87% (140/312), p=0.001] and four-year mortality [61.54% (192/312) vs 50.00% (156/312), p=0.004] (Table 2). As for survival analysis, the survival rate of the high BAR group was lower than that of the low BAR group during a four-year follow-up (p=0.003) (Figure 3B).

Prognostic Predictive Value of BAR

The prognostic and predictive value of BAR for four-year mortality after AMI was evaluated using ROC curve analysis. Compared with SOFA score [0.6364, 95% CI (0.6111–0.6616), p<0.001], APS III score [0.7015, 95% CI (0.6776–0.7255), p<0.001] and SIRS score [0.5388, 95% CI (0.5124–0.5652), p=0.004], BAR had a larger area under the curve

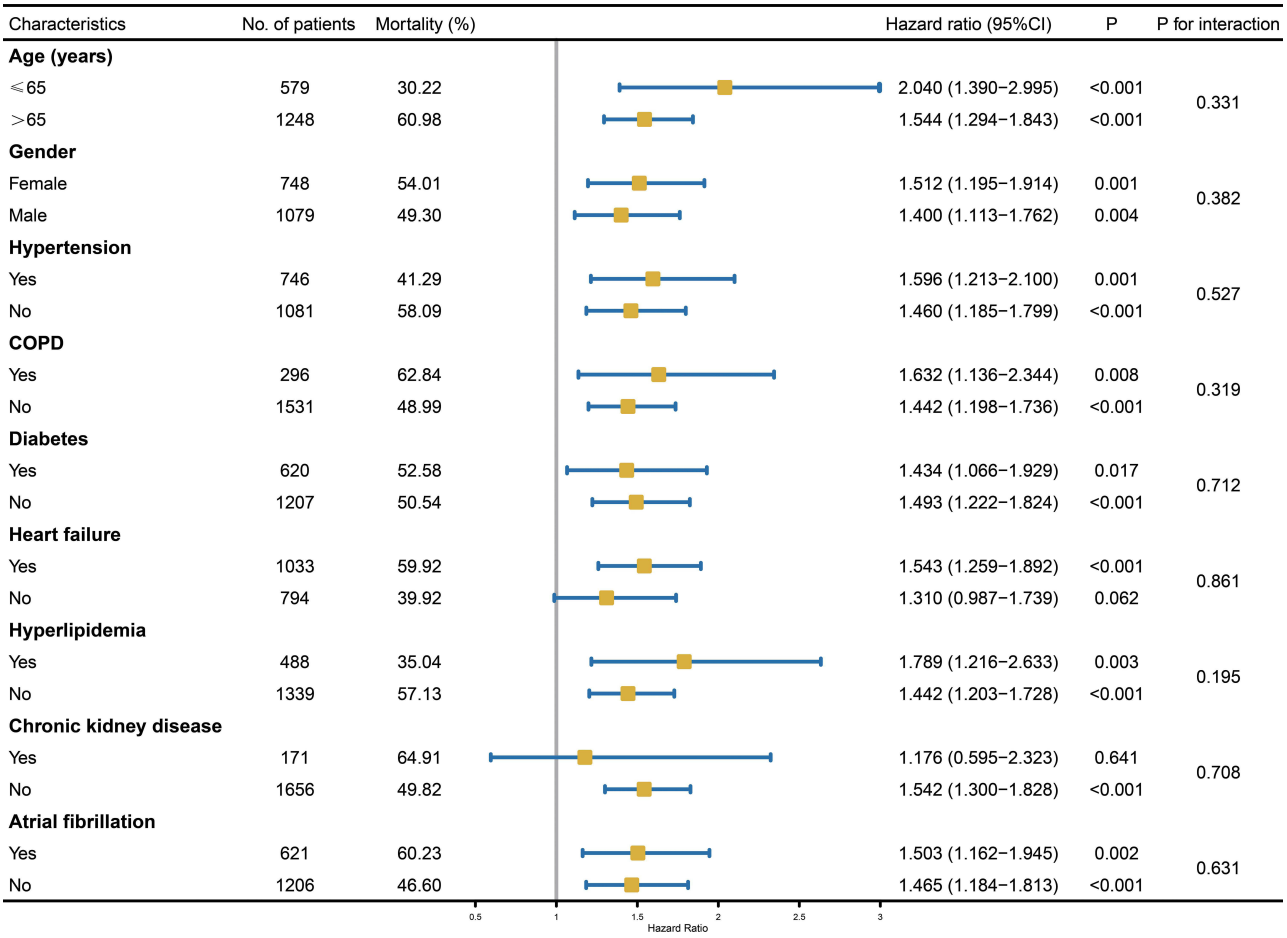

Figure 4 Multivariate-adjusted hazard ratios and 95% confidence intervals for four-year all-cause mortality in patients with high BAR values versus low BAR values according to subgroups of baseline characteristics.
Abbreviation: COPD, chronic obstructive pulmonary disease.

(AUC) [0.7351, 95% CI (0.7124–0.7579), p<0.001] (Figure 5A). In addition, the ROC of prediction model based on multivariate Cox regression analysis was also plotted (Figure 5B) and the AUC of ROC was 0.8216 [95% CI (0.8026–0.8405), p<0.001]. When the maximum value of the Youden index reached 0.5050, at this time the sensitivity of the model was 0.7575, and the specificity was 0.7475.

Discussion

The present study investigated the relationship between BAR and four-year all-cause mortality among patients with a history AMI. A higher BAR on admission to ICU was significantly associated with an increased risk of four-year mortality in AMI patients. And BAR could serve as an independent predictive factor of four-year mortality after AMI. After adjustment for covariates through PSM, long-term mortality remained statistically different between the high and low BAR groups and the K-M curve also presented a poorer long-term survival in the high BAR group. To the best of our knowledge, this is the first and largest study exploring the relationship between BAR and long-term mortality in patients with AMI.

The multivariable Cox regression analysis suggested that hyperlipidemia was associated with lower mortality in patients with AMI. According to our knowledge, several factors might be associated with the above results. First, patients with hyperlipidemia are more likely to use statins to help lower cholesterol levels in the blood. Statins not only reduce low-density lipoprotein cholesterol (LDL-C) levels, but also delay coronary atherosclerotic lesions through anti-inflammatory, antioxidant, and antithrombotic effects, thereby reducing long-term mortality in patients with AMI. Studies have shown that the use of statins can reduce the probability of recurrence of cardiovascular events and improve long-term survival.[19–21]

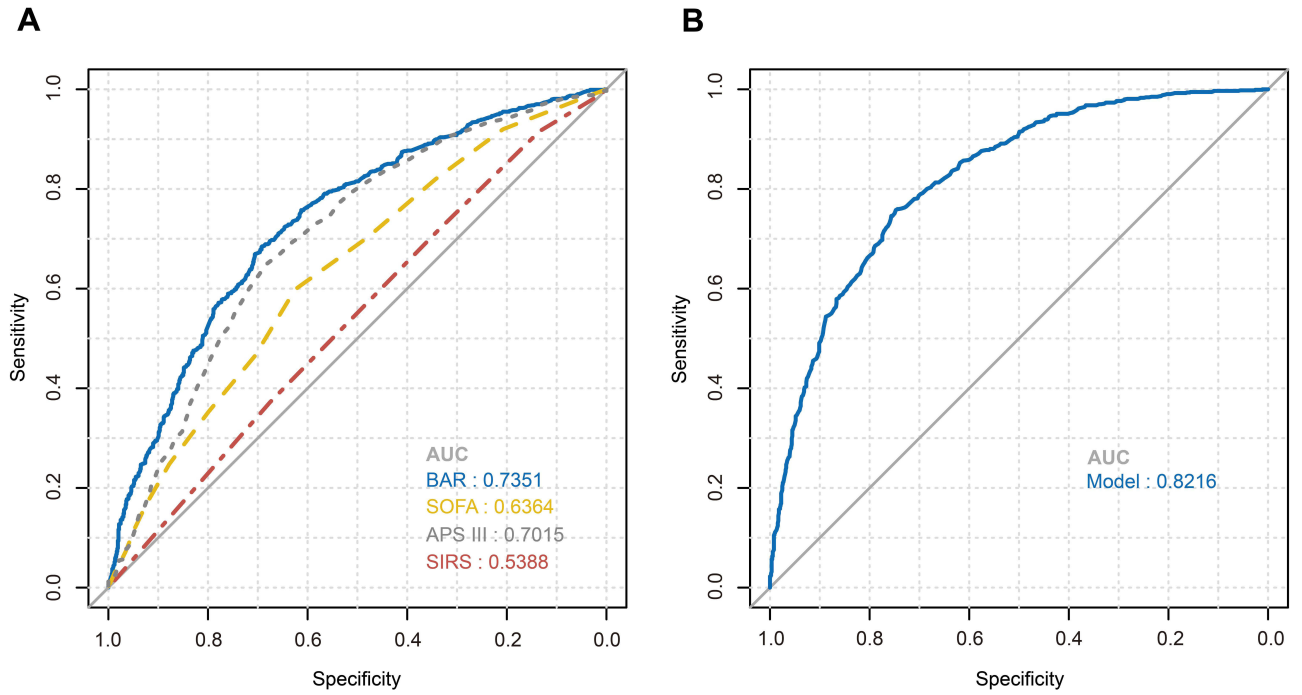

Figure 5 The ROC curves analysis. Comparison of AUCs among BAR, SOFA, APS III and SIRS in the entire cohort (**A**). The AUC of predictive model incorporated BAR based on multivariate Cox regression analysis in the entire cohort (**B**).
Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; BAR, blood urea nitrogen to albumin ratio; SOFA, sequential organ failure assessment; APS III, acute physiology score III; SIRS, systemic inflammatory response syndrome.

Hyperlipidemia itself has some of the protective properties of statins such as neutralizing free radicals and endothelial protection.[22,23] Besides, hyperlipidemia might be a general marker for better treatment of acute myocardial infarction patients after admission. Thus, hyperlipidemia may be associated with a lower risk of death in acute myocardial infarction patients. The identification of patients with HF is fundamental for the evaluation of the prognostic impact of BAR on mortality. HF complicated one fifth of the AMI events and had a significant impact on long-term mortality.[24] Congestion is a key feature of HF and related to a poor prognosis.[25] Studies have confirmed that a variety of biomarkers of "hemodynamic" congestion, such as brain natriuretic peptide (BNP), estimated plasma volume status (ePVS), bioimpedance vector analysis (BIVA), and blood urea nitrogen to creatinine ratio (BUN/Cr), could be used as prognostic factors of HF.[26,27] And BAR might have a better performance in predicting long-term mortality after AMI by incorporating with these biomarkers. Pharmacological treatment during hospitalization may impact the prognosis of patients. In our study, both univariate and multivariate Cox regression analyses showed that vasoactive use were independently associated with four-year mortality after AMI. When a patient with acute myocardial infarction manifesting with shock fails to respond to aggressive administrations of fluids, vasoactive agents should be considered to stabilize hemodynamic variables with adequate tissue perfusion. Therefore, the use of vasoactive agents indicates that the patient had a worse condition. It had been suggested that Vasoactive Inotropic Score (VIS), an objective measure of the magnitude of vasoactive agent support, was a predictor of clinical outcomes in cardiac surgery.[28] In addition, VIS was significantly associated with increased in-hospital mortality in adult patients with cardiogenic shock.[28] The results of our study were consistent with the previous evidence.

Renal insufficiency is associated with hypertension, diabetes mellitus, and MI.[29] And patients with renal insufficiency are at an increased risk for major adverse cardiovascular outcomes such as AMI.[30] Granger et al found that the creatinine level was an important marker of in-hospital death in patients with acute coronary syndrome (ACS) in the Global Registry of Acute Coronary Events (GRACE).[31] The estimated glomerular filtration rate (eGFR), an another indicator of kidney function, has also been shown to be associated with the prognosis of AMI.[9] However, several studies suggested that the estimated GFR, as measured by creatinine, was not a precise reflection of kidney function.[32,33] BUN is an end product of protein metabolism normally excreted via the kidney. And several other factors such as systemic

hypoperfusion, low cardiac output and neurohormonal activation also affect the concentration of BUN, which often occurs in the acute phase of myocardial infarction.[14,34] Therefore, in patients with AMI, BUN reflects not only cardiorenal function but also neurohumoral activation. Saygitov et al showed that the increased level of BUN rather than creatinine was a more important risk factor for adverse outcomes in ACS.[35] Smith et al suggested that BUN was an independent predictor in patients with various cardiovascular diseases.[36] Other studies also found that BUN was correlated with a worse prognosis in patients with acute decompensated heart failure (ADHF), stroke and AF.[37–39]

The role of albumin in cardiovascular diseases has received burgeoning attention recently. After a ten-year follow-up, Plakht et al revealed that decreased albumin level was significantly associated with long-term all-cause mortality in hospital survivors of AMI.[15] Yang et al demonstrated that low albumin level on admission was an independent predictor of long-term all-cause, cardiovascular and cardiac mortality in patients with first-onset AMI.[40] Several potential mechanisms might be responsible for this association. There is accumulating evidence suggesting that inflammation plays an important role throughout the atherosclerotic process.[41,42] Physiological concentrations of albumin selectively inhibited vascular cell adhesion molecule-1 (VCAM-1) expression and monocyte adhesion induced by tumor necrosis factor-α (TNF-α) in human aortic endothelial cells (HAECs), showing anti-inflammatory effects.[43] As important factors in risk stratification after AMI, inflammatory biomarkers such as C-reactive protein and lipoprotein-associated phospholipase A2 are associated with hypoalbuminemia.[44,45] Besides, albumin is an important extracellular antioxidant. In the presence of hypoalbuminemia, free radicals and reactive oxygen species (ROS) are significantly increased, which leads to worse long-term outcomes in AMI patients.[46] In addition, albumin could protect endothelial cell function, maintain vascular integrity, inhibit platelet activation and coagulation, and finally reduce the occurrence of thrombotic events.[47] Moreover, AMI patients with hypoalbuminemia are prone to developing heart failure (HF), which might increase long-term risk of cardiovascular mortality.[15]

In this study, we calculated the ratio of BUN to albumin and explored the relationship between BAR and long-term outcome in AMI patients. An independent predictive ability of BAR for four-year mortality following AMI was identified. In addition, the AUC value of BAR is higher than that of APS III score, SOFA score and SIRS score, and BAR could be calculated easily and quickly in routine clinical practice. Moreover, we found that the BAR-based predictive model also had a more favorable prognostic efficiency for 4-year mortality. Thus, BAR might serve as an additional factor with the ability to increase the predictive value of present risk models such as the Global Registry of Acute Coronary Events (GRACE) risk score.

Limitations

Nevertheless, there were several limitations within this study. First, this was a single-center retrospective study based on the MIMIC III database, in which potential selection bias was inevitable. In addition, the applicability of our results to other cohorts remains to be validated. Second, a large number of patients were admitted without BUN or albumin results, which could lead to selection bias. Third, this study only included BUN and albumin records from the first admission of eligible patients, and the prognostic effect of dynamic changes in BAR remains unclear. Fourth, although we used PSM to balance the covariates between the two groups, there were influencing variables that we did not take into account. Fifth, some important variables such as the types of HF, number of involved vessels, type of stents were not available because of the shortcoming of MIMIC III database. Last, we mainly investigated the association between BAR and long-term mortality in AMI patients. It was reported that more complications and deaths occurred within 24 hours after ICU admission, so the predictive value of BAR in this scenario is questionable.

Conclusions

In conclusion, our study showed that a higher BAR value was associated with a higher risk of long-term death in patients with AMI. The BAR could be used as an independent predictor for four-year mortality in AMI patients. Meanwhile, well-designed, prospective, multicenter studies including long-term follow-up are needed to validate our findings.

Data Sharing Statement

The clinical data used in this study were supplied by Monitoring in Intensive Care Database III version 1.4 (MIMIC-III v.1.4). Although the database is publicly and freely available, researchers must complete the online training course known as Data or Specimens Only Research to apply for permission to access the database.

Ethics Approval and Informed Consent

Our data are from a public research database. Since all subjects in the database were anonymous, informed consent and ethical approval were not required. Besides, Institutional Ethics Committee of Shandong Provincial Hospital have exempted this study from approval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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