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Blood Urea Nitrogen to Serum Albumin Ratio as A New Prognostic Indicator in Critically Ill Patients with Diabetic Ketoacidosis: A Retrospective Cohort Study

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Abstract:
Purpose: Diabetic ketoacidosis (DKA) remains a life-threatening medical emergency. Blood urea nitrogen to serum albumin (BAR) demonstrated good predictive ability in the mortality of patients with various diseases. The study aimed to investigate the predictive value of BAR for in- and out-of-hospital mortality in critically ill patients with DKA.
Methods: Data were obtained from the Medical Information Mart for Intensive Care III (MIMIC-III) database and all the eligible subjects were divided into two groups by a cutoff value of BAR. The multiple logistic regression analysis was conducted to determine the association between BAR and in-hospital mortality. The predictive performance of BAR was evaluated by Kaplan–Meier (K-M) analysis. Propensity score matching (PSM) was applied to control confounding factors between the low BAR and high BAR groups.
Results: A total of 589 critically ill DKA patients were enrolled. DKA patients with a higher BAR level were associated with higher in-hospital mortality and out-hospital mortality (all $p<0.001$). There was a significant four-year survival difference between the low and high BAR groups ($p<0.0001$). After PSM analysis, two PSM groups (202 pairs, $n = 404$) were generated, and similar results were observed in the K-M curve ($p<0.0001$).
Conclusions: Elevated levels of BAR were associated with an increased risk of in-hospital mortality in critically ill patients with DKA, and BAR could be an independent prognostic factor in in-hospital mortality and out-hospital mortality for patients diagnosed with DKA.

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Table 2 the characteristics associated with the in-hospital mortality among critically ill DKA patients

Variables	P value	Odds Ratio	Lower CI	Upper CI
Age	<0.001	1.0542	1.0282	1.0827
Mechanical ventilation	<0.001	10.8451	4.5882	26.9192
Urine output	0.007	0.9994	0.9990	0.9998
Mean temperature	0.028	0.4316	0.2052	0.9187
Mean arterial pressure	0.162	0.9713	0.9311	1.0103
Mean respiratory rate	<0.001	1.1835	1.0865	1.2879
BAR	<0.001	5.8351	2.3809	16.3961
Bicarbonate	0.17	1.0445	0.9823	1.1131
WBC	0.092	1.0355	0.9876	1.0792
Platelets	0.052	0.9959	0.9915	0.9998
Hemoglobin	0.041	0.8287	0.6886	0.9889
Blood glucose	0.024	0.9974	0.9949	0.9994
Sodium	0.007	1.0983	1.0263	1.1769
Chloride	0.01	1.0682	1.0173	1.1250
CHF	0.002	4.0220	1.6259	9.4916
Stroke	<0.001	13.0292	3.3015	44.0729
Malignancy	0.044	3.1940	0.8902	9.0636
Pneumonia	0.071	2.5808	0.8268	6.7620
Sepsis	0.004	4.1872	1.4508	10.6594

Abbreviations: BAR, blood urea nitrogen to albumin ratio; WBC, white blood cell; CHF, Congestive heart failure.

Table 3 Baseline Characteristics of Patients Categorized According to BAR Levels

Variables	Unmatched Cohort			Matched Cohort		
	Low group (n=387)	High group (n=202)	P value	Low group (n=202)	High group (n=202)	P value
Clinical parameters						
Age (y)	44.14(31.09-56.64)	56.51(46.69-66.33)	<0.001	53.31(41.29-63.11)	56.51(46.69-66.33)	0.038
Mechanical ventilation, n (%)	47 (12.1)	38 (18.8)	0.039	35 (17.3)	38 (18.8)	0.796
Urine output (ml)	2165(1425-3255)	1652(916-2480)	<0.001	1991(1280-2875)	1652(916-2480)	0.003
Use of NaHCO3, n (%)	28(7.2)	43(21.3)	<0.001	22 (10.9)	43(21.3)	0.007
Use of Albumin, n (%)	5(1.3)	9(4.5)	0.035	4 (2.0)	9(4.5)	0.259
Vital signs						
Mean temperature (°C)	36.89±0.50	36.77±0.654	0.017	36.92±0.51	36.77±0.64	0.008
Mean arterial pressure (mmHg)	80.52±10.66	81.27±11.84	0.433	81.63±11.23	81.27±11.84	0.757
Mean respiratory rate (min^{-1})	18.92±3.74	19.28±4.53	0.296	19.32±3.87	19.28±4.53	0.931
Comorbidities, n (%)						
Congestive heart failure	34(8.8)	53(26.2)	<0.001	28 (13.9)	53(26.2)	0.003
CKD	24(6.2)	72(35.6)	<0.001	24 (11.9)	72(35.6)	<0.001
Stroke	7(1.8)	6(3.0)	0.538	4 (2.0)	6(3.0)	0.749
Malignancy	18(4.7)	21(10.4)	0.013	15 (7.4)	21(10.4)	0.383
Pneumonia	31(8.0)	29(14.4)	0.023	20 (9.9)	29(14.4)	0.223
Sepsis	24(6.2)	26(12.9)	0.009	21 (10.4)	26(12.9)	0.535

Laboratory tests						
Serum pH	7.29(7.17-7.37)	7.305(7.2-7.38)	0.39	7.32 (7.21, 7.38)	7.305(7.2-7.38)	0.479
Bicarbonate (mEq/L)	18.26±7.13	18.07±6.36	0.749	18.30±6.94	18.07±6.36	0.735
Lactate (mmol/L)	1.9(1.4-2.95)	2.2(1.4-3.4)	0.19	2(1.50-3.10)	2.2(1.4-3.4)	0.541
Urine ketone, n (%)			<0.001			<0.001
Negative	97(25.1)	114(56.4)		67 (33.2)	114(56.4)	
Low	90(23.3)	66(32.7)		50 (24.8)	66(32.7)	
High	200(51.7)	22(10.9)		85 (42.1)	22(10.9)	
WBC (K/uL)	10.6(7.3-15.2)	12(8.7-14.7)	0.068	11.3(8.3-16.2)	12(8.7-14.7)	0.651
Lymphocyte (%)	11.8(7.1-18)	9(5.6-12.95)	<0.001	10(6.1-16)	9(5.6-12.95)	0.04
Platelets (K/uL)	279(215-368)	267.5(196-325)	0.017	270(199-342)	267.5(196-325)	0.475
Hemoglobin (g/dl)	12.76±2.34	11.46±2.36	<0.001	12.03±2.27	11.46±2.36	0.015
Blood glucose (mg/dl)	288(167-483)	382(179-707)	<0.001	308(200-571)	382(179-707)	0.062
Sodium (mEq/L)	137(133-140)	135.5(129-139)	0.0054	136(131-140)	135.5(129-139)	0.115
Chloride (mEq/L)	100(95-106)	99(89-105)	0.0028	100(93-106)	99(89-105)	0.105
Albumin (g/dL)	3.54±0.63	2.98±0.64	<0.001	3.45±0.66	2.98±0.64	<0.001
BUN (mg/dl)	17(12-24)	48(37-67)	<0.001	20(13-27)	48(37-67)	<0.001
Creatinine (mg/dl)	1(0.8-1.3)	2.3(1.6-4.3)	<0.001	1.2(0.8-1.6)	2.3(1.6-4.3)	<0.001
Scoring systems						
SAPSII	23(18-32)	35(29-42)	<0.001	28(21-38)	35(29-42)	<0.001
OASIS	24(20-31)	27(23-33)	<0.001	27(22-32)	27(23-33)	0.398
SOFA	2(1-3)	4(3-6)	<0.001	2(1-4)	4(3-6)	<0.001
APSIII	40(32-51)	53.5(46-65)	<0.001	43(33-56)	53.5(46-65)	<0.001

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: ICU, intensive care unit; CKD, chronic kidney disease; WBC, white blood cell; BUN, blood urea nitrogen; SAPSII, scoring systems included modified forms of the simplified acute physiology score; OASIS, Oxford acute severity of illness score; SOFA, sequential organ failure assessment; APS III, acute physiology score III.

Table 4 Clinical outcomes by BAR categories in critically ill patients with DKA

Clinical outcomes	Unmatched Cohort			Matched Cohort		
	Low group (n=387)	High group (n=202)	P value	Low group (n=202)	High group (n=202)	P value
Hospital mortality, n (%)	6(1.55)	17(8.42)	<0.001	5(2.48)	17(8.42)	0.009
ICU stay, hours	45(29-67)	48(28-85)	0.012	49(30-72)	48(28-85)	0.403
28-day mortality, n (%)	11(2.84)	23(11.39)	<0.001	10(4.95)	23(11.39)	0.018
90-day mortality, n (%)	16(4.13)	31(15.35)	<0.001	14(6.93)	31(15.35)	0.007
1-year mortality, n (%)	29(7.49)	59(29.21)	<0.001	19(9.41)	59(29.21)	<0.001
2-year mortality, n (%)	41(10.59)	71(35.15)	<0.001	27(13.37)	71(35.15)	<0.001
3-year mortality, n (%)	47(12.14)	79(39.11)	<0.001	32(15.84)	79(39.11)	<0.001
4-year mortality, n (%)	52(13.44)	88(43.56)	<0.001	36(17.82)	88(43.56)	<0.001

Abbreviations: BAR, blood urea nitrogen to albumin ratio; DKA, diabetic ketoacidosis; ICU, intensive care unit.

Table 1 Baseline characters of patients with DKA in-hospital survivors and non-survivors

Variable	All patients (n=589)	Survivors (n=566)	Non-survivors (n=23)	P value
Clinical parameters				
Age (y)	49.4(36.5-61.0)	48.5(36.3-60.5)	66.0(51.0-78.9)	<0.001
Gender (%, male)	290(49.2)	278(49.1)	12(52.2)	0.774
Ethnicity, n (%)				0.763
White	363(61.6)	349(61.7)	14(60.9)	
Black	127(21.6)	123(21.7)	4(17.4)	
Other	99(16.8)	94(16.6)	5(21.7)	
DM type, n (%)				0.920
T1DM	370(62.8)	355(62.7)	15(65.2)	
T2DM	216(36.7)	208(36.7)	8(34.8)	
Other	3(0.5)	3(0.5)	0(0)	
Weight(kg)	75(64.6-86.9)	75(64-87)	76.5(67-84.4)	0.659
Mechanical ventilation, n (%)	85(14.4)	71(12.5)	14(60.9)	<0.001
Urine output (ml)	1992(1250-3025)	2005(1280-3040)	1345(595-2375)	0.009
Use of NaHCO3, n (%)	71(12.1)	63(11.1)	8(34.8)	0.001
Use of Albumin, n (%)	14(2.4)	11(1.9)	3(13.0)	0.001
ICU stay time, hours	46(29-71)	45.5(28-69)	88(41-180)	<0.001
Vital signs[a]				
Mean temperature (°C)	36.8±0.6	36.9±0.5	36.6±1.2	0.031
Mean heartrate (min^{-1})	90.3±14.8	90.2±14.3	92.8±23.1	0.404
Mean arterial pressure (mmHg)	80.8±11.1	80.9±11.0	77.6±12.9	0.162
Mean respiratory rate (min^{-1})	19.0±4.0	18.9±3.9	22.4±5.4	<0.001
Comorbidities, n (%)				
Hypertension	194(32.9)	184(32.5)	10(43.5)	0.273
Congestive heart failure	87(14.8)	78(13.8)	9(39.1)	0.001
CKD	96(16.3)	90(15.9)	6(26.1)	0.195
Liver disease	27(4.6)	25(4.4)	2(8.7)	0.650
Stroke	13(2.2)	9(1.6)	4(17.4)	<0.001
Malignancy	39(6.6)	35(6.2)	4(17.4)	0.091
UTI	78(13.2)	74(13.1)	4(17.4)	0.776
Pneumonia	60(10.2)	55(9.7)	5(21.7)	0.062
Sepsis	50(8.5)	44(7.8)	6(26.1)	0.002
Laboratory tests[b]				
Serum pH	7.3(7.185-7.38)	7.3(7.18-7.38)	7.3(7.21-7.37)	0.008
Bicarbonate (mEq/L)	18.2±6.9	18.1±6.9	20.1±5.0	0.169
Lactate (mmol/L)	2(1.4-3.1)	1.9(1.4-3.1)	2.6(2-6.4)	0.003
Urine ketone, n (%)				0.001

Negative	211(35.8)	195(34.5)	16(69.6)	
Low	156(26.5)	150(26.5)	6(26.1)	
High	222(37.7)	221(39.0)	1(4.3)	
WBC (K/uL)	11.1(7.7-15)	10.9(7.7-14.8)	14.3(12.8-17.6)	0.013
Lymphocyte (%)	10.6(6.5-16.4)	10.75(6.5-16.4)	9.4(4.4-11.5)	0.160
Neutrophil (%)	82.7(76-88.9)	82.3(76-88.9)	85.6(69.7-89)	0.584
Monocyte (%)	3.6(2.6-5)	3.6(2.6-5)	3.7(2.2-5.8)	0.856
Platelets (K/uL)	274(204-349)	274(208-352)	210(170-302)	0.011
Hemoglobin (g/dl)	12.3±2.4	12.4±2.4	11.3±2.3	0.039
Blood glucose (mg/dl)	309(170-544)	309(170-560)	247(152-378)	0.047
Potassium (mEq/L)	4.4(3.9-5.1)	4.4(3.9-5.1)	4.3(3.9-5.1)	0.591
Sodium (mEq/L)	136(132-140)	136(131-140)	138(135-143)	0.015
Chloride (mEq/L)	100(94-106)	100(93-106)	104(99-109)	0.021
Total osmotic pressure (mmol/L)	301.7±14.9	301.7±14.9	301.4±14.0	0.912
Albumin (g/dL)	3.4±0.7	3.4±0.7	2.9±0.7	0.001
BUN (mg/dl)	24(14-39)	24(14-39)	37(20-64)	0.005
Creatinine (mg/dl)	1.3(0.9-2)	1.3(0.9-2)	1.6(1-2.2)	0.184
BAR	7.1(4.0-12.4)	7.0(3.9-11.8)	14(7.9-21.5)	<0.001
Scoring systems[c]				
SAPSII	28(20-37)	27(20-36)	48(36-59)	<0.001
OASIS	25(21-31)	25(21-31)	40(29-46)	<0.001
SOFA	2(1-4)	2(1-4)	6(4-11)	<0.001
APSIII	46(34-57)	45(34-55)	69(60-85)	<0.001

[a] Vital signs are calculated on the first 24 h of each ICU patients' stay

[b] Laboratory tests recorded the first result of each patients' ICU stay

[c] Severe score is calculated on the first day of each ICU patients' stay

Abbreviations: DKA, diabetic ketoacidosis; DM, Diabetic mellitus; T1DM, Type 1 diabetic mellitus; T2DM, Type 2 diabetic mellitus; ICU, intensive care unit; CKD, chronic kidney diseases; UTI, urinary tract infection; WBC, white blood cell; BUN, blood urea nitrogen; BAR, blood urea nitrogen to albumin ratio; SAPSII, simplified acute physiology score II; OASIS, oxford acute severity of illness score; SOFA, sequential organ failure assessment; APSIII, acute physiology score III.

Blood Urea Nitrogen to Serum Albumin Ratio as A New Prognostic Indicator in Critically Ill Patients with Diabetic Ketoacidosis: A Retrospective Cohort Study

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Abstract

To investigate the predictive value of the blood urea nitrogen to serum albumin ratio for in- and out-of-hospital mortality in critically ill patients with diabetic ketoacidosis. Data were obtained from the Medical Information Mart for Intensive Care III (MIMIC III) database, and all eligible participants were divided into two groups based on the BAR cutoff value. Multiple logistic regression analysis was conducted to determine the association between BAR and in-hospital mortality. The Kaplan–Meier (K–M) analysis was performed to evaluate the predictive performance of BAR. Propensity score matching (PSM) was applied to control confounding factors between the low and high BAR groups.A total of 589 critically ill patients with diabetic ketoacidosis were enrolled. Patients with diabetic ketoacidosis with a higher BAR level were associated with higher in- and out-hospital mortality (all $p < 0.001$). A significant 4-year survival difference was observed between the low and high BAR groups ($p < 0.0001$). After PSM analysis, two PSM groups (202 pairs, $n = 404$) were generated, and similar results were observed in the K–M curve ($p < 0.0001$). Elevated BAR levels were associated with an increased risk of in-hospital mortality in critically ill patients with diabetic ketoacidosis, and BAR could be an independent prognostic factor in in- and out-hospital mortality for patients diagnosed with diabetic ketoacidosis.

Keywords: Diabetic ketoacidosis, Blood urea nitrogen, Albumin, All-cause mortality, MIMIC-III database

Introduction

Diabetes mellitus (DM) is the current leading life-threatening problem worldwide. Diabetic ketoacidosis (DKA) is an acute lethal metabolic disorder in young patients diagnosed with DM [1, 2]. Recent studies have shown that the incidence of DKA has almost doubled over the past decades, and the economic burden of hospitalizations has increased from $5.28 billion in 2014 to $6.76 billion in 2017 in the USA [2, 3]. However, the standard treatment protocols are quite limited, partly because of unclear pathophysiological mechanisms[4]. Evaluating the severity and precisely predicting the outcomes will be beneficial for the clinical management of these patients.

DKA is characterized by severe hyperglycemia, ketosis, and metabolic acidosis resulting from absolute or relative insulin deficiency [5]. Blood urea nitrogen (BUN) is a nitrogenous end-product that reflects protein metabolism [6]. Dehydration is a common state among patients with DKA, leading to an increased BUN level [7]. Thus, BUN has been regarded as a tool to evaluate the disease severity, including DKA [8]. However, the clinical application of BUN is limited to the early prediction of critical diseases [9]. Previous studies have demonstrated that hypoalbuminemia was associated with poor outcomes in individuals experiencing acute diseases [10].

The BUN-to-serum albumin ratio (BAR), as a noninvasive, easily accessible, and inexpensive biomarker, has shown its utility in various diseases, such as cardiovascular diseases, gastrointestinal bleeding, and even coronavirus disease 2019 [11-13]. However, the prognostic value of BAR among patients with DKA has not

been illustrated in previous reports. Therefore, this study evaluated the predictive performance of BAR in critically ill patients with DKA.

Materials and methods

Data source

This single-center, longitudinal, retrospective cohort study used data obtained from the Medical Information Mart for Intensive Care (MIMIC) III (version 1.4) database, a large and freely available database published by the Massachusetts Institute of Technology[14]. All patients in the database were anonymous to protect their privacy. Thus, informed consent and ethical approval were waived. One author (TT Tao) completed the National Institutes of Health's Web-based course and then obtained permission to extract data from the database (certification number: 8892490).

Data extraction and management of missing data

All data were obtained from the first measurement recorded after admission. The following parameters were extracted for each patient: demographic characteristics, clinical interventions, vital signs, comorbidities, laboratory tests, scoring systems, and other variables. Demographic characteristics included age, sex, weight, and ethnicity. Clinical interventions included mechanical ventilation and the use of drugs ($NaHCO_3$ and albumin). Vital signs included temperature, heart rate, respiratory rate, arterial pressure, and urine output. Comorbidities included a history of hypertension, congestive heart failure (CHF), preexisting CKD, liver disease, stroke, malignancy,

urinary tract infection, pneumonia, and sepsis. Laboratory tests included serum pH, bicarbonate, lactate, urine ketone, white blood cell (WBC), lymphocyte, platelet, hemoglobin, blood glucose, potassium, sodium, chloride, total osmotic pressure, albumin, BUN, and serum creatinine levels. BAR was calculated by dividing BUN by albumin. Scoring systems included modified forms of the simplified acute physiology score (SAPSII), Oxford acute severity of illness score (OASIS), sequential organ failure assessment (SOFA), and acute physiology score III (APS III). The missing values of continuous variables were all <5% and were replaced with average or median values.

Study population and outcomes

All patients diagnosed with DKA and admitted to the intensive care unit (ICU) for the first time were included based on the International Classification of Disease 9 codes (24910, 24911, and 25010-25013). Patients who met the following criteria were excluded: (1) age <18 years, (2) repeated ICU admissions, (3) ICU stay for <48 h, (4) missing >5% of individual data, and (5) lack of BAR data. Finally, 589 patients were enrolled in the study and followed up for at least 4 years. The primary outcome was the incidence of in-hospital mortality. The secondary outcomes were the length of ICU stay, 28- and 90-day mortality, and 1-, 2-, 3-, and 4-year all-cause mortality.

Statistical analysis

Continuous variables were presented as means ± standard deviations or medians

(interquartile ranges) and analyzed using a t-test or Mann–Whitney U-test. Categorical variables were presented as percentages and compared using the chi-square test or Fisher's exact test. Then, all the identified variables from the above analyses ($P < 0.05$) were selected for multivariate logistic regression models. Variables with a variance inflation factor (VIF) ≥1.71 were removed to avoid hypercollinearity. A stepwise backward elimination method was used to remove variables with $P > 0.05$. To explore the crude association between BAR and in-hospital mortality and long-term mortality, the Mann–Whitney U-test was performed. Meanwhile, all patients were divided into low BAR and high BAR groups based on the optimal BAR cutoff value. The optimal cutoff value was determined by calculating the Youden index of the receiver operating characteristic (ROC) curve. To control the potential confounding factors between the low and high BAR groups, propensity score matching (PSM) (1:1) was performed. Finally, 202 pairs were generated for further analysis. Survival analysis was performed to explore the association between the BAR value and in- and out-hospital mortality among patients with DKA. Kaplan–Meier curves were applied to assess the differences between the two groups in the 4-year overall survival rate.

All statistical analyses were conducted using the IBM SPSS Statistics version 22.0 and R software 4.0.5.

Results

Baseline characteristics

We initially identified 877 ICU admissions with DKA diagnosis from the MIMIC-III database. A total of 589 patients were enrolled in the final study. The selection flowchart is detailed in **Fig. 1.** Death before hospital discharge occurred in 23 patients (3.9%). The baseline characteristics of survivors and nonsurvivors are listed in **Table 1**. Compared with the survivor's groups, patients in the nonsurvivor group had significantly higher BAR levels ($p < 0.001$). The results also revealed that nonsurvivors tended to be older ($p < 0.001$), more likely to have a history of congestive CHF ($p = 0.001$), stroke ($p < 0.001$), sepsis ($p = 0.002$), and more frequent to conduct clinical interventions such the use of $NaHCO_3$ ($p = 0.001$), albumin ($p = 0.001$), and mechanical ventilation ($p < 0.001$). Patients with in-hospital mortality had significantly higher respiratory rates ($p < 0.001$) and serum pH ($p = 0.008$), lactate ($p = 0.003$), WBC ($p = 0.013$), sodium ($p = 0.015$), chloride ($p = 0.021$), BUN ($p = 0.005$), SAPS II score ($p < 0.001$), OASIS score ($p < 0.001$), SOFA score ($p < 0.001$), APSIII score ($p < 0.001$), and lower temperature ($p = 0.031$), urine ketone ($p = 0.001$), platelet ($p = 0.011$), hemoglobin ($p = 0.039$), blood glucose ($p = 0.047$), and albumin ($p = 0.001$) levels.

Relationship between the BAR and outcomes

We conducted the univariate logistic regression between the survivor and nonsurvivor groups. The in-hospital mortality was positively associated with age (odds ratio [OR: 1.05, 95% confidence interval [CI]: 1.03 to 1.08), respiratory rates (OR: 1.18, 95% CI: 1.09 to 1.29); BAR (OR: 5.84, 95% CI: 2.38 to 16.40), sodium (OR: 1.10, 95%

CI: 1.03 to 1.77), and chloride (OR: 1.07, 95% CI: 1.02 to 1.13) levels; the therapy of mechanical ventilation (OR: 10.85, 95% CI: 4.59 to 26.92); and the history of CHF (OR: 4.02, 95% CI: 1.63 to 9.49), stroke (OR: 13.03, 95% CI: 3.30 to 44.07), malignancy (OR: 3.19, 95% CI: 0.89 to 9.06), and sepsis (OR: 4.19, 95% CI: 1.45 to 10.66). Negative correlations were observed in the urine volume, temperature, and hemoglobin and glucose levels (OR: 0.9994, 95% CI: 0.9990–0.9998; 0.43, 0.21 to 0.92; 0.83, 0.69 to 0.99; and 0.9974, 0.9949 to 0.9994, respectively). The results are shown in **Table 2.** Multivariate logistic regression analysis was performed to explore the prognostic role of BAR in in-hospital mortality. To avoid hypercollinearity, variables with VIF ≥1.71 were removed. As shown in **Fig. 2**, among patients with DKA, the in-hospital mortality was positively associated with age, respiratory rates, history of stroke, mechanical ventilation therapy, and BAR, WBC, and hemoglobin levels (OR: 1.03, 95% CI: 1.00 to 1.07; 1.22, 1.10 to 1.37; 7.78, 1.42 to 38.10; 7.08, 2.38 to 22.80; 4.14, 1.39 to 13.6; 1.05, 0.99 to 1.10; and 1.34, 1.01 to 1.79, respectively) (**Fig. 2**). Interestingly, negative correlations were observed between the glucose level and in-hospital mortality (OR:0.9962, 95% CI: 0.9924 to 0.9992) (**Fig. 2**).

Moreover, compared with the survival group, patients in the nonsurvivor group had a significantly higher BAR level (in-hospital mortality: $p < 0.001$; 28-day mortality: $p < 0.001$; 90-day mortality: $p < 0.0001$; 1-year mortality: $p < 0.0001$; 2-year mortality: $p < 0.0001$; 3-year mortality: $p < 0.0001$; 4-year mortality: $p < 0.0001$, respectively) (**Fig. 3**).

Prognostic role of BAR before PSM

After conducting the ROC curve to obtain the Youden index, the optimal cutoff value of BAR for 4-year mortality was determined as 9.89 mg/g (**Fig. 4**). Although the area under the curve (AUC) of SAPS II and SOFA scores were larger than BAR in our study, BAR was easier and more convenient for physicians to assess the DKA severity (**Fig. S1**). We then stratified all the patients into a low BAR group (≤9.89, n = 387) and a high BAR group (>9.89, n = 202). The baseline characteristics of patients categorized based on BAR levels are shown in **Table 3**. Before PSM, patients in the high BAR group were more elderly; more likely treated with mechanical ventilation ($p = 0.039$), albumin ($p = 0.035$), and $NaHCO_3$ ($p < 0.001$); had a higher prevalence of CHF ($p < 0.001$), CKD ($p < 0.001$), malignancy ($p = 0.013$), pneumonia ($p = 0.023$), and sepsis ($p = 0.009$); and significantly lower urine output ($p < 0.001$), lymphocyte ($p < 0.001$), urine ketone ($p < 0.001$), platelet ($p = 0.017$), hemoglobin ($p < 0.001$), sodium ($p = 0.0054$), chloride ($p = 0.0028$), and albumin ($p < 0.001$) levels. Also, patients in the high BAR group had increased glucose ($p < 0.001$), BUN ($p < 0.001$), creatinine ($p < 0.001$), SAPS II score ($p < 0.001$), OASIS score ($p < 0.001$), SOFA score ($p < 0.001$), and APS Ⅲ score ($p < 0.001$) levels.

The clinical outcomes by BAR categories in critically ill patients with DKA are presented in **Table 4**. Patients with high BAR levels had a longer duration of ICU stay [48 (28–85) vs. 45 (29–67), $p = 0.012$] and a significantly higher rate of in-hospital mortality (8.42% vs. 1.55%, $p < 0.001$), 28-day mortality (11.39% vs. 2.84%, $p <$

0.001), 90-day mortality (15.35% vs. 4.13%, $p < 0.001$), 1-year mortality (29.21% vs. 7.49%, $p < 0.001$), 2-year mortality (35.15% vs. 10.59%, $p < 0.001$), 3-year mortality (39.11% vs. 12.14%, $p < 0.001$), and 4-year mortality (43.56% vs. 13.44%, $p < 0.001$).

Results of the survival analysis for 4-year mortality stratified by BAR levels are shown in **Fig. 5**. Before PSM, a significantly lower 4-year survival probability was identified in patients in the high BAR group ($p < 0.001$) (**Fig. 5A**).

Prognostic role of BAR after PSM

PSM was performed to minimize heterogeneity between the two groups, and the overall propensity score was well-balanced (**Fig. S2**). The imbalance was further adjusted for particular covariates, such as age, temperature, respiratory rates, blood pressure, bicarbonate, WBC count, platelets, hemoglobin, glucose, sodium, chloride, history of CHF, CKD, stroke, malignancy, pneumonia, and sepsis, therapy of mechanical ventilation, and use of albumin and $NaHCO_3$.

As shown in **Table 3**, in the matched cohort patients of the BAR high group tended to be at a more advanced age ($p = 0.038$); more frequently treated with $NaHCO_3$ ($p = 0.007$); more likely to have a history of CHF ($p = 0.003$) and CKD ($p < 0.001$); and had lower temperature ($p = 0.008$), urine output ($p = 0.003$), lymphocyte ($p = 0.04$), hemoglobin ($p = 0.015$), urine ketone ($p < 0.001$), and albumin ($p < 0.001$) levels. Elevated BAR levels were associated with higher BUN ($p < 0.001$), creatinine ($p < 0.001$), SAPS II score ($p < 0.001$), SOFA score ($p < 0.001$), and APSIII score ($p <$

0.001) levels.

After PSM, the statistically significant difference in almost all clinical outcomes between the low BAR and high BAR groups could still be identified in **Table 4**. Patients in the high BAR group had an elevated in-hospital (8.42% vs. 2.48%, $p = 0.009$), 28-day (11.39% vs. 4.95%, $p = 0.018$), 90-day (15.35% vs. 6.93%, $p = 0.007$), 1-year (29.21% vs. 9.41%. $p < 0.001$), 2-year (35.15% vs. 13.37%, $p < 0.001$), 3-year (39.11% vs. 15.84%, $p < 0.001$), and 4-year mortality (43.56% vs. 17.82%, $p < 0.001$) rates. However, the relationship between BAR levels and length of ICU stay disappeared after matching. As indicated in **Fig. 4B**, patients in the matched cohort with high BAR levels still had a significant decrease in the 4-year survival probability.

Discussion

This study aimed to determine whether BAR could predict the clinical outcomes in critically ill patients diagnosed with DKA. By retrospectively analyzing the large free accessible critical care database, high BAR levels were positively related to in- and out-of-hospital mortality in these patients. First, we found that in patients diagnosed with DKA, the group with in-hospital mortality had higher BAR levels. In addition, multiple logistic regression analysis confirmed that BAR was an independent predictive factor. To avoid confounding variables that might interfere with the association between BAR levels and all-cause mortality, the PSM algorithm was performed, and BAR still revealed a good capacity to predict all-cause mortality. To the best of our knowledge, this is the first study to discuss the potential predictive

role of BAR in predicting critically ill patients with DKA during mixed ICU admission.

DKA is a life-threatening but avoidable metabolic complication of diabetes [15]. Although DKA is often perceived as a common complication of type 1 diabetes, recent studies have revealed that almost one-third of DKA events occur in patients with type 2 DM, and DKA is usually a fatal problem among young patients[16-18]. In particular, increased DKA and hyperglycemic hyperosmolar state rates were correlated with higher incidences of acute vascular events, such as myocardial infarction and stroke [18, 19]. Therefore, early and accurate identification of patients with DKA is of great importance. However, poor early detection of DKA is quite common even in developed countries. Traditionally, previous studies found that unspecific symptoms such as vomiting, abdominal pain, and weakness can predict the onset of DKA [20, 21]. Laboratory studies for DKA should include blood glucose levels, ketone testing, and arterial blood gas, among others [22]. However, accurately predicting the clinical outcomes of critically ill patients with DKA admitted to the ICU remains a great challenge.

BUN is usually regarded as an important indicator of blood volume. Although many patients with DKA are complicated with acute renal failure, dehydration is the most common state among patients with DKA due to hypovolemia and hypotension [23]. Moreover, most patients with DKA are found in young patients diagnosed with DM, who have better kidney function than elderly people. Compared with the serum creatinine, BUN was a better index to reflect the DKA severity. Previous studies have

also revealed that high BUN levels are correlated with poor prognosis in ICU patients [24, 25]. As high BUN was also found to be related to the poor prognosis of patients with acute heart failure, acute respiratory disease syndrome, and hepatic decompensation [26-28], BUN might reflect the degree of injury of multiple important organs, which were also found to be an important risk factor of critically ill patients.

Albumin is another component of BAR. In this study, serum albumin concentration was inversely associated with in-hospital mortality in patients diagnosed with DKA. Previous studies involving patients with diabetes have demonstrated similar findings [29, 30]. Insulin is an important regulator of albumin synthesis, which may explain the above correlation between hypoalbuminemia and insulin deficiency. Therefore, serum albumin concentration may indirectly indicate the clinical outcomes of DKA inpatients.

In recent years, BAR has been a promising novel biomarker for predicting the severity and outcomes in patients suffering from severe diseases, such as severe pneumonia, acute pulmonary embolism, and heart failure [31-33]. BAR includes two important predictors, urea nitrogen and albumin, the routine test issues for patients admitted to the hospital. Compared with urea nitrogen and albumin, BAR has better power in predicting the clinical outcomes of critically ill patients, which was also validated in our study. Patients with high BAR values (>9.89) had short- and long-term all-cause mortalities of patients increased even after multiple covariates adjustment by PSM. Therefore, close monitoring may be necessary for patients with

DKA having a BAR level of 9.89 or higher because it may indicate a higher risk for mortality. The mechanisms between high BAR levels and poor prognosis remain unclear; however, the two components might both play important roles in predicting the severity of critically ill patients, while the ratio amplified the clinical significance.

This study had several limitations. First, all the data of this single-center retrospective study were obtained from the MIMIC-III database, which increases the inevitable selection bias. Second, some related variables were missing too much due to the retrospective nature. Third, we did not investigate the dynamic development of the BAR level during hospitalization, which may confirm better predictive values. Fourth, although BAR is a noninvasive and easily checkable marker for physicians, the AUC value of BAR was 0.726. Finally, although we performed PSM to balance the covariates, the other confounders still existed. Thus, a larger, well-designed, multicenter, randomized controlled trial is needed.

Conclusions

Our study demonstrated that elevated BAR levels were significantly associated with in- and out-hospital mortality. Moreover, BAR could be identified as a potential, independent, and easily accessible predictor of critically ill patients with DKA.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

HTT was responsible for study design and data collection. HJ contributed to analyzing the data and creating tables and figures. HGP and LJ were responsible for manuscript preparation. TTT was responsible for writing and reviewing the paper. All authors contributed to the article and approved the submitted version.

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Data Availability Statement

All the data referred to in our study can be found in the publicly available ICU database (https://mimic.mit.edu/).

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Figure legends

Fig. 1 Flow chart of the study population.

Abbreviations: ICU, intensive care unit; DKA, diabetic ketoacidosis; BUN, blood urea nitrogen; BAR, blood urea nitrogen to albumin ratio.

Fig. 2 Forrest plot of the adjusted ORs from multivariable logistic regression with 95% confidence interval (CI).

The mean-variance inflation factor (VIF) was 2.62.

Abbreviations: BAR, blood urea nitrogen to albumin ratio; WBC, white blood cell.

Fig. 3 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. ***p<0.001, **** p<0.0001.

Abbreviations: BAR, blood urea nitrogen to albumin.

Fig. 4 Receiver operating characteristic (ROC) curves for initial BAR values during ICU admission

Abbreviations: BAR, blood urea nitrogen to albumin

Fig. 5 Kaplan-Meier curves before and after PSM.

A significantly lower four-year survival probability can be identified in the higher BAR group in patients before (A) and after (B) PSM. The P-value was calculated by the Log-rank test. The survival time was given in days.

Abbreviations: BAR, blood urea nitrogen to albumin; PSM, propensity score matching.

Fig. S1 Receiver operating characteristic (ROC) curves for initial SOFA score, SAPS II score and APS III during ICU admission

Abbreviations: SOFA, sequential organ failure assessment; SAPSII, the simplified acute physiology score ; APS III, acute physiology score III

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443 **Fig. S2 Kernel density plots of the propensity score before and after propensity**

444 **score matching**

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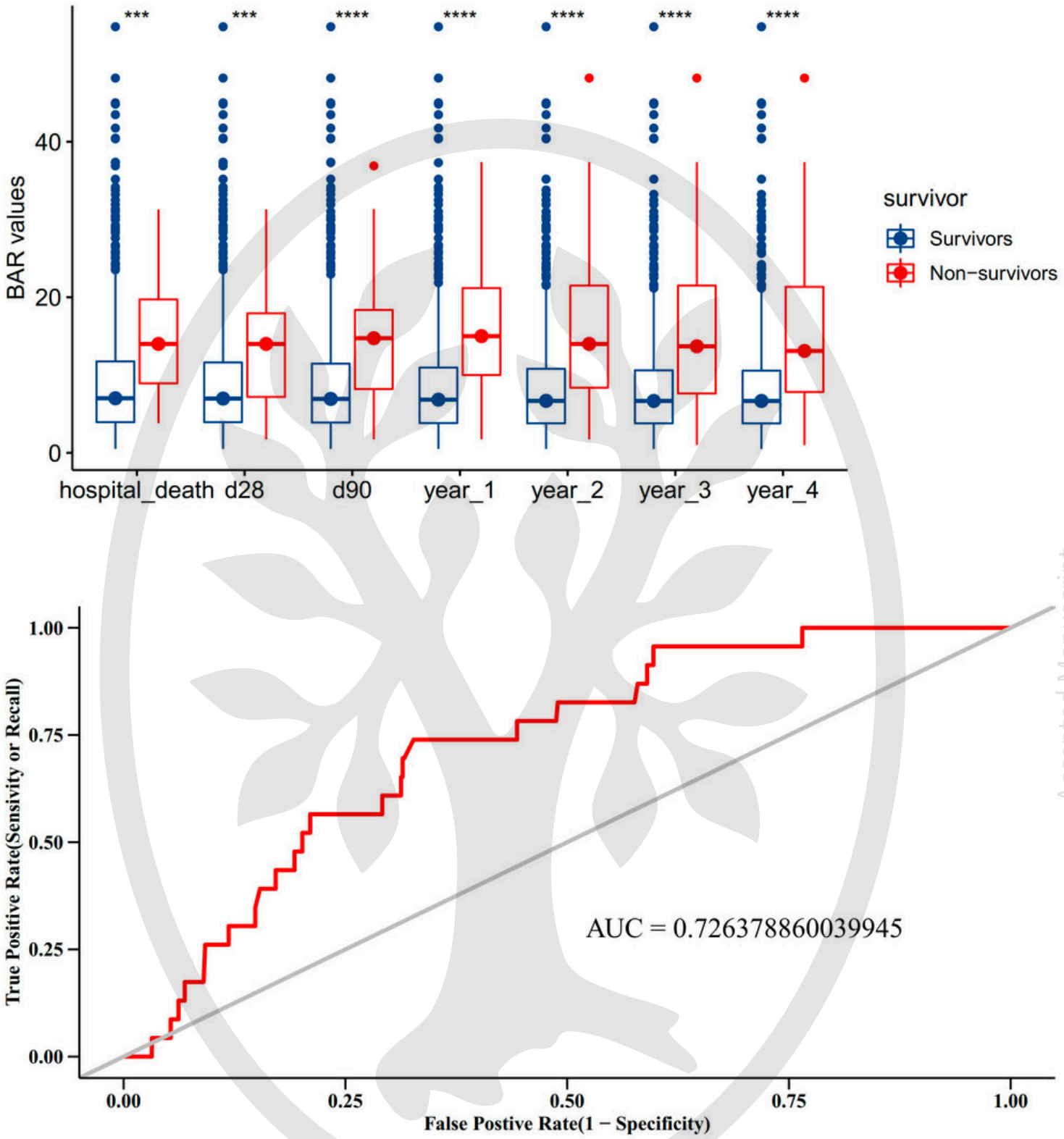

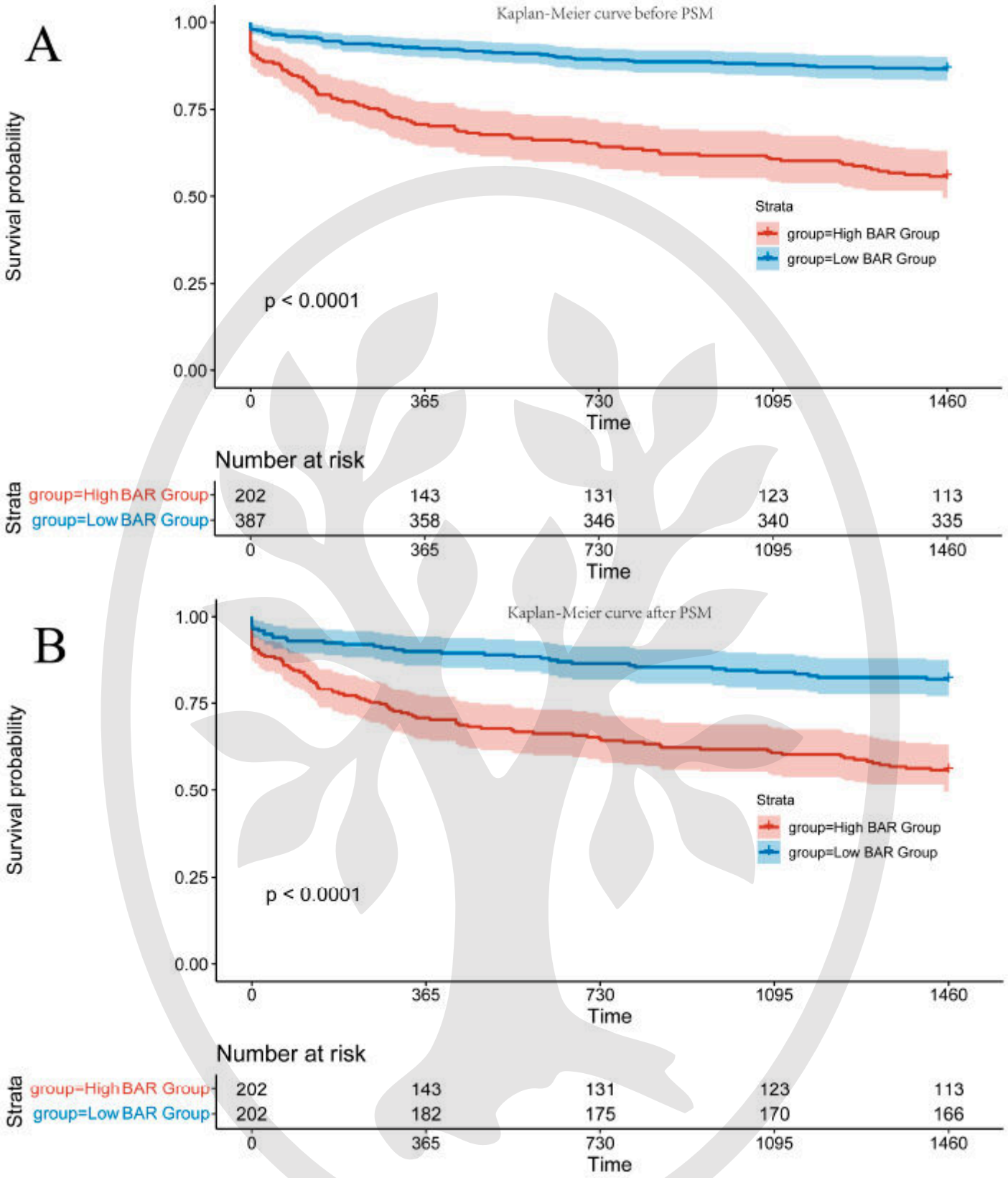

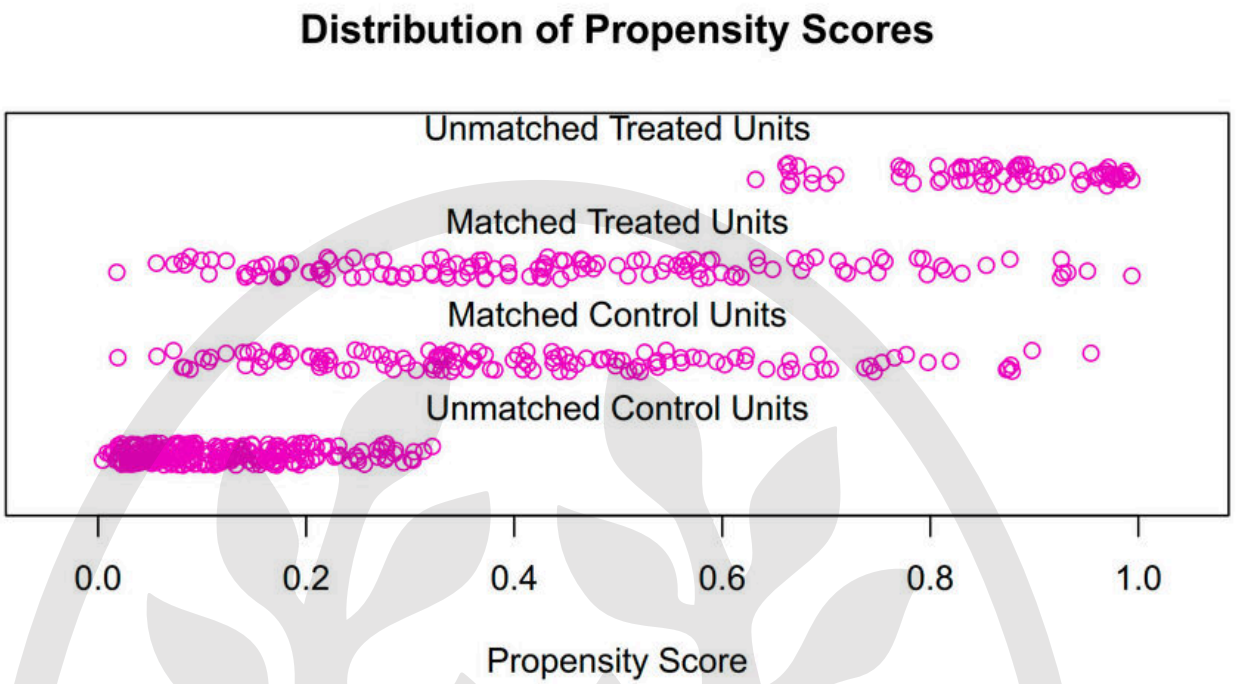

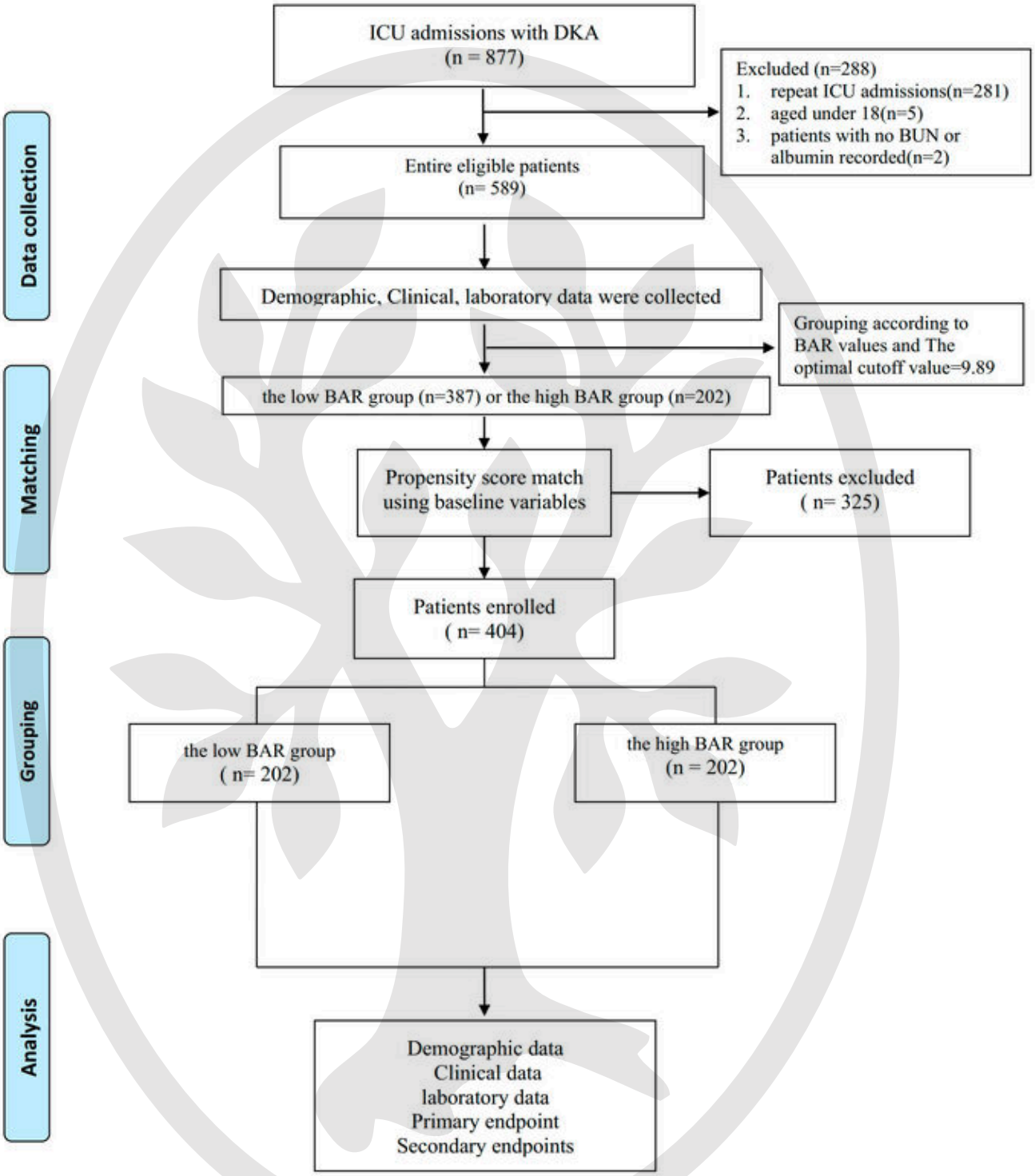

variable	OR (95% CI)	P
age	1.03(1.00−1.07)	0.0281
vent	7.08(2.38−22.8)	0.0006
urineoutput	0.99(0.99−0.99)	0.0708
tempc	0.51(0.24−1.04)	0.0698
resprate	1.22(1.10−1.37)	0.0002
BAR	4.14(1.39−13.6)	0.0133
WBC	1.05(0.99−1.10)	0.0436
plt	0.99(0.99−1.00)	0.1637
hemoglobin	1.34(1.01−1.79)	0.0414
glucose	0.99(0.99−0.99)	0.0256
stroke	7.78(1.42−38.1)	0.0124