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Association between blood urea nitrogen-to-creatinine ratio and all-cause mortality in critically ill patients with sepsis: an analysis based on the MIMIC-IV database

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The blood urea nitrogen-to-creatinine ratio (BCR) is a routinely available indicator that can reflect renal perfusion, neurohormonal activation, and systemic catabolic stress. Although BCR has been linked to prognosis in several acute conditions, its relationship with mortality in critically ill patients with sepsis has not been fully characterized. In this cohort, BCR ranged from 1.7 to 116.0 (median 19.2; IQR 14.3–25.8), so a 20-unit increase corresponds to an approximate 22% higher hazard (1.01^20≈1.22), underscoring clinical interpretability of the per-unit HR. We performed a retrospective cohort study using the MIMIC-IV database. Adult ICU admissions meeting Sepsis-3 criteria were included. BCR was calculated from early blood urea nitrogen and serum creatinine values and categorized into quartiles. The primary outcomes were 28-day and 365-day all-cause mortality. Associations were evaluated using Kaplan–Meier methods and Cox proportional hazards models with stepwise adjustment for demographics, comorbidities, physiologic variables, and laboratory tests. Restricted cubic spline modeling was used to explore non-linear dose–response patterns, and prespecified subgroup analyses examined effect modification. Among 12,514 patients, 58.04% were male. The 28-day mortality was 20.90% and the 365-day mortality was 37.78%. Higher BCR was associated with lower survival probability. In fully adjusted models, BCR remained independently associated with 28-day mortality (hazard ratio 1.01 per 1-unit increase; 95% confidence interval 1.01–1.02) and 365-day mortality (hazard ratio 1.01 per 1-unit increase; 95% confidence interval 1.01–1.01). Compared with the lowest quartile, the highest quartile was associated with increased 28-day mortality (hazard ratio 1.49; 95% confidence interval 1.33–1.67) and increased 365-day mortality (hazard ratio 1.41; 95% confidence interval 1.30–1.54). Spline analyses suggested a J-shaped association. A significant interaction between sex and 365-day mortality was observed. Elevated BCR is associated with increased short- and long-term mortality among critically ill patients with sepsis, with evidence of a J-shaped risk pattern. BCR may serve as a pragmatic marker for early risk stratification in ICU practice.

Keywords: critical care, prognostic biomarker, renal perfusion, catabolic stress, ICU, restricted cubic spline

Introduction

Sepsis is a multiple organ dysfunction induced by a dysregulated host reaction due to infection[1]. It is a common reason for admission to intensive care units and remains a major contributor to preventable mortality worldwide[2,3]. The acute phase of sepsis is characterized by heterogeneous trajectories that range from rapid shock and multi-organ failure to partial stabilization followed by delayed complications. Importantly, the burden of sepsis extends beyond the hospital admission: survivors often experience persistent inflammation, immune dysfunction, functional decline, and a heightened risk of rehospitalization and death months after discharge[4]. Reliable early markers that capture both acute physiology and underlying reserve are therefore useful for clinical decision-making and for designing targeted follow-up[1,5-8].

Prognostic assessment in sepsis commonly relies on composite severity scores and indices of organ dysfunction. Tools such as SOFA and APACHE summarize physiologic abnormalities across organ systems and provide useful population-level prediction. However, these tools require multiple variables, depend on documentation completeness, and can be difficult to interpret as a bedside signal those points to a specific mechanism. In addition, a single global score can obscure distinct physiologic phenotypes that share similar overall severity but differ in the dominant drivers of organ failure. This motivates interest in simple markers that are readily available, mechanistically interpretable, and potentially complementary to global scoring systems[9].

Kidney involvement is frequent in sepsis and is strongly associated with adverse outcomes. Acute

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kidney injury (AKI) develops in a substantial proportion of septic ICU patients and is linked to both short-term death and long-term morbidity[10-12]. Sepsis-associated kidney dysfunction is multifactorial. It can reflect reduced effective circulating volume, microvascular dysfunction, inflammatory tubular injury, venous congestion, nephrotoxic exposure, or combinations of these processes. Kidney-related biomarkers measured early in the ICU course may therefore provide information about both current physiologic stress and baseline resilience[10,13-15].

Blood urea nitrogen (BUN) and serum creatinine are routine tests used to assess renal function, but both are influenced by factors beyond glomerular filtration. BUN is affected by protein intake, gastrointestinal bleeding, catabolic rate, hepatic urea synthesis, and neurohormonal activation. Creatinine reflects muscle mass and creatine metabolism and may be altered by tubular secretion and fluid balance in addition to filtration[10]. Because these influences differ, clinicians often interpret BUN and creatinine jointly rather than in isolation[16-19].

The blood urea nitrogen-to-creatinine ratio (BCR) integrates information from both markers. Traditionally, an elevated ratio has been used to support clinical reasoning about prerenal physiology and reduced effective circulating volume, because reduced perfusion enhances urea reabsorption relative to creatinine handling[8,10]. Beyond perfusion, a higher ratio may also capture systemic catabolic stress. Urea production can rise with accelerated protein breakdown, while creatinine generation can be reduced in frail patients and those with low skeletal muscle mass, shifting the ratio upward even without large changes in filtration[20]. Prior studies have linked elevated BCR to poor outcomes in conditions where hemodynamic compromise and neurohormonal activation are prominent, such as heart failure and ischemic stroke[12,21-24].

In sepsis, interpretation of BCR may be complicated by competing mechanisms that could produce non-linear associations with outcomes. Fluid resuscitation, vasopressor therapy, renal replacement therapy, and nutritional support can modify BUN and creatinine trajectories. Hepatic dysfunction can reduce urea synthesis and lower BUN, while chronic kidney disease can elevate creatinine disproportionately. Muscle injury may raise creatinine, whereas sarcopenia may lower it. These processes raise the possibility that the BCR–mortality relationship is not strictly linear and that both extreme high and extreme low ratios may correspond to distinct high-risk phenotypes[25].

Given that BUN and creatinine are universally measured early in ICU care, clarifying the prognostic meaning of BCR in sepsis could offer a low-cost tool to complement existing severity scores. We therefore investigated the association between early BCR and both short-term (28-day) and long-term (365-day) all-cause mortality in critically ill patients with sepsis using the MIMIC-IV database[26]. We modeled BCR as both a continuous and quartile-based exposure, assessed non-linear dose–response patterns using restricted cubic splines, and explored effect modification with prespecified subgroup analyses. We hypothesize that early BCR is independently associated with mortality in sepsis, that this relationship is non-linear (J-shaped), and that the association may be modified by patient sex .

Prior evidence on BCR supports its plausibility as a prognostic marker but leaves important gaps for sepsis. In cardiovascular populations, elevated BCR has been interpreted as a signal of neurohormonal activation and reduced effective arterial blood volume and has been associated with adverse outcomes in acute heart failure[27]. In neurologic emergencies such as acute ischemic stroke, BCR has been linked to mortality and functional outcomes, potentially reflecting dehydration, stress response, and comorbidity burden[24]. These settings share features relevant to sepsis, including hemodynamic stress and systemic inflammation, but they differ in the dominant drivers of kidney biomarkers and in the timing of catabolic changes. In sepsis, the simultaneous presence of infection-driven inflammation, circulatory dysregulation, and multi-organ dysfunction may reshape the BUN–creatinine relationship, and it is therefore uncertain whether findings from other acute illnesses generalize directly.

Another challenge is that sepsis is increasingly recognized as a syndrome with multiple phenotypes. Some patients primarily manifest distributive shock with profound vasodilation, while others exhibit mixed shock states with cardiogenic components or significant venous congestion. Similarly, the metabolic response varies: some patients display marked hypercatabolism, while others present with impaired urea production due to hepatic dysfunction. These factors make it plausible that BCR might not have a simple linear association with risk, and they

motivate the use of flexible modeling to evaluate non-linearity. Establishing whether BCR provides independent prognostic information after adjustment for established scores could support its use as a rapid, low-cost, bedside marker[28].

Methods

Study design and data source

We conducted a retrospective observational cohort study using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. MIMIC-IV is a large, de-identified critical care dataset containing detailed time-stamped information from ICU admissions to a tertiary academic medical center. The database includes demographics, diagnoses, laboratory results, bedside charted physiologic variables, procedures, medication orders, and outcomes. Database access requires completion of required training and acceptance of data use agreements. Because the dataset is de-identified, individual informed consent is waived under the database governance framework.

Study population and eligibility criteria

We screened adult patients (age ≥18 years) admitted to the ICU who met Sepsis-3 criteria during the ICU stay. Sepsis was operationalized using a standardized definition combining evidence of infection with acute organ dysfunction. We included patients from all ICU types to capture diverse sepsis presentations. To reduce correlation from repeated admissions and to represent risk at index critical illness, we selected the first eligible ICU stay per patient. We excluded ICU stays lacking BUN or creatinine measurements required to compute BCR within the early exposure window. We also excluded implausible laboratory values strongly suggestive of data entry errors. When both BUN and creatinine were present but the computed ratio was extreme due to very low creatinine, we examined plausibility through accompanying laboratory context and retained values considered clinically possible, recognizing that low creatinine may reflect low muscle mass or dilution.

Exposure definition

The primary exposure was BCR, computed as BUN (mg/dL) divided by serum creatinine (mg/dL). To align with bedside availability and reduce bias from later measurements influenced by ICU treatments, we defined exposure using early laboratory values after ICU admission. When multiple measurements were available within the early window, we selected the earliest BUN and creatinine values for primary analyses. BCR was analyzed as a continuous variable and categorized into quartiles (Q1–Q4) based on the distribution in the analytic cohort. The lowest quartile served as the reference group. Specifically, the primary exposure used the first (earliest) paired BUN and creatinine values recorded within the first 24 hours after ICU admission .

Outcomes

The primary outcomes were 28-day and 365-day all-cause mortality, defined as death from any cause within 28 or 365 days of ICU admission. Time zero was ICU admission, and follow-up time was computed using available mortality data. Patients who did not die within the specified horizon were censored at the end of follow-up. To ensure interpretability across clinically relevant horizons, we also examined ICU mortality and in-hospital mortality in sensitivity analyses.

Covariates and variable definitions

We prespecified covariates based on clinical relevance and potential confounding of the association between BCR and mortality. Demographic covariates included age and sex. Comorbidities were derived from diagnosis codes and included atrial fibrillation, hypertension, diabetes mellitus, coronary artery disease, heart failure, chronic lung disease, stroke, chronic kidney disease, and malignancy. These comorbidities can influence baseline kidney biomarkers, susceptibility to sepsis-related organ dysfunction, and mortality risk.

Physiologic covariates were extracted from bedside charting and included heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, oxygen saturation, and temperature. We summarized measurements within the first 24 hours after ICU admission to represent early physiologic state. For instability indicators such as mean arterial pressure, we used worst values (e.g., minimum mean arterial pressure) because transient hypotension may carry prognostic significance in sepsis. For other variables, we used first available or typical early values to reduce susceptibility to treatment effects.

Laboratory covariates included white blood cell count, hemoglobin, platelet count, sodium, potassium, chloride, bicarbonate, glucose, lactate, bilirubin, and albumin. These variables capture inflammation,

perfusion, metabolic stress, hepatic function, and nutritional status and are commonly used in sepsis prognostic models. We also included other routinely measured laboratory markers when available and clinically relevant. Severity of illness was captured using available ICU severity indices and/or their components, reflecting the degree of multi-organ dysfunction early after ICU admission.

We additionally extracted information on major ICU interventions that reflect severity and may influence outcomes, including use of vasopressors, mechanical ventilation and so on. These variables were considered as markers of illness severity and clinical trajectory. Because interventions may also lie on the pathway between early physiology and outcome, we evaluated their inclusion in sensitivity models to confirm stability of the exposure–outcome association.

Repeated measurements and outliers

ICU datasets contain repeated measurements with heterogeneous sampling frequency. For exposure definition, we used the earliest BUN and creatinine values in the early window. For covariates, we used variable-specific rules that favored clinical interpretability: worst values were used for instability measures, and early values were used for baseline markers. We screened continuous variables for extreme values that were inconsistent with physiologic plausibility and treated such values as missing. When extreme values were plausible given the clinical context, we retained them to avoid bias from excluding the sickest patients. Missingness is common in ICU data due to differences in clinical ordering practices and documentation. For primary Cox models, we used complete-case analysis within each model, restricting each model to patients with complete data on included covariates. To assess robustness and reduce the likelihood that findings were driven by missingness patterns, we performed sensitivity analyses using reduced covariate sets that prioritized high-availability variables and by adding missingness indicators for selected covariates with moderate missingness. We compared effect estimates across these approaches. No additional observations were excluded from Models 1–3 because all model covariates were available in the final analytic dataset.

Statistical analysis

Baseline characteristics were summarized across BCR quartiles. Continuous variables were described using mean (standard deviation) or median (interquartile range) depending on distribution, and categorical variables were described using counts (percentages). Between-group differences were assessed using appropriate tests for continuous and categorical variables. Baseline characteristics across BCR quartiles are summarized in (Table 1).

Table 1 — Baseline characteristics of the sepsis population according to BCR quartiles.

	Total (n = 12,514)	Q1 (n = 3,039)	Q2 (n = 3,210)	Q3 (n = 3,123)	Q4 (n = 3,142)	*P*
Demographics						
Age, years	65.39 ± 16.53	57.76 ± 17.13	64.63 ± 16.06	68.90 ± 15.34	70.05 ± 14.72	<0.001
Gender, n (%)						<0.001
female	5251 (41.96)	1093 (35.97)	1241 (38.66)	1370 (43.87)	1547 (49.24)	
male	7263 (58.04)	1946 (64.03)	1969 (61.34)	1753 (56.13)	1595 (50.76)	
Weight, kg	83.28 ± 24.77	86.42 ± 25.33	85.43 ± 23.86	82.36 ± 23.77	78.96 ± 25.43	<0.001
Laboratory tests						
WBC, K/μL	13.71 ± 12.01	13.64 ± 12.27	13.80 ± 13.45	13.71 ± 12.00	13.67 ± 10.08	0.955
RBC, m/μL	3.51 ± 0.79	3.58 ± 0.82	3.58 ± 0.78	3.51 ± 0.77	3.39 ± 0.78	<0.001
Platelet, K/μL	197.28 ± 116.16	196.59 ± 113.08	197.44 ± 107.24	198.37 ± 116.55	196.69 ± 127.01	0.925
RDW, %	15.39 ± 2.44	15.26 ± 2.41	15.00 ± 2.22	15.26 ± 2.36	16.07 ± 2.63	<0.001
Sodium, mmol/L	138.33 ± 5.77	137.87 ± 5.38	138.25 ± 5.07	138.20 ± 5.46	139.00 ± 6.95	<0.001
Potassium, mmol/L	4.22 ± 0.79	4.23 ± 0.88	4.18 ± 0.74	4.22 ± 0.76	4.25 ± 0.79	0.008
Calcium, mg/dL	8.16 ± 0.95	8.09 ± 1.00	8.13 ± 0.92	8.19 ± 0.89	8.21 ± 0.98	<0.001
Chloride, mmol/L	104.22 ± 7.11	103.13 ± 6.96	104.67 ± 6.43	104.46 ± 6.68	104.60 ± 8.16	<0.001
Glucose, mg/dL	151.56 ± 79.93	145.36 ± 74.26	152.15 ± 79.53	154.81 ± 83.39	153.73 ± 81.81	<0.001
Anion gap, mmol/L	15.49 ± 4.75	16.66 ± 5.55	15.20 ± 4.46	15.19 ± 4.36	14.95 ± 4.36	<0.001
PT, sec	17.18 ± 9.90	16.95 ± 9.61	16.36 ± 7.82	17.22 ± 9.72	18.20 ± 11.94	<0.001
PTT, sec	38.71 ± 23.12	39.13 ± 23.60	38.57 ± 23.23	38.76 ± 23.00	38.42 ± 22.64	0.650
ALT, u/dL	139.34 ± 569.16	202.21 ± 826.09	126.39 ± 492.54	132.28 ± 523.62	98.77 ± 323.15	<0.001
AST, u/dL	230.04 ± 1029.04	366.64 ± 1539.89	202.60 ± 904.58	210.57 ± 900.28	145.32 ± 506.95	<0.001

(*Contd*.)

Table 1 — Baseline characteristics of the sepsis population according to BCR quartiles — (*Contd.*)

	Total (n = 12,514)	Q1 (n = 3,039)	Q2 (n = 3,210)	Q3 (n = 3,123)	Q4 (n = 3,142)	*P*
Disease scores						
SOFA score	6.53 ± 3.68	7.05 ± 4.01	6.24 ± 3.58	6.29 ± 3.52	6.56 ± 3.55	<0.001
APS III score	53.69 ± 22.40	53.45 ± 23.96	50.23 ± 22.08	52.90 ± 21.66	58.25 ± 21.11	<0.001
SAPS II score	41.50 ± 14.61	39.37 ± 15.22	39.72 ± 14.39	42.05 ± 14.07	44.85 ± 14.12	<0.001
OASIS score	34.88 ± 8.49	34.42 ± 8.89	34.39 ± 8.49	34.88 ± 8.20	35.83 ± 8.30	<0.001
Vital signs						
Heart rate, beats/minute	92.47 ± 21.25	94.95 ± 21.72	90.86 ± 20.52	91.15 ± 21.12	93.04 ± 21.42	<0.001
SBP, mmHg	120.28 ± 25.05	120.39 ± 26.00	121.27 ± 25.21	120.25 ± 24.90	119.19 ± 24.03	0.012
DBP, mmHg	74.08 ± 604.94	69.10 ± 19.81	68.24 ± 18.88	90.25 ± 1204.37	68.78 ± 122.76	0.395
MBP, mmHg	101.85 ± 1649.81	83.73 ± 111.35	118.71 ± 2119.01	80.07 ± 18.57	123.81 ± 2498.39	0.614
Respiratory rate, breath/minute	20.09 ± 6.58	20.24 ± 6.72	19.80 ± 6.51	19.92 ± 6.61	20.39 ± 6.46	0.001
SpO_2, %	97.53 ± 87.37	99.97 ± 176.43	97.10 ± 15.90	96.66 ± 4.67	96.45 ± 4.21	0.356
Temperature, ℃	36.75 ± 2.22	36.83 ± 2.32	36.79 ± 2.34	36.76 ± 1.87	36.64 ± 2.33	0.006
Comorbidities						
Atrial fibrillation, n(%)						<0.001
no	8587 (68.62)	2361 (77.69)	2254 (70.22)	2004 (64.17)	1968 (62.64)	
yes	3927 (31.38)	678 (22.31)	956 (29.78)	1119 (35.83)	1174 (37.36)	
AKI, n (%)						0.757
no	2081 (16.63)	510 (16.78)	550 (17.13)	512 (16.39)	509 (16.20)	
yes	10433 (83.37)	2529 (83.22)	2660 (82.87)	2611 (83.61)	2633 (83.80)	
Hypertension, n (%)						<0.001
no	7538 (60.24)	2062 (67.85)	1873 (58.35)	1757 (56.26)	1846 (58.75)	
yes	4976 (39.76)	977 (32.15)	1337 (41.65)	1366 (43.74)	1296 (41.25)	
Type 2 DM, n (%)						<0.001
no	8986 (71.81)	2307 (75.91)	2301 (71.68)	2187 (70.03)	2191 (69.73)	
yes	3528 (28.19)	732 (24.09)	909 (28.32)	936 (29.97)	951 (30.27)	
Heart failure, n (%)						<0.001
no	8894 (71.07)	2369 (77.95)	2362 (73.58)	2124 (68.01)	2039 (64.89)	
yes	3620 (28.93)	670 (22.05)	848 (26.42)	999 (31.99)	1103 (35.11)	
Myocardial infarction, n (%)						0.045
no	11501 (91.91)	2811 (92.50)	2950 (91.90)	2835 (90.78)	2905 (92.46)	
yes	1013 (8.09)	228 (7.50)	260 (8.10)	288 (9.22)	237 (7.54)	
Malignant tumors, n (%)						<0.001
no	10535 (84.19)	2685 (88.35)	2705 (84.27)	2600 (83.25)	2545 (81.00)	
yes	1979 (15.81)	354 (11.65)	505 (15.73)	523 (16.75)	597 (19.00)	
Stroke, n (%)						0.022
no	11432 (91.35)	2780 (91.48)	2930 (91.28)	2818 (90.23)	2904 (92.43)	
yes	1082 (8.65)	259 (8.52)	280 (8.72)	305 (9.77)	238 (7.57)	
COPD, n (%)						<0.001
no	11469 (91.65)	2833 (93.22)	2984 (92.96)	2862 (91.64)	2790 (88.80)	
yes	1045 (8.35)	206 (6.78)	226 (7.04)	261 (8.36)	352 (11.20)	
Therapeutic measures						
CRRT, n (%)						<0.001
no	11512 (91.99)	2597 (85.46)	2969 (92.49)	2962 (94.84)	2984 (94.97)	
yes	1002 (8.01)	442 (14.54)	241 (7.51)	161 (5.16)	158 (5.03)	
Ventilation, n (%)						0.019
no	1506 (12.03)	401 (13.20)	396 (12.34)	332 (10.63)	377 (12.00)	
yes	11008 (87.97)	2638 (86.80)	2814 (87.66)	2791 (89.37)	2765 (88.00)	
Prognostic indicators						
LOS of hospital, days	15.08 ± 14.11	15.69 ± 15.16	14.83 ± 14.41	14.44 ± 12.45	15.37 ± 14.26	0.002
Los of ICU, days	6.81 ± 7.65	7.03 ± 8.01	6.81 ± 7.98	6.61 ± 7.31	6.81 ± 7.29	0.207
hospital mortality, n (%)						<0.001
no	10234 (81.78)	2540 (83.58)	2746 (85.55)	2596 (83.13)	2352 (74.86)	
yes	2280 (18.22)	499 (16.42)	464 (14.45)	527 (16.87)	790 (25.14)	

(*Contd.*)

Table 1 — Baseline characteristics of the sepsis population according to BCR quartiles — (*Contd.*)

	Total (n = 12,514)	Q1 (n = 3,039)	Q2 (n = 3,210)	Q3 (n = 3,123)	Q4 (n = 3,142)	*P*
ICU mortality, n (%)						<0.001
no	10899 (87.09)	2661 (87.56)	2872 (89.47)	2755 (88.22)	2611 (83.10)	
yes	1615 (12.91)	378 (12.44)	338 (10.53)	368 (11.78)	531 (16.90)	
28d mortality, n (%)						<0.001
no	9899 (79.10)	2502 (82.33)	2698 (84.05)	2503 (80.15)	2196 (69.89)	
yes	2615 (20.90)	537 (17.67)	512 (15.95)	620 (19.85)	946 (30.11)	
180d mortality, n (%)						<0.001
no	8363 (66.83)	2211 (72.75)	2372 (73.89)	2109 (67.53)	1671 (53.18)	
yes	4151 (33.17)	828 (27.25)	838 (26.11)	1014 (32.47)	1471 (46.82)	
365d mortality, n (%)						<0.001
no	7786 (62.22)	2079 (68.41)	2237 (69.69)	1961 (62.79)	1509 (48.03)	
yes	4728 (37.78)	960 (31.59)	973 (30.31)	1162 (37.21)	1633 (51.97)	

BCR, blood urea nitrogen to creatinine ratio; WBC, white blood cell; RBC, red blood cell; RDW, red blood cell distribution width; PT, prothrombin time; PTT, partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate transaminase; SOFA, sequential organ failure assessment; APS III, acute physiology score III; SAPS II, simplified acute physiology score II; OASIS, oxford acute severity of illness score; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO2, percutaneous arterial oxygen saturation; AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CRRT, continuous renal replacement therapy; LOS, length of stay; ICU, intensive care units.
Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as number (%).

The analytic sample size was N=12,514 for Models 1–3; model-specific complete-case rules did not further reduce the cohort because all covariates required for Models 2–3 were available in the analytic dataset .

To explore non-linear dose–response relationships, we fitted restricted cubic spline models for BCR with knots placed at prespecified percentiles of the BCR distribution. Evidence of non-linearity was evaluated by comparing spline models to linear models. Prespecified subgroup analyses evaluated effect modification, including sex stratification. Interaction terms were included in fully adjusted models to formally test effect modification. We used 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of BCR (8.57, 16.25, 22.63, 42.38) and tested non-linearity by likelihood-ratio comparison against a linear term (Pnon-linearity<0.001 for both 28-day and 365-day outcomes) .

Sensitivity and robustness analyses

To evaluate robustness, we performed several prespecified sensitivity analyses. First, we repeated the primary models using alternative definitions of the exposure, including use of the minimum and maximum BCR within the first 24 hours, to explore whether early variability materially altered associations. Second, we evaluated models after excluding patients with extreme creatinine values that could reflect advanced chronic kidney disease or acute rhabdomyolysis, because such conditions may distort the interpretation of the ratio. Third, because AKI is both a predictor and a potential mediator, we tested models with additional adjustment for AKI-related indicators and with stratification by baseline kidney function, recognizing that AKI criteria such as those in KDIGO emphasize changes in creatinine and urine output over time. Fourth, to reduce the possibility that a single comorbidity drove the effect, we repeated analyses excluding patients with severe chronic liver disease, since impaired urea synthesis could lower BUN independently of renal perfusion.

Model diagnostics and assumptions

We examined key model assumptions and diagnostics. Proportional hazards assumptions were evaluated using standard approaches, and we assessed whether the BCR effect appeared time-varying across early and late follow-up. We inspected functional form by comparing linear models with restricted cubic spline models. We also evaluated collinearity among laboratory covariates and severity indicators to ensure stable estimation. Because large ICU datasets can yield statistically significant results for small effects, we emphasized clinical interpretability, reporting effect sizes alongside confidence intervals and considering whether observed differences were plausible given known physiology. Where appropriate, we explored whether adding BCR to baseline models improved model fit, while noting that prediction metrics can be sensitive to outcome incidence and censoring. The correlation matrix of BCR and severity scores is provided in Supplementary Table S1, and variance inflation

factors for all Model 3 covariates are provided in Supplementary Table S2.

Operational definitions and reproducibility

To support reproducibility, variable extraction used consistent time windows anchored to ICU admission. When multiple measurements existed, selection rules were applied uniformly across the cohort. Comorbidity flags were defined using diagnosis coding approaches consistent with prior work in ICU databases. The study was designed to complement, rather than replace, established clinical assessment, and our modeling decisions prioritized interpretability and transportability. The analysis used a single-center database, so external validation in other cohorts will be required before clinical deployment.

Subgroup definitions and prespecified effect modification

We prespecified clinically relevant subgroups for effect modification analyses. Sex was examined a priori because creatinine generation differs by muscle mass and because sex-related differences in immune response and recovery have been reported in critical illness. We also explored subgroups defined by age category, presence of chronic kidney disease, and presence of major cardiovascular comorbidity. Subgroup analyses were implemented by including interaction terms between BCR (continuous or quartiles) and subgroup indicators in fully adjusted Cox models and by reporting stratum-specific hazard ratios. These analyses were interpreted as exploratory and hypothesis-generating. All code followed a predefined workflow, with versioned scripts and fixed time windows to minimize analytic drift. Detailed model estimates are presented in (Table 2).

Results

Cohort characteristics

The final cohort comprised 12,514 critically ill adults with sepsis (Fig 1), and 58.04% were male.

Table 2 — Association between BCR and mortality of Cox proportional hazards models

Outcome	Exposure	Model 1	Model 2	Model 3	*P* for trend (M3)
28-day mortality					
	BCR (per 1-unit increase)	1.02 (1.02–1.03)	1.02 (1.02–1.02)	1.02 (1.01–1.02)	<0.001
	BCR quartiles (ref: Q1)				
	Q2	0.89 (0.79–1.00)	0.78 (0.69–0.88)	1.01 (0.89–1.15)	
	Q3	1.13 (1.01–1.27)	0.92 (0.81–1.03)	1.18 (1.04–1.33)	
	Q4	1.81 (1.63–2.01)	1.43 (1.28–1.60)	1.68 (1.50–1.88)	<0.001
365-day mortality					
	BCR (per 1-unit increase)	1.02 (1.02–1.03)	1.02 (1.02–1.02)	1.02 (1.01–1.02)	<0.001
	BCR quartiles (ref: Q1)				
	Q2	0.94 (0.86–1.03)	0.81 (0.74–0.89)	1.01 (0.92–1.11)	
	Q3	1.21 (1.11–1.32)	0.95 (0.87–1.03)	1.16 (1.07–1.27)	
	Q4	1.91 (1.77–2.07)	1.46 (1.34–1.58)	1.58 (1.45–1.73)	<0.001

Table: Model 1: unadjusted. Model 2: adjusted for age, sex, and weight. Model 3: adjusted for age, sex, weight, WBC, RBC, RDW, sodium, potassium, chloride, anion gap, PT, PTT, SOFA, heart rate, SBP, respiratory rate, atrial fibrillation, AKI, hypertension, heart failure, myocardial infarction, malignant tumor, and CRRT.

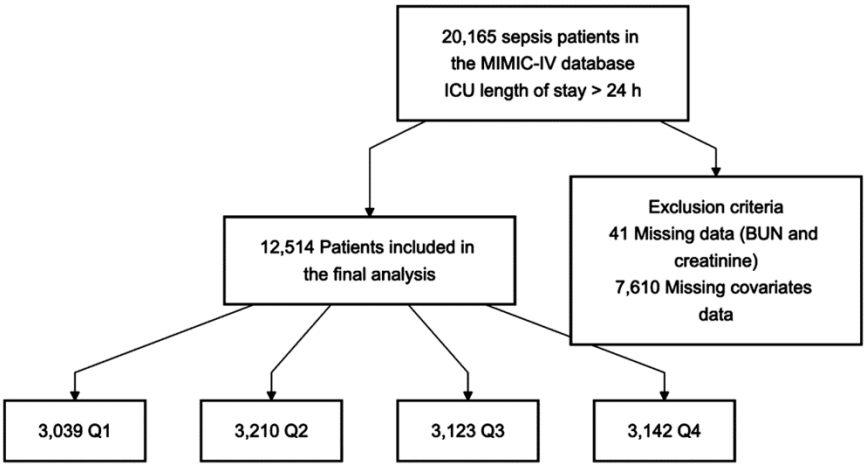

Fig. 1 — Flow chart showing patient screening and inclusion.

Mortality was substantial, with 20.90% of patients dying within 28 days and 37.78% dying within 365 days. BCR exhibited a broad distribution at ICU admission, reflecting heterogeneous perfusion states, renal function, metabolic stress, and baseline physiologic reserve.

Across BCR quartiles, patients with higher ratios tended to be older and to carry a higher burden of chronic disease, including cardiovascular conditions and kidney-related comorbidity. Higher BCR was also associated with greater physiologic derangement early in the ICU stay, including hemodynamic instability and laboratory patterns consistent with metabolic stress and organ dysfunction (Table 1). These patterns suggest that BCR captures clinically meaningful variation in sepsis phenotype at presentation. (Table 1) provides the full baseline profile across quartiles, with variable definitions and abbreviations summarized in the table note.

Association between BCR and 28-day mortality

Survival analyses demonstrated progressively lower survival probability with increasing BCR quartiles (Fig 2). In Cox regression modeling BCR as a continuous exposure, higher BCR was associated with an increased hazard of death at 28 days (Table 2). After full adjustment for demographics, comorbidities, early vital signs, laboratory covariates, and severity indicators, BCR remained independently associated with 28-day mortality (hazard ratio 1.02 per 1-unit increase; 95% confidence interval 1.01–1.02). In quartile analyses, patients in the highest quartile (Q4) had higher 28-day mortality risk compared with those in the lowest quartile (Q1) (hazard ratio 1.68; 95% confidence interval 1.50–1.88) after full adjustment. Intermediate quartiles showed smaller risk increases, consistent with a gradient that intensified at higher BCR levels. Collinearity diagnostics supported stable estimation in the fully adjusted model (Supplementary Tables S1 and S2).

Association between BCR and 365-day mortality

Higher BCR was also associated with increased long-term mortality (Table 2). In the fully adjusted Cox model, BCR remained independently associated with 365-day mortality (hazard ratio 1.02 per 1-unit increase; 95% confidence interval 1.01–1.02). Compared with Q1, Q4 remained associated with increased 365-day mortality (hazard ratio 1.58; 95% confidence interval 1.45–1.73). The persistence of this association suggests that early BCR captures prognostic information relevant not only to the acute ICU phase but also to longer-term recovery and vulnerability.

Non-linear dose–response relationship

Restricted cubic spline models suggested a J-shaped association between BCR and both 28-day and 365-day mortality (Fig 3). Risk was comparatively lower within an intermediate BCR range and increased more steeply at higher ratios, consistent with a high-risk phenotype at extreme elevations of BCR. Associations between BCR and mortality were broadly consistent across prespecified subgroups (Fig 4). Notably, there was a significant interaction

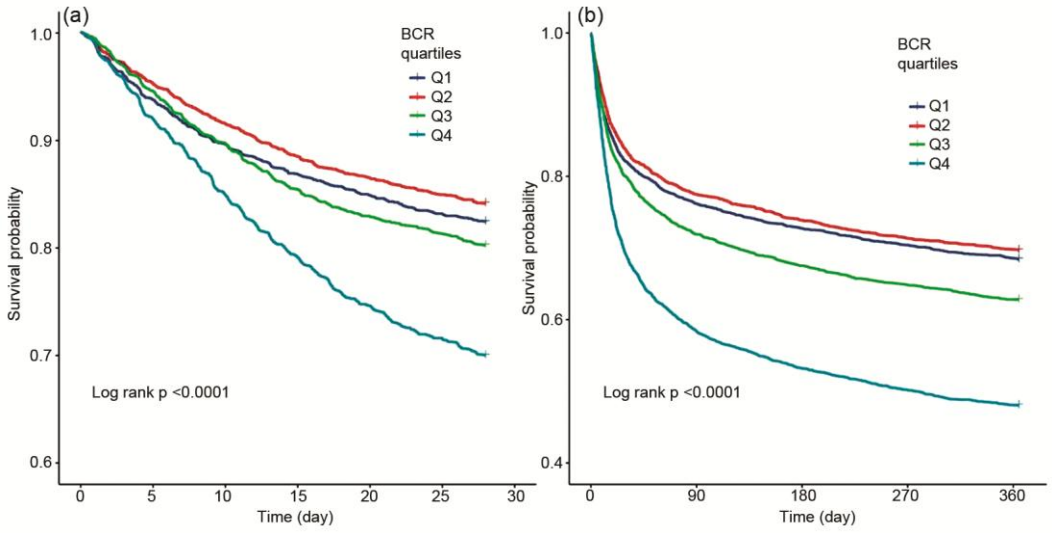

Fig. 2 — Kaplan-Meier analysis. (a) 28-day mortality; (b) 365-day mortality.

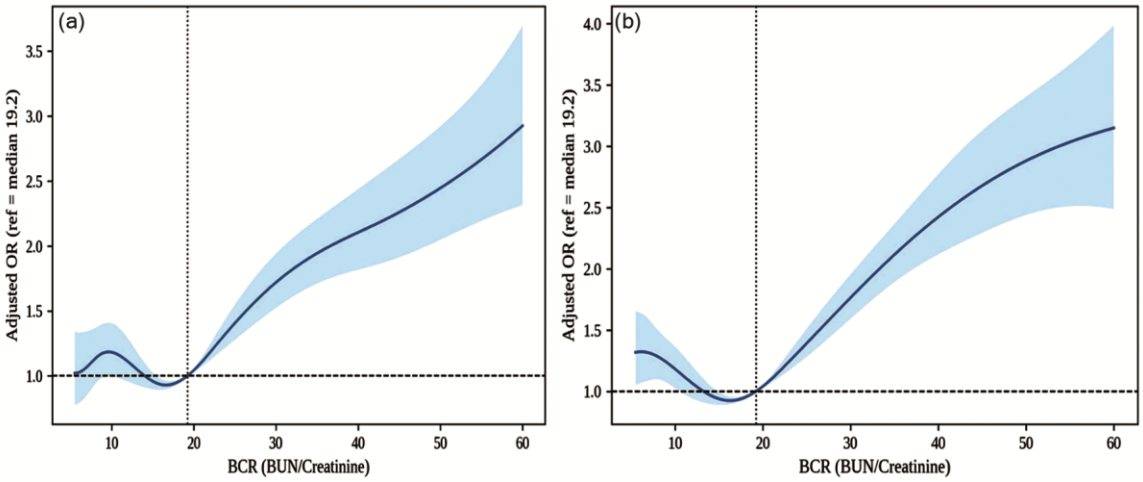

Fig. 3 — Dose-response association between BCR and all-cause mortality in patients with critical sepsis. (a) 28-day mortality; (b) 365-day mortality. (a) Spline model for 28-day mortality. Knots at 5th/35th/65th/95th percentiles; P(non-linearity)=3.1e-05. (b) Spline model for 365-day mortality. Knots at 5th/35th/65th/95th percentiles; P(non-linearity)=9.27e-13.

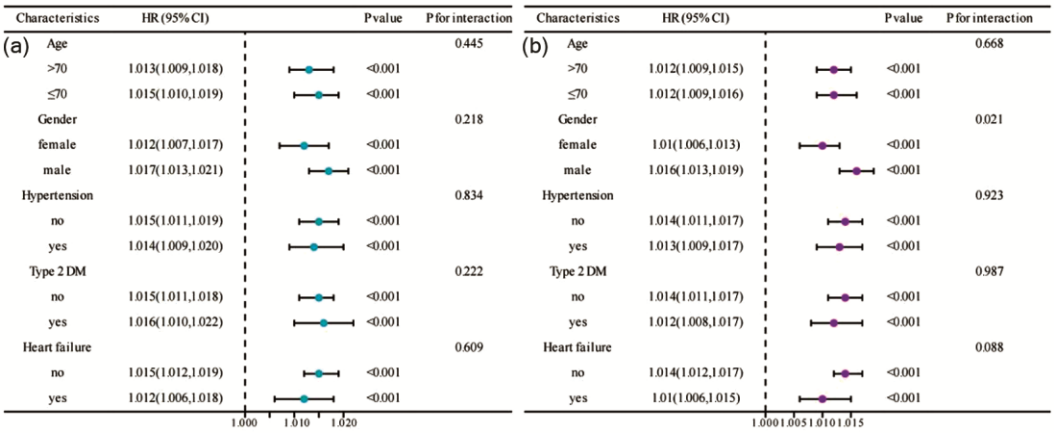

Fig. 4 — Subgroup analysis between BCR and mortality in critically ill sepsis. (a) 28-day mortality; (b) 365-day mortality. Interaction P values are displayed above each subgroup stratum in the revised figure; sex interaction was significant for 365-day mortality.

between sex and 365-day mortality, suggesting that the relationship between BCR and longer-term outcomes may differ between males and females. Effect modification for 28-day mortality was less pronounced.

Additional analyses supporting robustness

In models that progressively adjusted for confounders, the association between BCR and mortality attenuated but remained statistically and clinically meaningful, indicating that BCR is not merely a proxy for age or baseline comorbidity. Non-linear modeling consistently demonstrated an inflection at higher BCR values, where risk rose more steeply. This behavior supports the interpretation that very high ratios represent a distinct, high-risk physiologic state rather than incremental variation around normal physiology. Adding BCR to the age-, sex-, and SOFA-based model increased the AUC from 0.686 to 0.701 for 28-day mortality and from 0.684 to 0.699 for 365-day mortality (Supplementary Table S3).

In subgroup analyses, the pattern of association persisted across clinically relevant strata, suggesting that the BCR signal is broadly applicable in critically ill sepsis populations. The interaction between sex and 365-day mortality indicates that the same absolute ratio may correspond to different physiologic meaning across sexes. Because creatinine generation differs by muscle mass, a similar BCR could be achieved via different combinations of BUN and creatinine in males and females. This observation reinforces the need to interpret BCR with clinical context and suggests that future risk models may require sex-specific calibration.

Discussion

In this large cohort of critically ill patients with sepsis, higher early blood urea nitrogen-to-creatinine ratio was independently associated with increased all-cause mortality at both 28 days and 365 days. The association persisted after adjustment for demographics, comorbidities, early physiologic variables, laboratory markers, and severity indicators, suggesting that BCR provides prognostic information beyond conventional risk factors. Non-linear modeling suggested a J-shaped relationship between BCR and mortality, and sex modified the association for 365-day outcomes[4,29]. An elevated BCR is commonly interpreted as a marker of prerenal physiology, where reduced effective circulating volume increases urea reabsorption relative to creatinine. Sepsis can reduce effective arterial blood volume through systemic vasodilation, capillary leak, and relative hypovolemia. Even when clinicians maintain blood pressure with vasopressors, microvascular dysfunction and maldistribution of blood flow can limit renal oxygen delivery and filtration[23]. Under these conditions, BUN may rise due to enhanced urea reabsorption and reduced renal clearance, while creatinine may change more slowly, producing a higher ratio. Thus, a high BCR may signal clinically important circulatory stress that is not fully captured by a single snapshot of blood pressure[17].

In addition to prerenal physiology, sepsis-associated kidney dysfunction involves inflammatory and microvascular mechanisms. Endothelial activation, cytokine release, oxidative stress, and mitochondrial dysfunction contribute to tubular injury and dysregulated transport. Venous congestion and increased intra-abdominal pressure can reduce renal perfusion pressure. These mechanisms can influence solute handling and alter the relationship between BUN and creatinine. Because BCR integrates both markers, it may serve as a composite signal of renal stress rather than a specific diagnostic discriminator[1,5,14,30].

BCR is also sensitive to systemic catabolism. Urea production increases with protein breakdown and neuroendocrine stress responses, while creatinine generation depends largely on skeletal muscle mass and creatine metabolism. Critically ill patients with sepsis often exhibit hypermetabolism and accelerated proteolysis, particularly during prolonged inflammation or inadequate nutrition. Meanwhile, many patients—especially older adults and those with chronic illness—have low skeletal muscle mass, which lowers creatinine generation and can elevate BCR even if filtration is not severely impaired[31]. In this context, a high BCR may reflect a combination of acute stress physiology and limited physiologic reserve. This interpretation is consistent with the finding that BCR remained associated with 365-day mortality, a time horizon influenced by baseline reserve, persistent inflammation, and post-ICU complications[20]. The J-shaped association observed in spline analyses suggests that risk does not increase uniformly across the full range of BCR. The steep rise at high ratios is biologically plausible and may represent severe hypoperfusion, intense catabolism, or both. Conversely, very low BCR values may correspond to alternative high-risk phenotypes. Low ratios can occur when creatinine is disproportionately elevated, such as in intrinsic kidney dysfunction, muscle injury, or advanced chronic kidney disease, or when BUN is relatively low due to impaired hepatic urea synthesis or dilution from aggressive fluid administration. These distinct mechanisms may confer elevated risk through different pathways, leading to a non-linear overall pattern. Clinically, this emphasizes that BCR should be interpreted in context rather than as a simple linear risk factor. In particular, very low BCR values may reflect (i) low urea production due to hepatic dysfunction, (ii) dilutional lowering of BUN from aggressive fluid resuscitation, (iii) disproportionate creatinine elevation from intrinsic renal injury or muscle injury (e.g., rhabdomyolysis), or (iv) altered muscle mass/creatinine generation patterns—distinct phenotypes that may confer risk through different pathways in sepsis.

Our findings align with prior studies suggesting that BCR and related urea-based indices provide prognostic information in acute illness. Elevated BCR has been associated with worse outcomes in cardiovascular disease and in ischemic stroke, where it may reflect hemodynamic compromise and neurohormonal activation[24,27]. Sepsis shares key features of circulatory stress, neurohormonal activation, and catabolism, making it plausible that BCR would track risk in this setting. The present study extends the evidence by evaluating both short-term and long-term mortality in a large ICU cohort and by demonstrating non-linear patterns and effect modification[15,18,32].

BCR has pragmatic advantages: it is inexpensive, routinely measured, and available early in nearly all ICU patients. If validated in external cohorts, BCR could complement established severity scores by providing a simple laboratory-based signal of combined perfusion stress and metabolic reserve. A

markedly elevated BCR early after ICU admission may prompt clinicians to reassess perfusion adequacy, monitor for evolving kidney injury, and consider early nutritional and rehabilitation strategies aimed at mitigating catabolic loss. Because BCR reflects components of both renal physiology and systemic stress, it may be particularly useful when interpreted alongside hemodynamic data, lactate trends, and other markers of organ dysfunction.

The observed interaction between sex and 365-day mortality suggests that the long-term prognostic meaning of BCR may differ between males and females. Sex differences in muscle mass and creatinine generation can shift BCR even when renal perfusion is similar, and biological differences in immune response and recovery trajectories may further influence long-term risk. These observations suggest that BCR-based thresholds or models may require sex-aware calibration, especially for long-term prediction and post-discharge follow-up planning[11]. This interaction was also observed when modeling BCR as quartiles (highest vs lowest quartile showing a stronger association in females for 365-day mortality), consistent with sex-related differences in baseline muscle mass (creatinine generation) and potentially in post-sepsis recovery trajectories.

This study leveraged a large ICU database with rich time-stamped clinical data, enabling robust adjustment for confounding and evaluation of both short-term and long-term mortality. We modeled BCR in multiple ways and explored non-linearity using spline methods, improving physiologic interpretability. However, limitations should be noted. First, the retrospective design prevents causal inference, and residual confounding from unmeasured factors (pre-hospital hydration, nutritional status, medication exposure, and clinician decisions) may persist. Second, exposure was defined using early values, but BCR may change dynamically during resuscitation and recovery; trajectory analyses could provide additional insights. Third, the data derive from a single health system, and external validation is required. Finally, without direct measures of muscle mass or baseline diet, mechanistic attribution of BCR changes remains incomplete.

Future research should validate these findings across multiple institutions and sepsis subtypes and evaluate whether adding BCR improves performance of existing prediction models. Dynamic modeling of BCR trajectories may identify clinically actionable patterns, such as rapidly rising ratios suggesting ongoing hypoperfusion or accelerating catabolism. Mechanistic studies integrating hemodynamic monitoring, biomarkers of proteolysis and inflammation, and measures of body composition could clarify the drivers of the J-shaped relationship. Prospective work could also explore whether BCR-guided management strategies improve outcomes. Future work should quantify incremental predictive performance (e.g., change in C-statistic, calibration, and net reclassification improvement) when adding BCR to a parsimonious baseline model (age, sex, and a single severity score such as SOFA) to clarify its clinical added value.

Conclusion

Higher early blood urea nitrogen-to-creatinine ratio is independently associated with increased 28-day and 365-day all-cause mortality in critically ill patients with sepsis. The association appears J-shaped, and sex may modify long-term risk. BCR is a simple and widely available marker that may support early risk stratification in ICU sepsis care. Although BUN and creatinine are universally available in ICU practice, the prognostic meaning of their ratio (BCR) in sepsis—particularly for both short- and long-term mortality and potential non-linearity—remains insufficiently characterized.

In our cohort, the highest BCR quartile had 49% higher 28-day mortality risk and 41% higher 365-day mortality risk versus the lowest quartile after full adjustment, supporting the study objective of evaluating BCR as an early, pragmatic risk-stratification marker in sepsis ICU care.

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Consent to Publish

The manuscript has neither been previously published nor is under consideration by any other journal. The authors have all approved the content of the paper.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Competing interests

The authors declare no competing interests.

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