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J-shaped association between blood urea nitrogen-to-creatinine ratio and mortality in critically ill patients with acute pancreatitis: a retrospective cohort study using the MIMIC-IV database

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Abstract

Background Both blood urea nitrogen (BUN) and creatinine (Cr) are indicators of kidney function, and the BUN/Cr ratio has been identified as an independent prognostic marker for adverse outcomes in critically ill patients with various conditions. However, the relationship between the BUN/Cr ratio and long-term mortality in critically ill patients with acute pancreatitis (AP) remains unclear. Hence, the primary objective of this study was to determine the prognostic value of the BUN/Cr ratio in patients with AP.

Methods We conducted a retrospective cohort study using data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. The primary exposure variable was the BUN/Cr ratio at intensive care unit (ICU) admission, and the primary outcome was 365-day all-cause mortality. Kaplan–Meier analyses and multivariate Cox proportional hazards models were used to assess this relationship, while restricted cubic spline (RCS) was used to explore potential non-linear associations. In addition, subgroup analyses were conducted to assess consistency between groups.

Results A total of 850 critically ill patients with AP were included, with a mean age of 59.61 years, 58.59% male, and an overall 365-day mortality rate of 20.94%. Patients in the highest BUN/Cr quartile had significantly higher mortality rates compared to those in lower quartiles. Multivariate Cox regression analysis demonstrated that, even after adjusting for potential confounders, an elevated BUN/Cr ratio remained an independent predictor of increased 28-day and 365-day mortality. RCS analysis confirmed a J-shaped relationship between the BUN/Cr ratio and 28-day and 365-day mortality, with a sharp increase in the risk of death above the 16.80 threshold. Subgroup analysis indicated that this association was consistent across various patient characteristics.

Conclusion This study identified a non-linear relationship between the BUN/Cr ratio and 365-day mortality in critically ill patients with AP, suggesting that the BUN/Cr ratio may serve as an easily accessible, cost-effective, and accurate prognostic marker for this population.

Keywords Acute pancreatitis, Blood urea nitrogen, Creatinine, Mortality, MIMIC-IV

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Introduction

Acute pancreatitis (AP) is a rapidly occurring inflammatory disorder of the pancreas, marked by overactivation of digestive enzymes within the organ, which results in the pancreas digesting its own tissue [1]. The global incidence of acute pancreatitis has been steadily increasing in recent years, reaching an annual rate of 13–45 cases per 100,000 individuals [2]. This rise is largely attributed to the growing prevalence of obesity, alcohol consumption, and gallstone disease [3]. The severity of AP can vary greatly, ranging from mild cases to severe forms. Approximately 80% of AP cases are mild and self-limiting, requiring only symptomatic treatment, intravenous fluids, and supportive care [4]. However, about 20% progress to severe AP, often requiring intensive care unit (ICU) admission due to complications such as pancreatic necrosis or organ failure [5]. Unfortunately, even with ICU admission, the prognosis for patients with severe AP remains poor, with mortality rates reaching as high as 40% during their ICU stay [6, 7]. As a result, it is essential to establish methods for forecasting outcomes in AP patients in the ICU, allowing clinicians to promptly identify high-risk patients and apply targeted interventions.

Currently, various commonly used scoring systems, including the Acute Physiology and Chronic Health Evaluation (APACHE-II), the Balthazar CT Severity Index, as well as the Bedside Index for Severity in AP (BISAP) [8–10], are utilized to evaluate AP severity and forecast patient outcomes. However, these systems often rely heavily on a combination of clinical, imaging, and laboratory parameters, which can make them complex and time-consuming. Consequently, their limitations—including the need for extensive data collection and delayed evaluation—underscore the need for faster, simpler, and more reliable prognostic tools to improve the timely management of AP patients.

Blood urea nitrogen (BUN) is a waste product formed during protein metabolism in the liver and is removed through the kidneys. It is commonly used to assess kidney function, hydration status, and other metabolic conditions. For example, elevated BUN levels typically indicate impaired kidney function or dehydration [11]. However, increased BUN can also result from heart failure, gastrointestinal bleeding, or increased protein intake [12]. Similarly, creatinine (Cr) is a byproduct of the regular breakdown of muscle tissue and is removed from the blood by the kidneys. It is a reliable marker of kidney function, because it is produced at a relatively steady rate and eliminated exclusively by the kidneys. For instance, patients suffering from chronic kidney disease (CKD) or acute kidney injury (AKI) typically exhibit significantly elevated Cr levels [13]. However, Cr levels may also be impacted by factors including muscle mass, medications like cimetidine, trimethoprim, and sulfonamides, physical exercise, and liver function [14]. Since the use of BUN or Cr individually can be influenced by a wide range of unrelated factors, physicians are increasingly turning to the BUN/Cr ratio for its reliability as a better indicator. This ratio helps to mitigate the influence of individual fluctuations in BUN or Cr levels, providing a more consistent assessment [15]. Previous studies have shown that the BUN/Cr ratio serves as an independent predictor for adverse consequences among critically ill individuals suffering from conditions, such as stroke, nontraumatic intracranial hemorrhage, venous thromboembolism, cerebral infarction, and atrial fibrillation [16–20]. In addition, previous studies have shown that BUN levels are an independent risk factor for all-cause mortality in patients with severe AP [21]. Nevertheless, the relationship linking the BUN/Cr ratio and prognosis in critically ill AP patients has not been fully investigated.

Based on the current research gaps and previous findings, we designed this study to investigate the connection between the BUN/Cr ratio and mortality outcomes in critically ill patients suffering from AP. Utilizing data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, we gathered clinical information from AP patients to assess whether the BUN/Cr ratio at ICU admission is linked to mortality outcomes. Our findings could offer valuable insights into potential biomarkers for early risk stratification in this high-risk population.

Methods

Data source

This research leveraged the MIMIC-IV database, a widely available critical care dataset that provides comprehensive ICU patient records from Beth Israel Deaconess Medical Center, covering the years 2008 to 2019. The database contains extensive information on patient demographics, vital signs, lab results, comorbidities, treatments, and clinical outcomes of hospitalized individuals. The MIMIC-IV database is accessible through the PhysioNet platform. To gain access, to and utilize the data, one of the study's authors, Yu Wan, completed the CITI courses for human research (certificate number: 65947659).

Patient selection criteria

The study included ICU patients diagnosed with AP, identified using the ICD codes from both the 9th (577.0) and 10th (K85-K85.92) revisions of the International Classification of Diseases. Patients younger than 18 years or with incomplete BUN or Cr data at ICU admission

were excluded from the study. In cases where patients experienced more than one ICU admission related to AP, only information from the initial admission was included in the study. Finally, 850 patients fulfilled the inclusion criteria and were ultimately incorporated into the final analysis (Fig. 1).

Data collection

The data extraction process was conducted using Structured Query Language (SQL) with PostgreSQL (version: 12.7.0) to query the MIMIC-IV database. Other extracted variables included demographic information, vital signs, laboratory measurements, clinical severity scores, comorbidities, clinical treatments, and patient outcomes (28-day mortality as well as 365-day mortality).

If one of the variables is missing less than 20%, interpolation is done using random forests; otherwise, it is discarded.

Grouping and endpoint events

The main variable examined in this study was the BUN/Cr ratio. To minimize treatment-related interference, the BUN and Cr levels were extracted from the first laboratory results after ICU admission, and the BUN/Cr ratio was calculated by dividing the serum BUN level (mg/dL) by the serum Cr level (mg/dL). The primary endpoint was all-cause mortality at 28 days and 365 days following ICU admission.

Statistical analysis

In this study, categorical variables were expressed as frequencies and percentages. The normality of continuous variables was evaluated using the Kolmogorov–Smirnov test. For continuous variables following a normal distribution, data were presented as means ± standard deviation (SD), while non-normally distributed variables were reported as medians with interquartile ranges (IQR). For comparisons of normally distributed continuous variables, one-way analysis of variance (ANOVA) or Student's t test was used, whereas for non-normally distributed continuous variables, the Kruskal–Wallis test or Mann–Whitney U test was applied. Pearson's χ^2 test or Fisher's exact test was used for categorical variable comparisons. Kaplan–Meier curves and multivariate Cox proportional hazards regression models were utilized to assess the association between the BUN/Cr ratio and mortality, with the latter adjusting for a great variety of confounders (including demographic characteristics, laboratory measurements, clinical severity scores, comorbidities, and clinical treatment) and reporting hazard ratios (HRs) and 95% confidence intervals (CIs). Since the restricted cubic spline (RCS) is a commonly used method for exploring non-linear relationships, allowing for flexible modeling between continuous variables and outcomes, we employed RCS here to analyze the non-linear relationship between the BUN/Cr ratio and mortality. This approach enabled a more precise assessment of how variations in the BUN/Cr ratio are associated

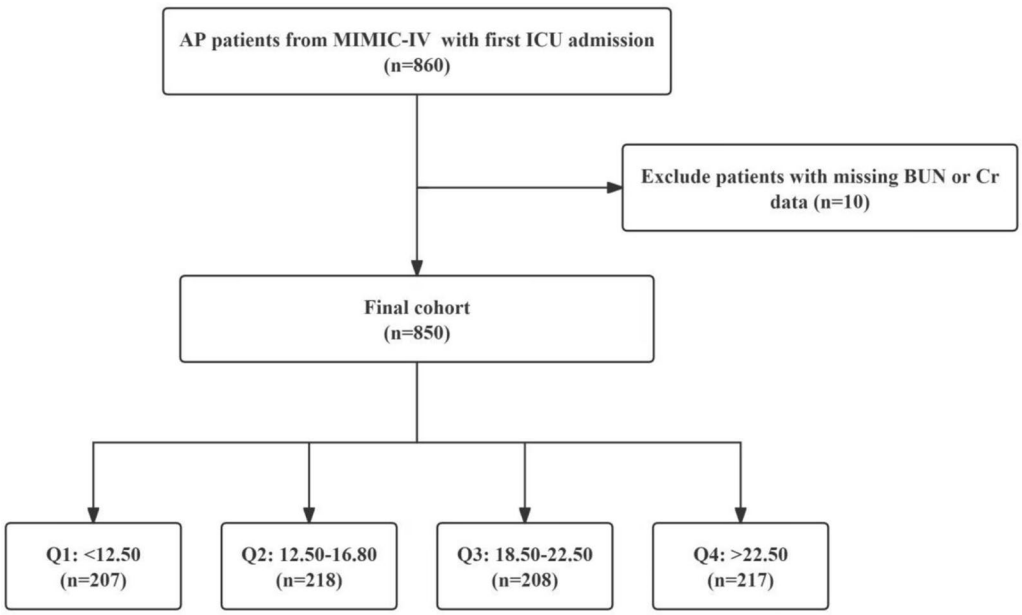

Fig. 1 Flowchart of our critically ill patients with AP

with changes in mortality risk. Finally, we performed a subgroup analysis to explore whether the BUN/Cr ratio had any differential effects across various subgroups of critically ill AP patients.

R statistical program (version 4.0.0, R Foundation for Statistical Computing, Austria) was applied for our analysis in this study, and a two-tailed *P* value of less than 0.05 was deemed statistically significant.

Results

Baseline characteristics

In this research, 850 critically ill patients diagnosed with AP were selected according to the predefined eligibility standards. The mean age of the entire cohort was 59.61 years, with 58.59% (498) being male. The baseline traits of the study participants, grouped according to BUN/Cr ratio quartiles, are shown in Table 1. Individuals with higher BUN/Cr ratios tended to be older, had a higher percentage of females, exhibited faster respiratory rates, and had a greater prevalence of comorbid conditions, such as AKI, hypertension, heart failure, malignant tumors, and sepsis. They also showed higher mean APS III and SAPS II scores, indicating greater disease severity. In terms of laboratory values, patients with higher BUN/Cr ratio exhibited elevated levels of WBC, platelet, sodium, chloride, and glucose, but decreased levels of hemoglobin, anion gap, ALT, and AST. In terms of treatments, patients with higher BUN/Cr ratios had a lower incidence of CRRT use but a higher frequency of treatment with beta-blockers and octreotide. Additionally, patients in the highest BUN/Cr quartile exhibited greater 28-day and 365-day mortality rates compared to those in the lower quartiles.

The study population was then divided into survival and non-survival groups based on their status at 365 days following ICU admission. Table 2 summarizes the baseline traits of these two groups. In comparison to the survival group, individuals in the non-survival group were typically of an older age, had lower body weight, and exhibited significantly higher levels of WBC, anion gap, PTT, RDW, potassium, BUN, and Cr. Conversely, they had lower levels of RBC and hemoglobin. Additionally, the non-survival group demonstrated higher SOFA, APS III, and SAPS II scores, indicating greater disease severity. Comorbidities including AKI, cancer, respiratory failure, and sepsis were more common in the non-survival group. Additionally, the non-survival group required CRRT, octreotide, and vasopressin treatment more frequently than the survival group. Most notably, the non-survival group exhibited significantly higher BUN/Cr ratios compared to the survival group (22.46 ± 12.08 vs. 17.91 ± 9.84, $p < 0.001$).

Relationship between BUN/Cr ratio and mortality

In Fig. 2, the Kaplan–Meier survival plot illustrates the association between the BUN/Cr ratio and the survival probability in critically ill AP patients. The results indicated that patients in the highest quartile had the poorest chances of survival (log-rank $p < 0.05$).

As presented in Table 3, the Cox proportional hazards models confirmed that higher BUN/Cr ratios were independently linked to a higher risk of 28-day and 365-day mortality. In the unadjusted model (Model 1), patients in the highest BUN/Cr quartile (Q4) had a significantly higher hazard of death within 28 days and 365 days compared to those in the lowest quartile (Q1) (28-day: HR = 2.68, 95% CI: 1.51–4.76, $p < 0.001$; 365-day: HR = 2.78, 95% CI: 1.78–4.34, $p < 0.001$). After full adjustment in Model 3, patients in the highest BUN/Cr quartile (Q4) still showed a markedly higher 28-day and 365-day mortality risk than those in the lowest quartile (Q1) (28-day: HR = 2.05, 95% CI: 1.03–4.11, $p = 0.042$; 365-day: HR = 1.79, 95% CI: 1.07–3.00, $p = 0.026$).

As shown in Fig. 3, the RCS plot further illustrated the non-linear association between the BUN/Cr ratio and mortality. The RCS curve revealed a J-shaped association (28-day: non-linear $p = 0.015$; 365-day: non-linear $p = 0.028$), where the risk of death initially decreased with rising BUN/Cr ratios but sharply increased beyond a certain threshold. Specifically, BUN/Cr ratios above 16.80 were associated with a significant elevation in 28-day and 365-day mortality risk.

Subgroup analysis

Table 4 outlines the subgroup analyses conducted to investigate the connection between the BUN/Cr ratio and mortality, considering different patient characteristics. The BUN/Cr ratio was divided into two groups using a threshold of 16.80, identified from the J-shaped curve in Fig. 3, where mortality risk sharply increases beyond this point.

The analysis demonstrated that the link between elevated BUN/Cr and higher mortality risk remained consistent across most subgroups, with no significant interactions detected (*P* for interaction > 0.05) in groups based on age, gender, or the use of CRRT, beta-blockers, octreotide, or ventilation.

Discussion

This study explored the association between the BUN/Cr ratio and mortality in critically ill patients with AP. Our results revealed a J-shaped association between the BUN/Cr ratio and mortality: initially, a modest increase in the BUN/Cr ratio was linked to a lower risk of death, but once a certain threshold was exceeded, the mortality

Table 1 Baseline characteristics of the AP population stratified by BUN/Cr ratio quartiles

	Total (*n* = 850)	**Q1 (*n* = 207)**	**Q2 (*n* = 218)**	**Q3 (*n* = 208)**	**Q4 (*n* = 217)**	***P***
Age, years	59.61 ± 17.54	49.73 ± 15.26	59.51 ± 17.10	62.75 ± 17.41	66.12 ± 16.05	< 0.001
Gender, *n* (%)						0.020
Female	352 (41.41)	82 (39.61)	77 (35.32)	85 (40.87)	108 (49.77)	
Male	498 (58.59)	125 (60.39)	141 (64.68)	123 (59.13)	109 (50.23)	
Weight, kg	86.08 ± 24.01	87.11 ± 25.60	87.02 ± 22.63	87.81 ± 26.12	82.49 ± 21.32	0.084
WBC, K/μL	13.83 ± 8.09	11.98 ± 6.33	13.03 ± 7.09	15.02 ± 8.96	15.26 ± 9.17	< 0.001
RBC, m/μL	3.71 ± 0.81	3.76 ± 0.76	3.77 ± 0.75	3.70 ± 0.93	3.63 ± 0.80	0.292
Platelet, K/μL	211.59 ± 127.27	191.87 ± 116.25	204.70 ± 99.77	217.88 ± 132.64	231.30 ± 151.88	0.010
Hemoglobin, g/dL	11.32 ± 2.37	11.57 ± 2.16	11.52 ± 2.23	11.19 ± 2.66	11.00 ± 2.38	0.038
RDW, %	14.95 ± 1.94	14.90 ± 1.94	14.72 ± 1.85	14.96 ± 1.91	15.20 ± 2.05	0.072
Sodium, mmol/L	138.24 ± 5.58	136.66 ± 5.44	137.96 ± 5.27	138.61 ± 5.43	139.65 ± 5.78	< 0.001
Potassium, mmol/L	4.12 ± 0.82	4.14 ± 0.80	4.15 ± 0.81	4.18 ± 0.98	4.01 ± 0.65	0.168
Calcium, mg/dL	7.88 ± 1.06	7.76 ± 1.15	7.84 ± 1.02	7.94 ± 1.07	7.99 ± 1.00	0.110
Chloride, mmol/L	104.26 ± 6.88	102.34 ± 6.94	104.18 ± 6.57	104.77 ± 6.44	105.67 ± 7.14	< 0.001
Glucose, mg/dL	152.65 ± 108.73	137.28 ± 58.57	148.26 ± 86.24	164.40 ± 161.31	160.47 ± 101.71	0.045
Anion gap, mmol/L	16.08 ± 5.21	17.00 ± 5.94	16.08 ± 5.02	15.86 ± 5.22	15.43 ± 4.50	0.016
BUN, mg/dL	26.88 ± 24.43	20.40 ± 24.31	21.67 ± 19.85	28.97 ± 24.30	36.29 ± 25.70	< 0.001
Cr, mg/dL	1.62 ± 1.79	2.39 ± 2.89	1.49 ± 1.38	1.47 ± 1.19	1.17 ± 0.75	< 0.001
BUN/Cr ratio	18.86 ± 10.51	8.98 ± 2.28	14.64 ± 1.18	19.44 ± 1.64	31.97 ± 11.86	< 0.001
PT, sec	16.56 ± 9.58	16.95 ± 14.62	16.03 ± 6.13	16.63 ± 7.20	16.65 ± 8.29	0.791
PTT, sec	34.71 ± 15.98	35.92 ± 18.50	35.09 ± 16.92	34.60 ± 16.04	33.29 ± 11.85	0.387
ALT, u/dL	224.71 ± 797.05	352.63 ± 1251.78	219.58 ± 738.44	211.89 ± 623.07	120.12 ± 236.50	0.027
AST, u/dL	364.55 ± 1488.38	608.21 ± 1994.32	371.42 ± 1574.42	334.28 ± 1516.48	154.22 ± 342.98	0.019
SOFA score	5.63 ± 4.16	5.84 ± 4.84	5.43 ± 4.07	5.74 ± 4.06	5.53 ± 3.61	0.735
APS III score	51.02 ± 24.35	49.69 ± 27.05	47.89 ± 23.62	50.89 ± 24.03	55.57 ± 22.05	0.008
SAPS II score	35.82 ± 16.17	31.89 ± 17.46	33.94 ± 14.91	37.83 ± 16.65	39.54 ± 14.53	< 0.001
Heart rate, beats/minute	98.50 ± 21.98	99.93 ± 22.39	96.96 ± 22.56	97.50 ± 21.21	99.64 ± 21.72	0.399
Respiratory rate, breath/minute	21.09 ± 6.78	20.87 ± 6.83	20.87 ± 6.29	20.38 ± 6.43	22.21 ± 7.39	0.034
AKI, *n* (%)						0.029
No	287 (33.76)	73 (35.27)	89 (40.83)	64 (30.77)	61 (28.11)	
Yes	563 (66.24)	134 (64.73)	129 (59.17)	144 (69.23)	156 (71.89)	
COPD, *n* (%)						0.918
No	814 (95.76)	197 (95.17)	210 (96.33)	200 (96.15)	207 (95.39)	
Yes	36 (4.24)	10 (4.83)	8 (3.67)	8 (3.85)	10 (4.61)	
Hypertension, *n* (%)						0.012
No	446 (52.47)	126 (60.87)	110 (50.46)	112 (53.85)	98 (45.16)	
Yes	404 (47.53)	81 (39.13)	108 (49.54)	96 (46.15)	119 (54.84)	
Type 2 DM, *n* (%)						0.567
No	620 (72.94)	154 (74.40)	165 (75.69)	147 (70.67)	154 (70.97)	
Yes	230 (27.06)	53 (25.60)	53 (24.31)	61 (29.33)	63 (29.03)	
Heart failure, *n* (%)						< 0.001
No	714 (84.00)	190 (91.79)	186 (85.32)	156 (75.00)	182 (83.87)	
Yes	136 (16.00)	17 (8.21)	32 (14.68)	52 (25.00)	35 (16.13)	
Myocardial infarction, *n* (%)						0.699
No	826 (97.18)	203 (98.07)	210 (96.33)	203 (97.60)	210 (96.77)	
Yes	24 (2.82)	4 (1.93)	8 (3.67)	5 (2.40)	7 (3.23)	
Malignant tumors, *n* (%)						0.003
No	774 (91.06)	200 (96.62)	195 (89.45)	191 (91.83)	188 (86.64)	
Yes	76 (8.94)	7 (3.38)	23 (10.55)	17 (8.17)	29 (13.36)	

Table 1 (continued)

	Total ($n=850$)	Q1 ($n=207$)	Q2 ($n=218$)	Q3 ($n=208$)	Q4 ($n=217$)	*P*
Stroke, *n* (%)						0.294
No	795 (93.53)	197 (95.17)	207 (94.95)	193 (92.79)	198 (91.24)	
Yes	55 (6.47)	10 (4.83)	11 (5.05)	15 (7.21)	19 (8.76)	
Obesity, *n* (%)						0.578
No	747 (87.88)	182 (87.92)	190 (87.16)	179 (86.06)	196 (90.32)	
Yes	103 (12.12)	25 (12.08)	28 (12.84)	29 (13.94)	21 (9.68)	
Respiratory failure, *n* (%)						0.316
No	533 (62.71)	139 (67.15)	140 (64.22)	124 (59.62)	130 (59.91)	
Yes	317 (37.29)	68 (32.85)	78 (35.78)	84 (40.38)	87 (40.09)	
Sepsis, *n* (%)						0.049
No	323 (38.00)	92 (44.44)	85 (38.99)	78 (37.50)	68 (31.34)	
Yes	527 (62.00)	115 (55.56)	133 (61.01)	130 (62.50)	149 (68.66)	
CRRT, *n* (%)						0.022
No	762 (89.65)	177 (85.51)	196 (89.91)	184 (88.46)	205 (94.47)	
Yes	88 (10.35)	30 (14.49)	22 (10.09)	24 (11.54)	12 (5.53)	
Beta-blocker, *n* (%)						< 0.001
No	426 (50.12)	131 (63.29)	105 (48.17)	91 (43.75)	99 (45.62)	
Yes	424 (49.88)	76 (36.71)	113 (51.83)	117 (56.25)	118 (54.38)	
Metformin, *n* (%)						0.423
No	827 (97.29)	201 (97.10)	209 (95.87)	204 (98.08)	213 (98.16)	
Yes	23 (2.71)	6 (2.90)	9 (4.13)	4 (1.92)	4 (1.84)	
Octreotide, *n* (%)						0.009
No	782 (92.00)	193 (93.24)	206 (94.50)	195 (93.75)	188 (86.64)	
Yes	68 (8.00)	14 (6.76)	12 (5.50)	13 (6.25)	29 (13.36)	
Statin, *n* (%)						0.408
No	782 (92.00)	195 (94.20)	196 (89.91)	190 (91.35)	201 (92.63)	
Yes	68 (8.00)	12 (5.80)	22 (10.09)	18 (8.65)	16 (7.37)	
Vasopressin, *n* (%)						0.754
No	713 (83.88)	175 (84.54)	184 (84.40)	177 (85.10)	177 (81.57)	
Yes	137 (16.12)	32 (15.46)	34 (15.60)	31 (14.90)	40 (18.43)	
Ventilation, *n* (%)						0.248
No	200 (23.53)	57 (27.54)	55 (25.23)	44 (21.15)	44 (20.28)	
Yes	650 (76.47)	150 (72.46)	163 (74.77)	164 (78.85)	173 (79.72)	
28-day mortality, *n* (%)						< 0.001
No	757 (89.06)	191 (92.27)	204 (93.58)	188 (90.38)	174 (80.18)	
Yes	93 (10.94)	16 (7.73)	14 (6.42)	20 (9.62)	43 (19.82)	
365-day mortality, *n* (%)						< 0.001
No	672 (79.06)	180 (86.96)	180 (82.57)	165 (79.33)	147 (67.74)	
Yes	178 (20.94)	27 (13.04)	38 (17.43)	43 (20.67)	70 (32.26)	

Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as number (%)

BUN blood urea nitrogen, *Cr* creatinine, *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, *AKI* acute kidney injury, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *CRRT* continuous renal replacement therapy

risk escalated sharply. This non-linear relationship persisted as significant even with adjustments for most of the potential confounders, highlighting an important and underexplored finding in the field. These results suggest that the BUN/Cr ratio may serve as a valuable prognostic indicator in the ICU setting, helping clinicians to identify high-risk AP patients early and guide timely intervention.

In the past, BUN was frequently applied as a standalone marker to assess the severity of AP and forecast patients' outcomes, with several studies demonstrating

Table 2 Baseline characteristics of the survival and non-survival groups based on 365-day mortality

	Total (*n* = 850)	**Survival (*n* = 672)**	**Non-survival (*n* = 178)**	***P***
Age, years	59.61 ± 17.54	57.29 ± 17.23	68.35 ± 15.94	< 0.001
Gender, *n* (%)				0.282
Female	352 (41.41)	272 (40.48)	80 (44.94)	
Male	498 (58.59)	400 (59.52)	98 (55.06)	
Weight, kg	86.08 ± 24.01	86.89 ± 24.82	83.01 ± 20.44	0.032
WBC, K/μL	13.83 ± 8.09	13.43 ± 7.57	15.34 ± 9.67	0.015
RBC, m/μL	3.71 ± 0.81	3.76 ± 0.79	3.56 ± 0.87	0.004
Platelet, K/μL	211.59 ± 127.27	213.78 ± 124.90	203.34 ± 135.91	0.331
Hemoglobin, g/dL	11.32 ± 2.37	11.46 ± 2.33	10.78 ± 2.45	< 0.001
RDW, %	14.95 ± 1.94	14.67 ± 1.70	15.99 ± 2.39	< 0.001
Sodium, mmol/L	138.24 ± 5.58	138.06 ± 5.29	138.88 ± 6.53	0.124
Potassium, mmol/L	4.12 ± 0.82	4.07 ± 0.77	4.29 ± 0.96	0.006
Calcium, mg/dL	7.88 ± 1.06	7.89 ± 1.03	7.83 ± 1.19	0.490
Chloride, mmol/L	104.26 ± 6.88	104.12 ± 6.58	104.78 ± 7.90	0.313
Glucose, mg/dL	152.65 ± 108.73	152.11 ± 111.66	154.70 ± 97.13	0.777
Anion gap, mmol/L	16.08 ± 5.21	15.62 ± 4.92	17.82 ± 5.88	< 0.001
PT, sec	16.56 ± 9.58	16.25 ± 10.12	17.72 ± 7.08	0.068
PTT, sec	34.71 ± 15.98	33.45 ± 14.50	39.50 ± 19.97	< 0.001
ALT, u/dL	224.71 ± 797.05	227.48 ± 863.79	214.23 ± 467.48	0.844
AST, u/dL	364.55 ± 1488.38	331.47 ± 1392.31	489.42 ± 1804.75	0.208
BUN, mg/dL	26.88 ± 24.43	23.44 ± 21.50	39.85 ± 29.93	< 0.001
Creatinine, mg/dL	1.62 ± 1.79	1.50 ± 1.72	2.10 ± 1.96	< 0.001
BUN/Cr ratio	18.86 ± 10.51	17.91 ± 9.84	22.46 ± 12.08	< 0.001
SOFA score	5.63 ± 4.16	5.01 ± 3.82	7.98 ± 4.54	< 0.001
APS III score	51.02 ± 24.35	46.77 ± 21.88	67.08 ± 26.47	< 0.001
SAPS II score	35.82 ± 16.17	32.65 ± 14.59	47.80 ± 16.26	< 0.001
Heart rate, beats/minute	98.50 ± 21.98	98.78 ± 22.12	97.46 ± 21.47	0.476
Respiratory rate, breath/minute	21.09 ± 6.78	21.04 ± 6.81	21.29 ± 6.66	0.657
AKI, *n* (%)				< 0.001
No	287 (33.76)	252 (37.50)	35 (19.66)	
Yes	563 (66.24)	420 (62.50)	143 (80.34)	
Hypertension, *n* (%)				0.003
No	446 (52.47)	335 (49.85)	111 (62.36)	
Yes	404 (47.53)	337 (50.15)	67 (37.64)	
Type 2 DM, *n* (%)				0.728
No	620 (72.94)	492 (73.21)	128 (71.91)	
Yes	230 (27.06)	180 (26.79)	50 (28.09)	
Heart failure, *n* (%)				0.084
No	714 (84.00)	572 (85.12)	142 (79.78)	
Yes	136 (16.00)	100 (14.88)	36 (20.22)	
Myocardial infarction, *n* (%)				0.130
No	826 (97.18)	656 (97.62)	170 (95.51)	
Yes	24 (2.82)	16 (2.38)	8 (4.49)	
Malignant tumors, *n* (%)				0.003
No	774 (91.06)	622 (92.56)	152 (85.39)	
Yes	76 (8.94)	50 (7.44)	26 (14.61)	
Stroke, *n* (%)				0.233
No	795 (93.53)	632 (94.05)	163 (91.57)	
Yes	55 (6.47)	40 (5.95)	15 (8.43)	

Table 2 (continued)

	Total (*n* = 850)	Survival (*n* = 672)	Non-survival (*n* = 178)	*P*
Obese, *n* (%)				0.006
No	747 (87.88)	580 (86.31)	167 (93.82)	
Yes	103 (12.12)	92 (13.69)	11 (6.18)	
Respiratory failure, *n* (%)				< 0.001
No	533 (62.71)	448 (66.67)	85 (47.75)	
Yes	317 (37.29)	224 (33.33)	93 (52.25)	
Sepsis, *n* (%)				< 0.001
No	323 (38.00)	284 (42.26)	39 (21.91)	
Yes	527 (62.00)	388 (57.74)	139 (78.09)	
CRRT, *n* (%)				< 0.001
No	762 (89.65)	632 (94.05)	130 (73.03)	
Yes	88 (10.35)	40 (5.95)	48 (26.97)	
Beta-blocker, *n* (%)				0.380
No	426 (50.12)	342 (50.89)	84 (47.19)	
Yes	424 (49.88)	330 (49.11)	94 (52.81)	
Metformin, *n* (%)				0.229
No	827 (97.29)	651 (96.88)	176 (98.88)	
Yes	23 (2.71)	21 (3.12)	2 (1.12)	
Octreotide, *n* (%)				0.006
No	782 (92.00)	627 (93.30)	155 (87.08)	
Yes	68 (8.00)	45 (6.70)	23 (12.92)	
Statin, *n* (%)				0.314
No	782 (92.00)	615 (91.52)	167 (93.82)	
Yes	68 (8.00)	57 (8.48)	11 (6.18)	
Vasopressin, *n* (%)				< 0.001
No	713 (83.88)	611 (90.92)	102 (57.30)	
Yes	137 (16.12)	61 (9.08)	76 (42.70)	
Ventilation, *n* (%)				0.117
No	200 (23.53)	166 (24.70)	34 (19.10)	
Yes	650 (76.47)	506 (75.30)	144 (80.90)	

Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as number (%)

BUN blood urea nitrogen, *Cr* creatinine, *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, *AKI* acute kidney injury, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *CRRT* continuous renal replacement therapy

its value as a biomarker in this context [22, 23]. However, due to the influence of various external factors, the reliability of using BUN alone has been questioned. In recent years, the BUN/Cr ratio has proven to be a more reliable tool for anticipating outcomes in various critically ill patient populations [16–18], as it accounts for both BUN and Cr levels, providing a more comprehensive assessment of renal function and fluid status. Given the evidence supporting both BUN and the BUN/Cr ratio, this study aimed to investigate the prognostic significance of the BUN/Cr ratio among critically ill AP patients, particularly in relation to mortality risk.

Interestingly, we observed a J-shaped connection between the BUN/Cr ratio and mortality. Specifically, on the left side of the J-curve, as the BUN/Cr ratio rises, the risk of death gradually decreases. However, on the right side of the J-curve, a higher BUN/Cr ratio corresponds to a sharp increase in mortality risk. This non-linear relationship can be explained by relevant pathophysiological mechanisms.

On the one hand, as a byproduct of muscle metabolism, Cr reflects the rate of muscle breakdown or catabolism [24]. In patients experiencing significant muscle catabolism, Cr levels can rise rapidly, leading to a reduction in the BUN/Cr ratio. Therefore, the low BUN/Cr ratio seen on the left side of the J-curve may also indicate excessive muscle breakdown. Under these conditions, the breakdown of muscle cells releases large amounts of potassium,

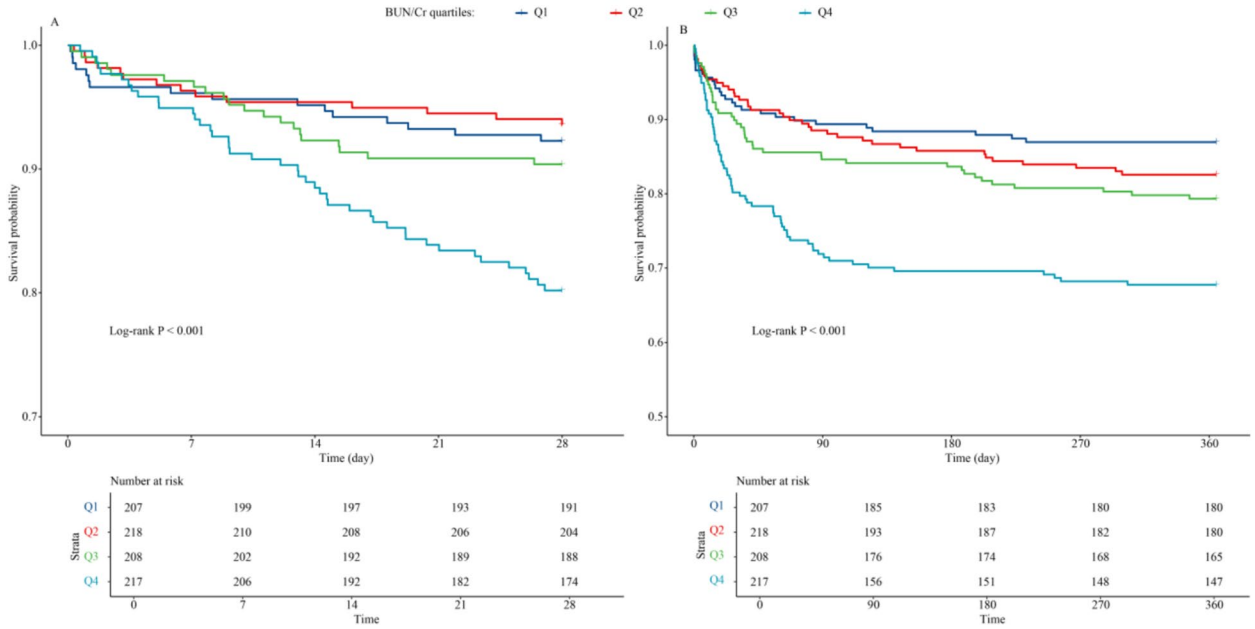

Fig. 2 Kaplan–Meier analysis between BUN/Cr ratio mortality in critically ill patients with AP (**A** 28- day mortality; **B** 365- day mortality)

Table 3 The relationship between BUN/Cr ratio and mortality in AP patients

	Model 1		Model 2		Model 3	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
28-day mortality						
BUN/Cr ratio	1.03(1.02, 1.04)	< 0.001	1.03(1.01, 1.04)	< 0.001	1.03(1.01, 1.04)	0.003
BUN/Cr ratio quartiles						
Q1	Ref		Ref		Ref	
Q2	0.82(0.40, 1.69)	0.597	0.68(0.33, 1.40)	0.290	0.83(0.39, 1.77)	0.631
Q3	1.25(0.65, 2.42)	0.501	0.96(0.49, 1.88)	0.896	0.88(0.43, 1.81)	0.729
Q4	2.68(1.51, 4.76)	< 0.001	1.93(1.06, 3.53)	0.032	2.05(1.03, 4.11)	0.042
P for trend		< 0.001		0.003		0.018
365-day mortality						
BUN/Cr ratio	1.02(1.02, 1.03)	< 0.0001	1.02(1.01, 1.03)	< 0.0001	1.02(1.01, 1.03)	0.001
BUN/Cr ratio quartiles						
Q1	Ref		Ref		Ref	
Q2	1.34(0.82, 2.19)	0.247	0.98(0.59, 1.63)	0.942	1.13(0.67, 1.90)	0.656
Q3	1.63(1.01, 2.65)	0.045	1.10(0.67, 1.81)	0.712	0.96(0.57, 1.61)	0.870
Q4	2.78(1.78, 4.34)	< 0.001	1.72(1.08, 2.75)	0.023	1.79(1.07, 3.00)	0.026
P for trend		< 0.001		0.005		0.025

Model 1: no adjustment

Model 2: adjusted for age, gender, and weight

Model 3: adjusted for age, gender, weight, WBC, RBC, hemoglobin, RDW, potassium, anion gap, PTT, SOFA score, APS III score, SAPS II score, AKI, hypertension, malignant tumors, obese, respiratory failure, sepsis, octreotide, vasopressin, and CRRT

BUN blood urea nitrogen, *Cr* creatinine, *WBC* white blood cell, *RBC* red blood cell, *RDW* red blood cell distribution width, *PTT* partial thromboplastin time, *SOFA* sequential organ failure assessment, *APS III* acute physiology score III, *SAPS II* simplified acute physiology score II, *AKI* acute kidney injury, *CRRT* continuous renal replacement therapy, *HR* hazard ratio, *CI* confidence interval

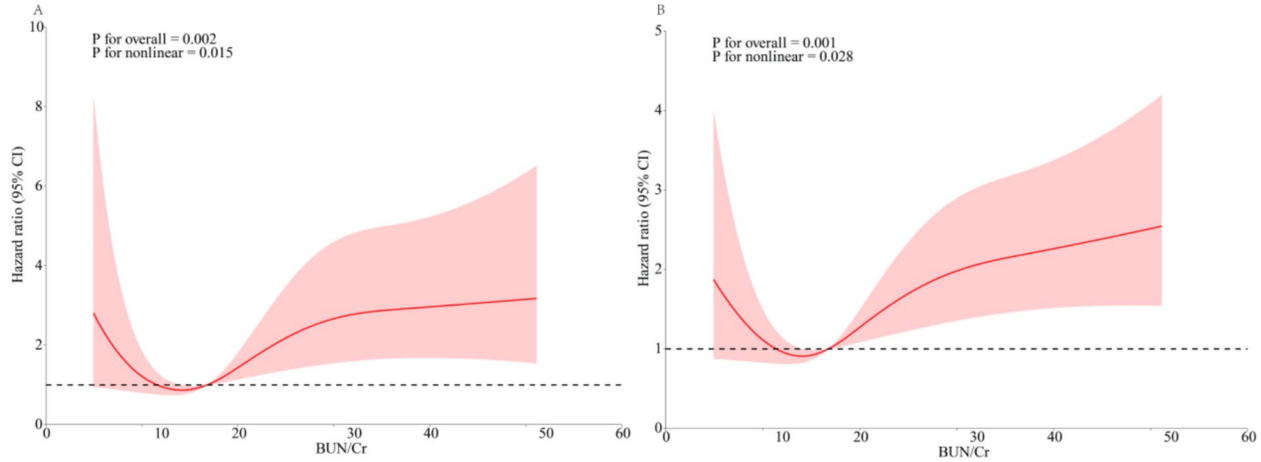

Fig. 3 RCS plot for all-cause mortality (**A** 28- day mortality; **B** 365- day mortality)

which can lead to life-threatening arrhythmias [25]. Thus, a decreasing BUN/Cr ratio due to rising Cr levels may signal a critical threshold of muscle catabolism. This catabolic state is associated with the onset of severe complications, such as hyperkalemia and arrhythmias, which increase the risk of death, even when the BUN/Cr ratio is low. This interpretation highlights the importance for clinicians to remain vigilant when encountering an abnormally low BUN/Cr ratio. A low ratio typically considered a less severe indicator, may actually mask the severity of the patient's condition, as the reduction is primarily due to a spike in Cr from muscle breakdown rather than an improvement in kidney function.

On the other hand, our results revealed that a higher BUN/Cr ratio (after exceeding the cut-off value) was related to a poorer prognosis in AP patients. It is well established that a significant rise in the BUN/Cr ratio indicates a convergence of dehydration and stimulation of the renin–angiotensin–aldosterone system (RAAS) [26, 27]. Dehydration reduces the effectiveness of pancreatic perfusion, exacerbating local inflammation and pancreatic necrosis, which can lead to the failure of multiple organs [28]. As dehydration progresses, the body activates the RAAS in response to reduced perfusion pressures. This activation results in vasoconstriction, fluid retention, and the upregulation of inflammatory pathways, all of which contribute to worsening outcomes and even death [29].

In short, based on this J-shaped association, we propose that both a very low and a very high BUN/Cr ratio can be equally dangerous. A low ratio might reflect excessive muscle breakdown, whereas a high ratio indicates dehydration and RAAS activation, both of which can elevate the likelihood of death in critically ill AP patients.

Notably, prior research, including the work by Yi et al. and Li et al., has demonstrated that after applying various therapeutic interventions to alleviate AP, the BUN/Cr ratio consistently declined [30, 31]. This reduction in the BUN/Cr ratio following treatment improvements aligns with our study's conclusion that a higher BUN/Cr ratio is related to worse outcomes in AP patients.

The BUN/Cr ratio, used as a prognostic indicator for critically ill patients with AP, offers several advantages. It is easily accessible, cost-effective, and capable of providing rapid results [32]. Furthermore, our subgroup analysis demonstrated that its predictive value remained consistent across different patient subgroups, highlighting its stability and reliability in various clinical contexts.

Nonetheless, this study has a few limitations. First, being a retrospective analysis, this study is subject to potential residual confounding, even with attempts to account for known variables. Second, the lack of specific clinical data, such as detailed nutritional information or muscle mass assessments, may have affected the accuracy of the BUN/Cr ratio analysis. Third, our study relied solely on baseline BUN/Cr data at ICU admission, without considering potential changes in the ratio during the ICU stay, which could offer more valuable insights.

Conclusion

In summary, our study may be the first to identify a J-shaped association linking the BUN/Cr ratio to short- and long-term mortality in critically ill AP patients, with both extremely low and elevated BUN/Cr values possibly linked to a higher risk of death. This research underscores the BUN/Cr ratio as a readily accessible, cost-effective, and practical prognostic marker for predicting long-term outcomes in this population. Its

Table 4 Subgroup analysis for the association between BUN/Cr ratio and mortality in critically ill patients with AP

	***n* (%)**	**< 16.80**	**≥ 16.80**	**HR (95%CI)**	***P***	***P* for interaction**
All patients	850 (100.00)	30/425	63/425	1.65 (1.01,2.70)	0.045	
28-day mortality						
Age						0.348
< 60	425 (50.00)	15/267	12/158	1.03 (0.37,2.91)	0.952	
≥ 60	425 (50.00)	15/158	51/267	1.96 (1.00,3.82)	0.049	
Gender						0.867
Female	352 (41.41)	10/159	31/193	2.05 (0.84,4.97)	0.113	
Male	498 (58.59)	20/266	32/232	2.19 (1.11,4.33)	0.024	
CRRT						0.203
No	762 (89.65)	14/373	45/389	2.44 (1.22,4.88)	0.012	
Yes	88 (10.35)	16/52	18/36	1.81 (0.71,4.58)	0.214	
Beta-blocker						0.192
No	426 (50.12)	22/236	33/190	1.62 (0.81,3.27)	0.176	
Yes	424 (49.88)	8/189	30/235	2.12 (0.92,4.90)	0.078	
Octreotide						0.938
No	782 (92.00)	25/399	51/383	1.76 (1.02,3.03)	0.042	
Yes	68 (8.00)	5/26	12/42	1.51 (0.07,34.31)	0.797	
Ventilation						0.397
No	200 (23.53)	7/112	9/88	3.65 (0.58,22.96)	0.168	
Yes	650 (76.47)	23/313	54/337	1.72 (0.99,2.97)	0.054	
365-day mortality						
Age						0.741
< 60	425 (50.00)	26/267	25/158	1.56 (0.81,3.00)	0.187	
≥ 60	425 (50.00)	39/158	88/267	1.19 (0.78,1.81)	0.421	
Gender						0.927
Female	352 (41.41)	24/159	56/193	1.41 (0.81,2.44)	0.224	
Male	498 (58.59)	41/266	57/232	1.85 (1.16,2.93)	0.009	
CRRT						0.163
No	762 (89.65)	41/373	89/389	1.63 (1.08,2.44)	0.019	
Yes	88 (10.35)	24/52	24/36	1.25 (0.56,2.80)	0.580	
Beta-blocker						0.899
No	426 (50.12)	35/236	49/190	1.55 (0.91,2.62)	0.106	
Yes	424 (49.88)	30/189	64/235	1.40 (0.88,2.24)	0.155	
Octreotide						0.857
No	782 (92.00)	57/399	98/383	1.48 (1.03,2.12)	0.034	
Yes	68 (8.00)	8/26	15/42	0.78 (0.10,6.08)	0.814	
Ventilation						0.369
No	200 (23.53)	15/112	19/88	1.12 (0.46,2.75)	0.800	
Yes	650 (76.47)	50/313	94/337	1.37 (0.94,2.00)	0.102	

predictive value remained significant after adjusting for confounding factors and was consistent across different patient subgroups, further supporting its clinical utility.

Author contributions

Yu Wan designed the study, performed the data analysis, and wrote the main manuscript text. Qiong Hu assisted with data collection and statistical analysis. Jing Shi contributed to the interpretation of the results and reviewed the manuscript. Limei Liu and Xiangsong Zhang helped in the literature review and edited the manuscript. Jianjun Huang and Haijiu wang provided guidance on the study design, supervised the research, and revised the manuscript critically. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study utilized the MIMIC database, which has been approved for research use by the Institutional Review Boards of both Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. A waiver of informed consent was granted due to the retrospective nature of the study and the use of de-identified data. All authors agreed to the publication of the article.

Competing interests
The authors declare no competing interests.

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