Association Between Blood Urea Nitrogen to Creatinine Ratio and in-hospital Mortality Among Patients With Acute Myocardial Infarction- A Retrospective Cohort Study

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Abstract

Purpose: This study aimed to determine the association between blood urea nitrogen (BUN) and creatinine(Cr) ratio and in-hospital mortality in patients with acute myocardial infarction(AMI).

Patients and Methods: This retrospective cohort study included adult patients (≥ 18 years of age) who were admitted to the intensive care unit (ICU) with a primary diagnosis of AMI were enrolled. Their data were collected from the eICU Collaborative Research Database (eICU-CRD) throughout the continental USA. The data collected from the database included demographic data, vital signs, laboratory test data, and comorbidities. The clinical endpoint was in-hospital mortality. The Cox proportional hazards model was used to evaluate the prognostic values of the basic BUN/Cr ratio, and the Kaplan–Meier method was used to plot survival curves. Subgroup analyses were performed to measure mortality across various subgroups.

Results: In total, 3,831 eligible patients were included. In the multivariate analysis, after being adjusted for age, sex, and ethnicity, the BUN/Cr ratio was found to be a significant risk predictor of in-hospital mortality. The nonlinear relationship between the BUN/Cr ratio and in-hospital mortality was explored in a dose-dependent manner with an apparent inflection point of 18. Furthermore, after adjusting for more confounding factors, the BUN/Cr ratio remained a significant predictor of in-hospital mortality (tertile 3 vs.tertile 1: hazard ratio 2.14; 95% confidence interval 1.16-3.97; $p<0.05$).The Kaplan–Meier curve for tertiles of the BUN/Cr ratio indicated that survival rates were highest and lowest when the BUN/Cr ratio was ≤ 15.12 and ≥ 19.41 , respectively, after adjustment for age, sex, and ethnicity($p<0.001$).

Conclusion: Our findings showed that a higher BUN/Cr ratio was associated with an increased risk of in-hospital mortality in patients with AMI. These results support a revision of how we predict the prognosis of patients with AMI.

Background

Acute myocardial infarction (AMI) is a fatal disease that results in high morbidity and mortality rates. Blood urea nitrogen (BUN) and creatinine (Cr) are the end products of nitrogen metabolism in humans. They are small molecules that can be filtered from nephrons. Usually, approximately 30–40% of BUN is reabsorbed from the kidney tubules. In contrast, Cr is not as well reabsorbed as BUN[1,2]. BUN is an important parameter that reflects the relationship between the patient's kidney condition, protein metabolism level, and nutritional status. Studies showed that urea nitrogen levels are closely related to mortality [3,4]. A high BUN level could be a useful predictor of in-hospital mortality in patients with AMI [5]. Clinically, Cr content is often used to detect changes in renal function, which aids in the detection of renal failure or improvement in renal function. This finding was augmented by that of Granger et al. [6]who reported that Cr was a marker of renal function, and the relationship between renal dysfunction and increased mortality was well established in patients with AMI.

The BUN/Cr ratio is defined as the ratio of BUN to serum Cr. As a new biomarker, the BUN/Cr ratio has emerged as an independent prognostic indicator of poor outcomes in different disease conditions, such as acute and chronic heart failure [7-9], acute and chronic kidney injury [10], and ischemic stroke [11]. Studies

demonstrated that an elevated BUN/Cr ratio was associated with poor prognosis in patients with acute heart failure(AHF). Moreover, an elevated BUN/Cr ratio was found to be an independent predictor of all-cause mortality [1,12].

There is existing research on the risk factors for mortality in patients with heart failure. However, the relationship between BUN/Cr ratio and in-hospital mortality has not been fully investigated in patients with AMI in the intensive care unit(ICU). In our study, we aimed to comprehensively evaluate the role of the BUN/Cr ratio in predicting the severity and survival of patients with AMI.

Material And Methods

Study design

This was a multicenter retrospective observational study. Analyses were carried out on data subsets obtained from participants in the electronic intensive care unit Collaborative Research Database (eICU-CRD), which was an open-access de-identified dataset of patients maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. The ICU-CRD covered patients at 208 US hospitals that were monitored by the eICU programs between 2014 and 2015 [13,14]. The database includes records of demographics, hourly physiologic readings from bedside monitors, disease diagnoses via the International Classification of Diseases, Ninth Revision codes, and other clinical data collected during routine medical care. Since all protected health information was de-identified, the requirement for individual patient consent was waived. The use of this database was approved by the institutional review boards of Massachusetts Institute of Technology (Cambridge,MA, USA). All authors of this manuscript completed the necessary training and received permission to access the database. One author (Xiangjie Duan) obtained access to the database and was responsible for data extraction (certification number:42039823).Bona fide researchers can apply to access the Collaborative Research Database via a standard application procedure (further details available at: <https://eicu-crd.mit.edu/about/eicu/>).

Clinical endpoints

The primary endpoint of this study was in-hospital mortality. The patients were divided into two groups: survivors and non-survivors. The intergroup differences in parameters measured in the ICU were then evaluated.

Study Population

Patients were diagnosed with AMI according to the International Classification of Diseases 9 code (ICD-9), which was 140.This study enrolled adult patients(≥ 18 years) admitted to the ICU. Only patients at the first admission with a first diagnosis of AMI were included. Patients were excluded if the date of death was less than the date of ICU hospitalization to avoid potential typographical errors in the original data. Patients without BUN and Cr measurements during ICU admission were also excluded from the study. Patients with

an eGFR ≥ 60 mL/min/per 1.73 m^2 were also excluded. The study population was comprised of 3,831 patients with AMI. The selection procedure for the study participants is summarized in Fig.1.

Definition of AMI

Clinical evidence of acute myocardial injury was defined as a rise and/or fall in the cardiac troponin (or cTn) values with at least one value >99 th percentile of the upper reference limit and at least one of the following symptoms of myocardial ischemia: symptoms of acute myocardial ischemia, new ischemic electrocardiogram (ECG) changes, development of pathological Q waves, and imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology [15,16].

Statistical analyses

Categorical variables are expressed as counts and percentages in each category. Continuous variables are specified as appropriate means and standard deviations or medians and interquartile ranges. The Student's t-test and Mann–Whitney U test were used for continuous variables. The χ^2 and Fisher's exact tests were used for categorical variables. First, we used multivariate models with crude and adjusted hazard ratios (HRs). We used the generalized additive model (GAM) to adjust the continuous variables in Model II. The covariates that were significantly associated with the response variable ($p < 0.05$) or those that changed the effect estimate by 10% or more were retained in the final adjusted model [17]. We then used the GAM to identify the nonlinear relationship between BUN/Cr ratio and in-hospital mortality. If a nonlinear correlation was detected, a two-piecewise linear regression model was used to determine the threshold effect of the BUN/Cr ratio on in-hospital mortality in accordance with the smoothing plot. If the BUN/Cr and in-hospital mortality ratio appeared in the smoothing plot, the inflection point was determined automatically by the recursive method using the maximum model likelihood [18-19]. Finally, we inspected the modification and interaction of the subgroups using the likelihood ratio test. We generated receiver operating characteristic (ROC) curves to measure the sensitivity and specificity of the BUN/Cr ratio and calculated the area under the curve (AUC) to ascertain the quality of the BUN/Cr ratio as a predictor of in-hospital mortality in patients with AMI. Moreover, we determined the relationship between BUN/Cr ratio and the classic scoring systems (APACHE scores).

All data were analyzed using R software (version 3.42) and Empower Stats version 2.17.8 (<http://www.empowerstats.com/cn/>). Statistical significance was defined as a p-value of less than 0.05, and all reported p-values were two-sided.

Results

Study participants and baseline characteristics

The data of a total of 6,616 AMI patients were extracted from the database. Patients without data for BUN (n=328) or Cr(n=50) levels were excluded from the study. Patients with an eGFR $\leq$ 60mL/min/per 1.73 m²were excluded. A total of 3,831 (57.9%) patients were included in the statistical analyses. The ICU admission rate of patients without a BUN or Cr level was 5.7% (378 out of 6,616 patients), and the overall in-hospital mortality rate was 3.71% (142 out of 3,831patients). The mean BUN/Cr ratio was 18.6 $\pm$ 8.2. A flow chart of the study is shown in Fig.1.

The baseline data of the study population are given in Table1. According to the BUN/Cr ratio, 1271, 1274, and 1286 patients fell into the first (<14.6), second (≥ 14.7 and <19.8), and third (≥ 20.0) tertiles, respectively. In general, the patients' mean age was 62.2 $\pm$ 12.4 years, and 2,689(70.2%) patients were male patients. No statistically significant differences were detected between the groups in terms of the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), international normalized ratio (INR), heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), capillary blood glucose (CABG),and incidence of percutaneous coronary intervention (PCI) between the different groups (all p values > 0.05). Factors observed among participants with high BUN/Cr ratio levels included having an older age, being a Caucasian, having a longer hospital stay, and having higher WBC, RDW, HDL, and potassium values(all p values <0.05). The opposite was observed for body mass index (BMI), red blood cell (RBC) count, levels of platelets, (total cholesterol)TC, triglycerides (TG), and low-density lipoprotein (LDL), heart rate (HR), and history of diabetes and hypertension (all p values <0.05).

We illustrated the in-hospital mortality of the two groups in supplementary Fig.1.The mortality rate of non-STEMI patients was 4.9%,which was significantly higher than that of the STEMI group (2.8%, p=0.001).

Kaplan–Meier Survival Curves of the BUN/Cr Ratio for Predicting the In-Hospital Mortality Among Patients with AMI

The Kaplan–Meier curve for the tertiles of the BUN/Cr ratio is shown in Fig.2. The figure indicated that survival rates were highest when the BUN/Cr ratio was ≤ 15.12 and lowest when the BUN/Cr ratio was ≥ 19.41 after adjustment for age, sex, and ethnicity (log-rank test p <0.001). The BUN/Cr ratio was used to distinguish between different survival statuses. It had good discrimination.

The BUN/Cr ratio as a Predictor of In-hospital Mortality

We constructed three different models to analyze the independent effects of the BUN/Cr ratio on the in-hospital mortality of critically ill patients with AMI grouped according to the BUN/Cr ratio tertiles. As shown in Table2, in model I, after adjustment for age, sex, and ethnicity, a higher BUN/Cr ratio was associated with an increased risk of in-hospital mortality compared with those in the first tertile. In model II, after adjusting for more confounding factors, the BUN/Cr ratio was found to be an independent predictor of in-hospital mortality in critically ill patients with AMI as well (tertile 3 vs.tertile 1: adjusted HR, 2.14; 95% CI, 1.16–3.97; p for trend <0.05).

Analyses of the nonlinear relationship between the BUN/Cr ratio and in-hospital mortality

It is essential to analyze the nonlinear relationships among continuous variables. In this study (Fig.3), we detected a nonlinear relationship between the BUN/Cr ratio and in-hospital mortality after adjusting for age, sex, and ethnicity. Using the two-piecewise linear regression model, we calculated the inflection point as 18. The HR (95%CI) and p values were 1.31 (1.15, 1.49) and <0.0001 , respectively, on the right of the inflection point. However, on the left of the inflection point, the BUN/Cr ratio–mortality relationship was insignificant (HR = 0.99, 95% CI: 0.91, 1.07; $p = 0.7299$; Table3).

Subgroup analyses

The results of the subgroup analyses are presented in Table4. After adjusting for potential confounders, we found that the test for the interaction was statistically significant for history of CHF (p for interaction <0.0001) and the AMI category (p for interaction = 0.0002). However, statistical significance was not observed for age, sex, BMI, history of diabetes, history of hypertension, PCI, CABG, glucose, heart rate, and LDL. We also found evidence of BUN/Cr–AMI category interactions. The effect of the BUN/Cr ratio on in-hospital mortality significantly differed among patients with different AMI categories. The BUN/Cr ratio was positively correlated with in-hospital mortality (HR = 1.25, 95% CI: [1.14, 1.37]) in patients with non-ST-segment elevation myocardial infarction (non-STEMI). However, there was no significant relationship between the BUN/Cr ratio and the in-hospital mortality in patients with ST-segment elevation myocardial infarction (STEMI). Moreover, we observed that the BUN/Cr ratio was positively correlated with the in-hospital mortality if the BUN/Cr ratio was > 18 .

Prediction of in-hospital mortality

The ROC curves generated using the indicated variables (BUN/Cr plus APACHE scores and APACHE scores) are plotted in Supplementary Fig. 2. The AUCs for the APACHE scores were 0.859 and 0.861 for BUN/Cr plus APACHE scores (all $p < 0.001$).

Discussion

The results of our study showed that an elevated BUN/Cr ratio indicated an increased risk of in-hospital death in patients with AMI. Even after adjusting for other mixed factors in the multivariate models, the BUN/Cr ratio was associated with adverse outcomes. Our results confirmed the findings of the aforementioned studies and even went a step further. We found that there was a nonlinear relationship between BUN/Cr and in-hospital mortality in patients with AMI. Upon conducting a subgroup analysis, it was found that BUN/Cr was associated with an increased risk of in-hospital death in critically ill AMI patients. The AUC of the BUN/Cr ratio plus APACHE score had a predictive value.

AMI is a common cause of hospital admissions, readmissions, and mortality worldwide [20]. Despite the widespread use of reperfusion techniques and improvements in adjunctive medical therapies, patients with AMI still face a substantial risk of further cardiovascular events and mortality [21].

BUN was not a specific marker of renal insufficiency; therefore, predictions based on BUN or Cr alone might have limitations. Cr is affected by extra renal factors, such as muscle mass, sex, age, nutrition, and race. Although estimated GFR improves the assessment of renal function, overestimation and underestimation still exist among patients with a wide range of serum Cr levels [22]. Similarly, the serum concentrations of BUN are influenced by many factors [23]. Hence, it is not necessarily a marker of decreased glomerular filtration rate [24]. Therefore, the BUN/Cr ratio has been proposed as a useful parameter for reducing the above influencing factors. The BUN/Cr ratio might be a more stable and accurate marker for evaluating the prognosis of patients with AMI than serum Cr or BUN individually [9,25]. Brisco et al. [26] also found a significant association between an elevated BUN/Cr ratio upon admission and increased mortality. An elevated BUN/Cr ratio usually indicated serious medical conditions and poor prognosis in patients with acute kidney injury and acute heart failure (AHF) [7,27]. Qian et al. [1] reported that AHF combined with elevated BUN/Cr ratio was associated with an increased risk of mortality in patients with AMI. This finding suggested that the BUN/Cr ratio had a predictive value for prognosis in patients with AMI complicated with AHF. Takaya et al. [23,28] found that a BUN/Cr ratio ≥ 22 was associated with poor survival prognosis in patients with AHF. In addition, Murata et al. [29] indicated that the BUN/Cr ratio played a vital role in the treatment and clinical follow-up of patients with AMI since there was a strong correlation between a high BUN/Cr ratio and long-term mortality in patients with AMI. In our study, we found that the BUN/Cr ratio had a predictive value for the prognosis of patients with AMI. However, Nunez [30] demonstrated that in patients with AMI without AHF, there was no correlation between the BUN/Cr ratio and prognosis. We considered that this might be related to some factors that might have affected the baseline BUN/Cr, such as high protein diet and hepatic insufficiency. In our study, we investigated patients with AMI who were enrolled in a multicenter registry. Younger patients and patients with severely impaired renal function were excluded. These patients were treated with standard treatments, including PCI and medical therapy. Therefore, these patients were part of a more representative AMI population than those in prior studies.

There is a close bidirectional relationship between the heart and kidney. This relationship is reflected in the cardiorenal syndrome (CRS). There are five types of the cardiorenal syndrome (CRS). CRS type 1 is characterized by the development of acute kidney injury and dysfunction in patients with acute cardiac illness [31]. Cardiac function in patients with AMI has a different degree of reduction in the short term [32-33]. Thus, the BUN/Cr ratio has a greater guiding value in the clinical treatment of AMI patients [1]. It is currently widely believed that activation of the RAAS and SNS systems is associated with adverse prognosis [34]. For patients with a complicated AMI, a higher BUN/Cr ratio reflected a more active neurohormonal system. The pathophysiology of renal dysfunction in AMI is complex, multifactorial, and not completely understood. Nonetheless, an imbalance between abnormal hemodynamic, neurohormonal activation inflammatory responses, intrinsic tubular damage, and heterogeneous response to therapeutic interventions have been proposed as the most common pathogenic pathways [24].

This study has several strengths. This study was the first to investigate the relationship between the BUN/Cr ratio and in-hospital mortality in patients with AMI based on a large and diverse population from a public database (the eICU-CRD database) [13], which increased the significance of our research results. In addition, after adjusting for several confounding factors, multiple Cox regression analyses were performed, and the relationship between the BUN/Cr ratio and in-hospital mortality was still observed, indicating the good stability of our results. Since the BUN/Cr ratio was the basic index of clinical blood routine, the parameters were simple to collect. Our research results can be used to support other death indexes and improve prognosis prediction accuracy for AMI patients. Therefore, the BUN/Cr ratio is recommended for use in predicting the in-hospital mortality of AMI because it is cost-effective and easy to apply.

Although our study was based on a large multicenter critical care database, it still has some limitations. First, this was a retrospective study derived from an observational study, which could not definitively establish causality. Second, as this was an observational study, although a multifactor analysis was performed, other confounding factors might still exist; third, the data were from the United States, and thus the results may not apply fully to ICUs elsewhere with different practices or resources. Fourth, only data from a single BUN/Cr test were available at admission; no repeated testing was performed during the long-term follow-up, which may have resulted in biases in the study results. Finally, data on patient use of intra aortic balloon pump (IABP) and left ventricular assist device (LAVD) were not available in this study.

Conclusions

Our findings showed that a higher BUN/Cr ratio was associated with an increased risk of in-hospital mortality in patients with AMI. These results supported a revision of how we predicted the prognosis of patients with AMI. Most importantly, these findings suggested that the BUN/Cr ratio might be a useful indicator for risk stratification in patients with critically ill AMI. Further prospective studies are required to confirm these findings.

Abbreviations

AMI, Acute myocardial infarction (AMI); BUN, blood urea nitrogen; Cr, creatinine; eICU-CRD, the eICU Collaborative Research Database; BMI, body mass index; eGFR, estimated glomerular filtration rate; RDW, red blood cell distribution width; ALT, alanine transaminase; AST, aspartate transaminase; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; INR: international normal ratio; HR: heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CHF, congestive heart failure; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; Non-STEMI, non-ST-segment elevation myocardial infarction; AHF, acute heart failure.

Declarations

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Authors' contributions

SH and XD conceived the study. SH, NG and YL carried out the research. XD, ZZ and QZ analysed the data. SH, LL and LG wrote the paper. All authors read and approved the final manuscript.

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Data availability

The data analyzed during the present study are currently stored in the eICU database (eicucrd.mit.edu). After completing the required training course(the Collaborative Institutional Training Initiative) and after requesting access to the eICU Collaborative Research Database, researchers can seek to use the database.

Ethics approval and consent to participate

The establishment of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA), and consent was obtained for the original data collection. The database is released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbor provision. The re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (HIPAA Certification no. 1031219-2). Since all protected health information was de-identified, the requirement for individual patient consent was waived. The Ethics Committee of the First People's Hospital of Changde(No.2021-244-01) approved this retrospective data-only study. In addition, they waived the need for informed consent due to the retrospective nature of the study.

Consent for publication

Not Applicable

Competing interests

The authors reported no conflicts of interest in this work.

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Tables

Table 1 Participants' Baseline Characteristics

BUN/Cr group	All	Tertiles of BNU/Cr			P-value
		T1	T2	T3	
N	3,831	1,271	1,274	1,286	
Age,years	65.00(55.00-75.0)	60.00(51.00-69.00)	65.00(56.00-73.00)	71.00(61.00-79.00)	<0.001
Gender,n(%)					<0.001
Female	1142(29.81%)	269 (33.85%)	329(32.45%)	544(40.72%)	
male	2689 (70.19%)	1002 (66.15%)	945 (67.55%)	742(59.28%)	
Ethnicity,n(%)					<0.001
Caucasian	2976 (78.88%)	911 (72.94%)	1012(80.64%)	1053(82.98%)	
Non-Caucasian	797 (21.12%)	338 (27.06%)	243 (19.36%)	216(17.02%)	
BMI,kg/m ²	28.26 (24.69-32.86)	28.42 (24.98-32.69)	28.59 (25.10-33.35)	27.82 (24.07-32.52)	<0.001
Length of stay hospital,days	3.85 (2.28-7.82)	3.11 (2.10-6.49)	3.46 (2.19-7.33)	5.25 (2.93-9.23)	<0.001
BUN/Cr	16.96(13.59-21.67)	12.20(10.38-13.57)	16.90(15.72-18.28)	24.48(21.63-28.77)	<0.001
eGFR,ml/min/per 1.73 m ²	86.08(73.85-103.11)	83.67(72.94-99.68)	85.80(74.03-102.21)	89.58(74.57-110.42)	<0.001
WBC,*10 ⁹	10.80 (8.30-13.90)	10.50(8.10-13.30)	10.73(8.20-13.60)	11.10(8.50-15.10)	<0.001
RBC,*10 ⁹	4.14 (3.61-4.60)	4.29 (3.78-4.72)	4.24 (3.71-4.62)	3.92 (3.43-4.39)	<0.001
RDW,%	13.90(13.30-15.00)	13.70(13.10-14.70)	13.80(13.20-14.80)	14.40(13.50-15.50)	<0.001
Platelets,*10 ⁹	203.00(163.00-250.00)	205.00(168.00-251.00)	203.00 (165.00-248.00)	200.00 (156.00-250.00)	0.008
AST,U/L	67.00(33.00-168.00)	70.00(33.00-161.25)	64.00(31.00-170.00)	64.00(33.00-173.25)	0.749
ALT,U/L	36.00(22.00-67.00)	34.50(22.75-61.00)	36.00(23.00-65.00)	36.00(22.00-73.00)	0.509
TC,mmol/L	158.00(130.00-188.00)	163.00(136.00-195.00)	158.00(131.00-186.00)	148.00(120.00-181.00)	<0.001
TG,mmol/L	117.00(83.00-171.25)	122.00(89.00-177.00)	115.00(83.25-172.00)	111.00(77.00-163.00)	<0.001
HDL,mmol/L	38.00(31.00-	38.00(31.00-	37.00(31.00-	39.00(31.00-	0.021

	46.00)	46.00)	46.00)	48.00)	
LDL,mmol/L	90.00(66.00-119.00)	95.00(70.00-124.50)	90.50(68.00-117.00)	82.00(59.00-111.00)	<0.001
Potassium,mmol/L	4.10 (3.80-4.40)	4.00 (3.70-4.30)	4.00 (3.80-4.30)	4.10 (3.80-4.50)	<0.001
Sodium,mmol/L	138.00(135.00-140.00)	138.00(135.00-140.00)	138.00(136.00-140.00)	138.00(135.00-140.00)	0.003
INR	1.20 (1.09-1.40)	1.20 (1.10-1.40)	1.20 (1.08-1.40)	1.20 (1.07-1.40)	0.413
HR,beats/minutes	81.00(69.00-94.00)	81.00(69.00-94.00)	81.00(70.00-94.00)	80.00(69.00-94.0)	0.851
SBP,mmHg	123.00(104.00-143.00)	123.00(104.00-143.00)	121.50 (103.00-143.25)	123.00 (104.00-143.00)	0.908
DBP,mmHg	62.00(51.00-74.0)	62.00(51.00-73.00)	63.00(51.00-74.00)	61.00(51.00-74.00)	0.898
PCI,n(%)					0.181
No	3309 (86.62%)	1100 (87.10%)	1084 (85.29%)	1125(87.75%)	
yes	511 (13.38%)	167 (14.71%)	187 (14.71%)	157(12.25%)	
CABG,n(%)					0.224
no	3568 (93.4%)	1191 (94.0%)	1192 (93.78%)	1185 (92.43%)	
yes	252 (6.6%)	76 (6.0%)	79 (6.22%)	97(7.57%)	
CHF,n(%)					<0.001
no	3584(93.82%)	1227 (96.84%)	1200(94.41%)	1157 (90.25%)	
yes	236(6.18%)	40(3.16%)	71(5.59%)	125(9.75%)	
Diabetes,n(%)					<0.001
No	2890 (75.65%)	1041 (82.16%)	951 (74.82%)	898(70.05%)	
yes	930 (24.35%)	226(17.84%)	320(25.18%)	384 (29.95%)	
Hypertension,n(%)					0.003
No	1905 (49.87%)	677(53.43%)	629 (49.49%)	599 (46.72%)	
yes	1915 (50.13%)	590(46.57%)	642 (50.51%)	683 (53.28%)	
AMI category,n(%)					<0.001
Non-STEMI	1615(42.16%)	484 (38.08%)	514(40.35%)	617(47.98%)	
STEMI	2216 (48.17%)	787(61.92%)	760(59.65%)	669(52.02%)	

Abbreviations: BMI,body mass index; eGFR,estimated glomerular filtration rate; RDW,red blood cell distribution width; ALT,alanine transaminase; AST,aspartate transaminase; TC,total cholesterol; TG,triglyceride; HDL,high density lipoprotein; LDL,low density lipoprotein; INR: international normal ratio; HR:heart rate; SBP,systolic blood pressure; DBP,diastolic blood pressure; PCI,percutaneous coronary intervention; CABG,coronary artery bypass grafting; CHF,congestive heart failure;AMI,acute myocardial infarction; STEMI,ST-segment elevation myocardial infarction; Non-STEMI,non-ST-segment elevation myocardial infarction

Table 2 The Relationship Between the BUN/Cr and in-hospital Mortality in Patients with AMI in Different Models

Exposure	Non-adjusted HR(95%CI)	P value	Adjust I HR(95%CI)	P value	Adjust II HR(95%CI)	P value
BUN/Cr	1.09(1.04, 1.14)	0.0004	1.08 (1.03, 1.13)	0.0017	1.21 (1.05, 1.40)	0.0070
BUN/Cr per SD increase	1.18(1.07, 1.29)	0.0004	1.16 (1.06, 1.27)	0.0017	1.45 (1.11, 1.89)	0.0070
BUN/Cr group						
T1	1.0		1.0		1.0	
T2	0.99(0.77, 1.27)	0.9285	1.00(0.77, 1.28)	0.9828	0.83(0.39, 1.73)	0.6137
T3	1.51(1.21, 1.88)	0.0003	1.45(1.16, 1.81)	0.0012	2.14(1.16, 3.97)	0.0155
P for trend		<0.0001		0.0004		0.0198

Notes: Models were derived from Cox proportional hazards regression models. Non-adjusted model adjust for: None Adjust I model adjust for: age; gender; ethnicity. Adjust II model adjust for: age; gender; ethnicity; BMI; HR*; HDL; LDL; ALT; AMI category; CABG; CHF; diabetes; hypertension; PCI.

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI,body mass index; HR*,heart rate; HDL,high density lipoprotein;LDL,low density lipoprotein; ALT,alanine transaminase; AMI,acute myocardial infarction; CABG,coronary artery bypass grafting; CHF,congestive heart failure; PCI,percutaneous coronary intervention.

Table 3 Threshold effect analysis of the relationship between the BNU/Cr ratio and mortality using a two-piecewise regression model

BUN/Cr ratio inflection point	In-hospital mortality HR[95%CI]	P value
<18	0.99 (0.91, 1.07)	0.7299
≥18	1.31 (1.15, 1.49)	<0.0001
P for log likelihood ratio test		0.003

Notes: adjust for age; gender; ethnicity; BMI; HR*; HDL; LDL; ALT; AMI group; CABG; CHF; diabetes; hypertension; PCI.

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; HR*, heart rate; HDL, high density lipoprotein; LDL, low density lipoprotein; ALT, alanine transaminase; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CHF, congestive heart failure; PCI, percutaneous coronary intervention.

Table 4 Effect size of the BUN/Cr ratio on in-hospital mortality in prespecified and exploratory subgroups

Characteristic	No of participants	Effect size(95%CI),p value	P for interaction
BUN/Cr			0.0012
<18	2163	1.02 (0.93, 1.12) 0.6817	
≥18	1668	1.41 (1.18, 1.67) 0.0001	
Gender			0.5221
female	1142	1.07 (1.00, 1.14) 0.0607	
male	2689	1.10 (1.03, 1.17) 0.0031	
Age,years			0.1371
<65	2174	1.41 (1.06, 1.87) 0.0183	
≥65	1657	1.11 (0.95, 1.30) 0.2078	
BMI,kg/m ²			0.3221
<28	1795	1.12 (1.05, 1.19) 0.0005	
≥28	1954	1.06 (0.99, 1.15) 0.0981	
CHF			<0.0001
No	3584	1.18 (1.12, 1.25) <0.0001	
yea	236	0.90 (0.83, 0.97) 0.0085	
Diabetes			0.0558
No	2890	1.13 (1.07, 1.20) <0.0001	
yea	930	1.03 (0.96, 1.11) 0.4147	
Hypertension			0.5008
No	1905	1.11 (1.04, 1.19) 0.0025	
yes	1915	1.08 (1.01, 1.15) 0.0252	
CABG			0.865
No	3568	1.11 (1.05, 1.16) <0.0001	
yes	252	0.97 (0.84, 1.11) 0.6480	
PCI			0.7885
No	3309	1.09 (1.04, 1.15) 0.0005	
yes	511	1.07 (0.93, 1.23) 0.3402	
Glucose, mg/dl			0.4807
<128	1799	1.07 (1.00, 1.15) 0.0407	

≥128	1891	1.11 (1.04, 1.19) 0.0030	
AMI category			0.0002
STIMI	1615	1.03 (0.97, 1.08) 0.3638	
Non-STIMI	2216	1.25 (1.14, 1.37) <0.0001	
Heart rate, beats/min			0.8459
<80	1781	1.09 (1.02, 1.17) 0.0102	
≥80	2020	1.08 (1.01, 1.16) 0.0172	
LDL,			0.6106
<90	1161	1.22 (1.06, 1.41) 0.0071	
≥90	1196	1.31 (1.05, 1.63) 0.0175	

Abbreviations: eGFR,estimated glomerular filtration rate;BMI,body mass index; CHF,congestive heart failure; CABG,coronary artery bypass grafting; PCI,percutaneous coronary intervention; AMI,acute myocardial infarction; STEMI,ST-segment elevation myocardial infarction; Non-STEMI,non-ST-segment elevation myocardial infarction; LDL,low density lipoprotein.

Figures

Figure 1

Flow diagram of the screening and enrollment of study patients. A total of 3,831 patients were included in the analysis.

Figure 2

The Kaplan–Meier curves of the BUN/Cr ratio for predicting in-hospital mortality with AMI. A high BUN/Cr ratio was significantly associated with a higher mortality than a medium or low BUN/Cr ratio ($p < 0.001$).

Figure 3

The non-linear relationship between BUN/Cr and in-hospital mortality.

Supplementary Files

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