Association between the 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. The present study aimed to determine the association between the blood urea nitrogen (BUN) and creatinine (Cr) ratio and in-hospital mortality in patients with acute myocardial infarction (AMI). The present 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. Medical records were obtained from the electronic ICU collaborative research database, which includes data from throughout continental USA. Data included demographic characteristics, vital signs, laboratory tests 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. In total, 5,965 eligible patients were included. In the Cox regression analysis, after being adjusted for age, sex, ethnicity and other confounding factors, the BUN/Cr ratio was found to be a significant risk predictor of in-hospital mortality. There was a non-linear relationship between the BUN/Cr ratio and in-hospital mortality after adjusting for potential confounders. A two-piecewise regression model was used to obtain a threshold inflection point value of 18. Furthermore, after adjusting for additional confounding factors (age, sex, ethnicity, BMI, heart rate, oxygen saturation, platelets, total protein, AMI category, heart failure, history of diabetes, history of hypertension, percutaneous coronary intervention, and administration of norepinephrine, dopamine and epinephrine), the BUN/Cr ratio remained a significant predictor of in-hospital mortality (third vs. first tertile: Hazard ratio, 1.50; 95% CI, 1.08-2.09; P<0.05). The Kaplan-Meier curve for tertiles of the BUN/Cr ratio indicated that in-hospital mortality rates were highest when the BUN/Cr ratio was ≥18.34 after adjustment for age, sex and ethnicity (P<0.05). The present findings demonstrated that a higher BUN/Cr ratio was associated with an increased risk of in-hospital mortality in patients with non-ST-segment elevation myocardial infarction. These results support a revision of how the prognosis of patients with AMI is predicted.

Introduction

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, 30-40% of BUN is reabsorbed from the kidney tubules (1). By contrast, Cr is not as well reabsorbed as BUN (1,2). BUN is an important parameter that reflects the relationship among the patient's kidney condition, protein metabolism level and nutritional status (2). Previous studies have demonstrated 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. The use of Cr in clinical practice is supported by the findings of the study by Granger *et al* (6), which reported that Cr is a marker of renal function and established a relationship between renal dysfunction and increased mortality in patients with AMI.

The BUN/Cr ratio is defined as the ratio of BUN to serum Cr. As a novel biomarker, the BUN/Cr ratio has emerged as an independent prognostic indicator of poor outcomes in

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Abbreviations: ACS, acute coronary syndrome; AHF, acute heart failure; AKI, acute kidney injury; ALT, alanine transaminase; AMI, acute myocardial infarction; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; Cr, creatinine; cTnI, cardiac troponin I; eICU-CRD, electronic ICU collaborative research database; HDL, high-density lipoprotein; ICU, intensive care unit; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction

Key words: eICU, eICU-CRD, ICU, BUN/Cr ratio, AMI, in-hospital mortality

different disease conditions, such as chronic and acute heart failure (AHF) (7-9), acute and chronic kidney injury (10), and ischemic stroke (11). Studies demonstrated that an elevated BUN/Cr ratio was associated with a poor prognosis in patients with AHF, and 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 HF (1). However, the relationship between the BUN/Cr ratio and in-hospital mortality has not been fully investigated in patients with AMI in the intensive care unit (ICU). In this context, the present study aimed to comprehensively evaluate the role of the BUN/Cr ratio in predicting severity and survival of patients with AMI.

Materials and methods

Study design. The present study was a multicentre retrospective observational study. Analyses were performed on data subsets (median age, 65.0 years; range, 56.0-75.0 years; 64.2% male) obtained from participants in the electronic ICU collaborative research database (eICU-CRD; https://eicu-crd.mit.edu), which is an open-access de-identified dataset of patients maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology (Cambridge, MA, USA). The eICU-CRD includes patients admitted to 208 US hospitals that were monitored by the eICU programs between 2014 and 2015 (13,14). The database stores records of demographic characteristics, hourly physiological readings from bedside monitors, disease diagnoses using the International Classification of Diseases Ninth Revision (ICD-9) code (15) and other clinical data collected during routine medical care. Since all protected health information was anonymized, the requirement for individual patient consent was waived. The use of this database was approved by the Institutional Review Boards of the 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 obtained access to the database and was responsible for data extraction (certification no. 42039823). *Bona fide* researchers can apply to access the eICU-CRD via a standard application procedure (further details available at https://eicu-crd.mit.edu/about/eicu/). The present study was performed following the Declaration of Helsinki. All methods follow the guidelines and regulations stated by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBY) Statement.

Data on demographics, comorbidities, vital signs, laboratory tests, use of vasoactive drugs and operations were obtained from the eICU-CRD. Used drugs included norepinephrine, dopamine and epinephrine. The serum laboratory variables measured during the first 24 h of ICU admission were used in the present study. If variables were measured multiple times in the first 24 h, the first measure was used in the present study. Records with >10% missing variables were excluded. For records with ≤10% missing variables, the multiple imputation method was used to deal with the missing data. The multiple imputation methods imputes multiple values for each missing value. This results in the creation of multiple complete data sets in which the missing values have been filled in with plausible values. The analysis of scientific interest is then conducted separately in each of these complete data sets and the results are pooled across the imputed data sets. In this way, the multiple imputation allows the user to explicitly incorporate the uncertainty about the true value of imputed variables (16).

Clinical endpoints. The primary endpoint of the present 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 ICD-9 code, which was 140. The following inclusion criteria were applied: i) Age ≥18 years; and ii) first ICU admission with a first diagnosis of AMI. AMI was identified from the ICD-9 code in the eICU-CRD. The following exclusion criteria were used: i) Non-first ICU admission; ii) ICU stay <24 h; iii) missing ICU outcome; iv) history of confirmed renal failure; v) blood transfusion received during the 24 h before admission; vi) evidence of thrombocytopenia; vii) coagulopathy; viii) history of injecting cephalosporins or any other drug interfering with BUN or Cr evaluation; ix) both upper and lower gastrointestinal bleeding; and x) missing Cr and BUN measurements after ICU admission or system error (6). The study population comprised 5,965 patients with AMI [median age, 65.0 years; range, 56.0-75.0 years; 3,832 (64.2%) male]. 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 I (cTnI) values with at least one value >99th 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 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 aetiology (17,18).

Definition and assessment of HF. HF is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral oedema). HF is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise. The criteria for diagnosis of HF require evidence of increased left ventricle filling pressures at rest, exercise, or other provocations. The criteria were fulfilled with findings of elevated levels of natriuretic peptides, echocardiographic diastolic parameters such as an E/e' ≥15 or other evidence of elevated filling pressures, or invasive hemodynamic measurement at rest or exercise (19,20).

Statistical analysis. For continuous variables, the Kolmogorov-Smirnov test was used to check the normality of data distribution. Continuous variables with skewed distribution are presented as the median (interquartile range) and comparison among groups was performed using the Kruskal-Wallis H test and Dunn's post hoc test. Categorical or dichotomous variables, which are presented as absolute values and percentages, were compared using the χ^2 test.

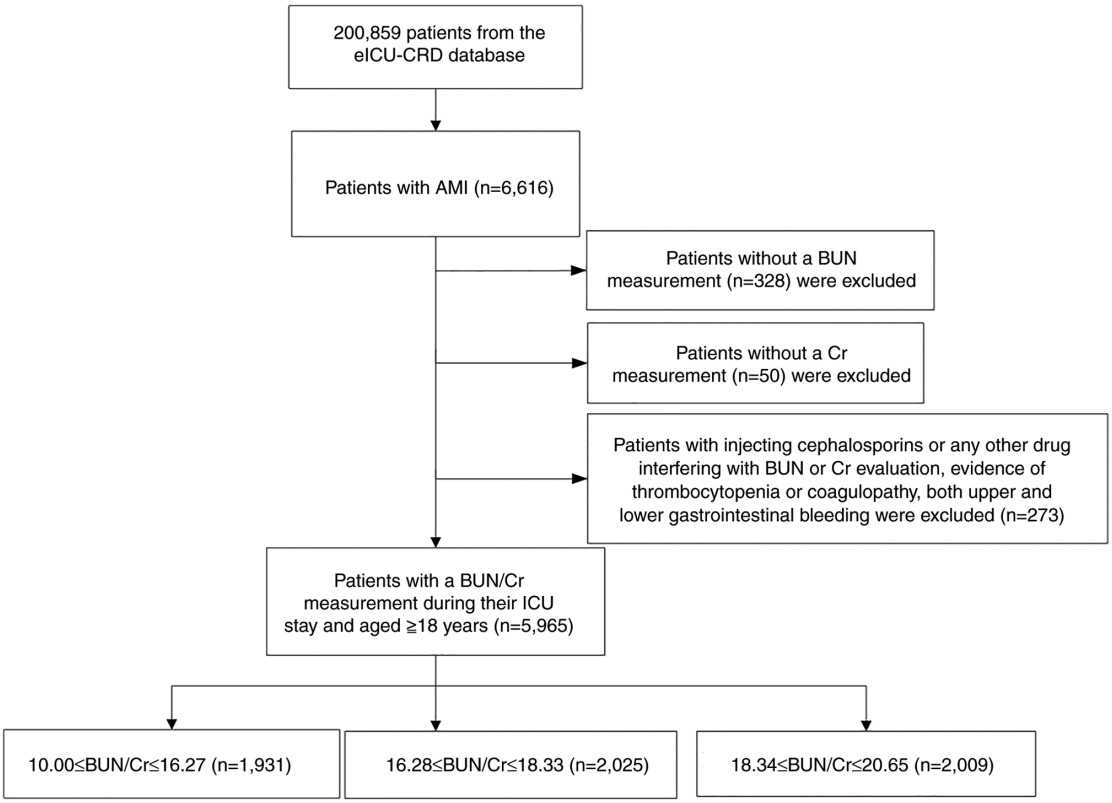

Figure 1. Flow diagram of the screening and enrolment of study patients. A total of 5,965 patients were included in the analysis. AMI, acute myocardial infarction; BUN, blood urea nitrogen; Cr, creatinine; eICU-CRD, electronic ICU collaborative research database; ICU, intensive care unit.

The cumulative survival rate was calculated using the Kaplan-Meier method and the log-rank test was used for comparison between groups. Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95% CI of the second and third tertiles relative to the first tertile for in-hospital mortality. Crude regression estimates and estimates adjusted for covariates are presented. After considering the clinical significance, the covariates that were significantly associated with the response variable (P<0.05) or those that changed the effect estimate by ≥10% were retained in the final adjusted model (21). The variables adjusted for in the micro adjustment model (adjusted model I) included age, sex and ethnicity. The variables adjusted for in the overall adjustment model (adjusted model II) included age, sex, ethnicity, BMI, heart rate, oxygen saturation, platelets, total protein, AMI category, coronary artery bypass grafting (CABG), HF, history of diabetes mellitus, history of hypertension, percutaneous coronary intervention (PCI), and administration of norepinephrine, dopamine and epinephrine.

Subsequently, a generalized additive model was used to identify the dose-response relationship between the BUN/Cr ratio and in-hospital mortality. If a non-linear association 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 (22,23). Finally, the modification and interaction of the subgroups were inspected using the likelihood ratio test. Receiver operating characteristic (ROC) curves were generated to calculate the sensitivity and specificity of the BUN/Cr ratio, while the area under the curve (AUC) was calculated to ascertain the quality of the BUN/Cr ratio as a predictor of in-hospital mortality in patients with AMI.

All data were analysed using R software (version 3.42; R Foundation for Statistical Computing) and Empower Stats version 2.17.8 (http://www.empowerstats.com/cn/). P<0.05 was considered to indicate a statistically significant difference and all reported P-values were two-sided.

Results

Study participants and baseline characteristics. The data of a total of 6,616 patients with AMI were extracted from eICU-CRD. Patients without data for BUN (n=328) or Cr (n=50) levels were excluded from the study. Patients with a history of confirmed renal failure, those who had received a blood transfusion during the 24 h before admission, those showing evidence of thrombocytopenia, coagulopathy or having a history of injecting cephalosporins or any other drug interfering with BUN or Cr evaluation, as well as patients with both upper and lower gastrointestinal bleeding (n=273), were excluded from the study. The ICU admission rate of patients without a BUN or Cr level was 5.7% (378 out of 6,616 patients) and a total of 5,965 patients were included in the statistical analysis. A flow chart of the study is shown in Fig. 1.

Baseline characteristics according to BUN/Cr tertiles are shown in Table I. The mean BUN/Cr ratio was 17.3±1.9. According to the BUN/Cr ratio, a total of 1,931, 2,025 and 2,009 patients fell into tertile 1, 2 and 3, respectively. The BUN/Cr tertiles were 10.00-16.27 (tertile 1), 16.28-18.33

Table I. Baseline characteristics of patients.

Characteristics	All patients	Tertiles of BUN/Cr			P-value
		Tertile 1 (10.00-16.27)	Tertile 2 (16.28-18.33)	Tertile 3 (18.34-20.65)	
No. of participants	5,965	1,931	2,025	2,009	
Age, years	65.00 (56.00-75.0)	60.00 (52.00-69.00)	65.00 (56.00-73.00)	71.00 (63.00-79.00)	<0.001
Sex, n (%)					<0.001
Female	2,133 (35.68)	662 (34.28)	650 (32.10)	821 (40.87)	
Male	3,832 (64.24)	1,269 (65.72)	1,375 (67.90)	1,188 (59.13)	
Ethnicity, n (%)[a]					<0.001
Caucasian	4,642 (77.82)	1,442 (75.78)	1,604 (80.32)	1,596 (80.40)	
Non-Caucasian	1,243 (20.84)	461 (24.22)	393 (19.68)	389 (19.60)	
BMI, kg/m^2	28.34 (24.79-32.97)	28.52 (25.05-32.82)	28.67 (25.14-33.39)	27.93 (24.20-32.75)	<0.001
Length of hospital stay, days	3.80 (2.26-7.59)	3.04 (2.08-6.05)	3.43 (2.20-7.14)	5.21 (2.90-9.07)	<0.001
BUN/Cr	17.39 (15.87-18.92)	15.38 (14.52-15.79)	17.35 (16.85-17.93)	19.35 (18.92-19.88)	<0.001
Estimated glomerular filtration rate, ml/min per 1.73 m^2	71.81 (47.36-93.10)	70.05 (43.48-89.07)	73.85 (50.73-93.52)	71.72 (47.79-96.72)	<0.001
White blood cells, x10^9	10.80 (8.40-14.00)	10.44 (8.18-13.20)	10.80 (8.34-13.70)	11.28 (8.70-15.20)	<0.001
Red blood cells, x10^9	4.17 (3.65-4.62)	4.31 (3.84-4.73)	4.25 (3.74-4.63)	3.95 (3.47-4.42)	<0.001
Red blood cell distribution width, %	13.90 (13.20-14.90)	13.70 (13.10-14.60)	13.70 (13.20-14.70)	14.30 (13.50-15.40)	<0.001
Platelets, x10^9	207.00 (169.00-252.00)	208.00 (173.00-253.00)	208.00 (169.00-250.00)	205.50 (164.00-254.00)	0.165
Aspartate transaminase, U/l	66.50 (32.00-163.00)	70.00 (32.00-155.00)	66.00 (31.00-169.50)	64.00 (33.00-171.25)	0.977
Alanine transaminase, U/l	35.00 (22.00-65.50)	34.00 (22.00-59.00)	36.00 (23.00-65.00)	36.00 (22.00-73.00)	0.165
Total cholesterol, mmol/l	158.00 (131.00-188.00)	165.00 (138.00-197.00)	158.00 (131.00-186.00)	150.00 (121.00-181.00)	<0.001
Triglyceride, mmol/l	117.00 (83.00-170.00)	122.00 (89.00-177.00)	114.00 (84.00-171.00)	113.00 (78.00-163.50)	0.002
High-density lipoprotein, mmol/l	38.00 (31.00-46.00)	38.00 (31.00-46.00)	37.00 (31.00-46.00)	39.00 (31.00-48.00)	0.020
Low-density lipoprotein, mmol/l	92.00 (67.00-120.00)	97.00 (71.00-126.00)	92.00 (68.50-117.00)	82.50 (59.00-111.75)	<0.001
Potassium, mmol/l	4.00 (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 (136.00-140.00)	138.00 (135.00-140.00)	138.00 (136.00-140.00)	138.00 (136.00-140.00)	0.025
Prothrombin time international normalized ratio	1.20 (1.09-1.40)	1.20 (1.10-1.40)	1.20 (1.09-1.40)	1.20 (1.07-1.40)	0.369
Heart rate, beats/min	81.00 (70.00-94.00)	81.00 (70.00-94.00)	81.00 (70.00-94.00)	80.00 (69.00-93.00)	0.610
Systolic blood pressure, mmHg	122.00 (103.00-142.00)	122.00 (102.00-142.50)	122.00 (103.00-143.00)	123.00 (104.00-142.00)	0.866

Table I. Continued.

Characteristics	All patients	Tertiles of BUN/Cr			P-value
		Tertile 1 (10.00-16.27)	Tertile 2 (16.28-18.33)	Tertile 3 (18.34-20.65)	
Diastolic blood pressure, mmHg	62.00 (51.00-74.00)	61.00 (50.00-72.00)	63.00 (51.00-74.00)	61.00 (51.00-74.00)	0.440
Percutaneous coronary intervention, n (%)					<0.001
No	3,788 (63.50)	1,140 (59.04)	1,241 (61.28)	1,407 (70.03)	
Yes	2,177 (36.50)	791 (40.96)	784 (38.72)	602 (29.97)	
Coronary artery bypass grafting, n (%)					0.023
No	5,199 (87.16)	1,714 (88.76)	1,760 (86.91)	1,725 (85.86)	
Yes	766 (12.84)	217 (13.09)	265 (13.09)	284 (14.14)	
Heart failure, n (%)					<0.001
No	5,168 (86.99)	1,738 (90.19)	1,822 (90.47)	1,605 (80.40)	
Yes	773 (13.01)	189 (9.81)	192 (9.53)	392 (19.60)	
History of diabetes n (%)					<0.001
No	4,057 (68.29)	1,449 (75.19)	1,392 (69.12)	1,216 (60.80)	
Yes	1,884 (31.71)	478 (24.81)	622 (30.88)	784 (39.20)	
History of hypertension, n (%)					<0.001
No	2,596 (43.70)	980 (50.86)	871 (43.25)	745 (37.25)	
Yes	3,345 (56.30)	947 (49.14)	1,143 (56.75)	1,255 (62.75)	
Acute myocardial infarction category,n (%)					<0.001
Non-STEMI	3,010 (50.46)	875 (45.31)	920 (45.43)	1,215 (60.48)	
STEMI	2,955 (49.54)	1,056 (54.69)	1,105 (54.57)	794 (39.52)	
Norepinephrine, n (%)					<0.001
No	4,223 (85.52)	1,455 (89.48)	1,428 (85.56)	1,340 (81.56)	
Yes	715 (14.48)	171 (10.52)	241 (14.44)	303 (18.44)	
Dopamine, n (%)					0.004
No	4,661 (94.39)	1,555 (95.63)	1,578 (94.55)	1,528 (93.00)	
Yes	277 (5.61)	71 (4.37)	91 (5.45)	115 (7.00)	
Epinephrine, n (%)					0.001
No	4,603 (93.22)	1,547 (95.14)	1,533 (91.85)	1,523 (92.70)	
Yes	335 (6.78)	79 (4.86)	136 (8.15)	120 (7.30)	

[a]n=5885 as ethnicity was not recorded for all patients at the time of admission. Continuous variables with skewed distribution are presented as the median (interquartile range) and comparison among groups was performed using the Kruskal-Wallis H test and Dunn's post hoc test. Categorical or dichotomous variables, which are presented as absolute values and percentages, were compared using the χ^2 test. P-values refer to comparisons among all three tertile groups. STEMI, ST-segment elevation myocardial infarction; BUN, blood urea nitrogen; Cr, creatinine.

(tertile 2) and 18.34-20.65 (tertile 3). No statistically significant differences were detected among the groups in terms of the levels of aspartate transaminase, alanine transaminase (ALT), levels of platelets, prothrombin time international normalized ratio, heart rate, systolic blood pressure, and diastolic blood pressure. Common characteristics among patients with high BUN/Cr ratio levels were older age, being a Caucasian, having a longer hospital stay, a higher white blood cell count and red blood cell distribution width, and greater high-density lipoprotein (HDL) and potassium values, CABG,

history of diabetes and history of hypertension (P<0.05). The opposite trend was observed for BMI, red blood cell count, total cholesterol, triglycerides, low-density lipoprotein (LDL) and PCI (P<0.05). Furthermore, patients with higher BUN/Cr levels made more use of vasoactive drugs (norepinephrine, dopamine and epinephrine) (P<0.05).

The overall in-hospital mortality rate was 8.35% (498 out of 5,965 patients). The in-hospital mortality of different groups based on tertiles of BUN/Cr is shown in Fig. S1. In-hospital mortality was more frequently observed in patients with higher BUN/Cr levels (1.73, 2.08 and 4.54% for the first, second and third tertiles, respectively; 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 curves for the tertiles of the BUN/Cr ratio are shown in Fig. 2. The figure indicates that in-hospital mortality rates were highest when the BUN/Cr ratio was ≥18.34 after adjustment for age, sex and ethnicity (log-rank test P<0.05). Similar results were seen in patients with AMI without HF. A BUN/Cr ratio was significantly associated with the increased hospital and ICU mortality in patients with AMI without HF (Table SI; Fig. S2). The BUN/Cr ratio was used to distinguish between different survival statuses and it was shown to have a good discrimination value.

BUN/Cr ratio as a predictor of in-hospital mortality. A total of three different models, the non-adjusted model and adjusted models I and II, were constructed to analyse the independent effects of the BUN/Cr ratio on the in-hospital mortality of critically ill patients with AMI that were grouped according to the BUN/Cr ratio tertiles. As shown in Table II, in adjusted 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 adjusted 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 (third vs. first tertile; adjusted HR, 1.50; 95% CI, 1.08-2.09; P<0.05 for trend). Consistent results were also obtained in patients with AMI but without HF (Table SI).

In addition, cTnI is a heart-specific protein released in the circulation upon myocardial injury and serves a role in the regulation of muscle contraction and cTns (24). Conventional assays for the analysis of cTnI levels are routinely used to exclude AMI events and to assess the 30- and 90-day prognoses of patients presenting with acute coronary syndrome (ACS) (25,26). Various studies have reported that the circulating levels of cTnI after ST-segment elevation myocardial infarction (STEMI) are related to clinical outcomes and are considered a prognostic predictor of major adverse cardiovascular events (27-29). The predictive values for in-hospital mortality of cTnI and the BUN/Cr ratio were compared in patients with AMI. ROC curves generated for BUN/Cr and cTnI are plotted in Fig. S3. The AUC for the BUN/Cr ratio was 0.619 (range, 0.586-0.652), whereas it was 0.499 (range, 0.467-0.532) for cTnI (P<0.001).

Analysis of the association between the BUN/Cr ratio and in-hospital mortality. The present study (Fig. 3) revealed a non-linear relationship rather than a linear interaction between

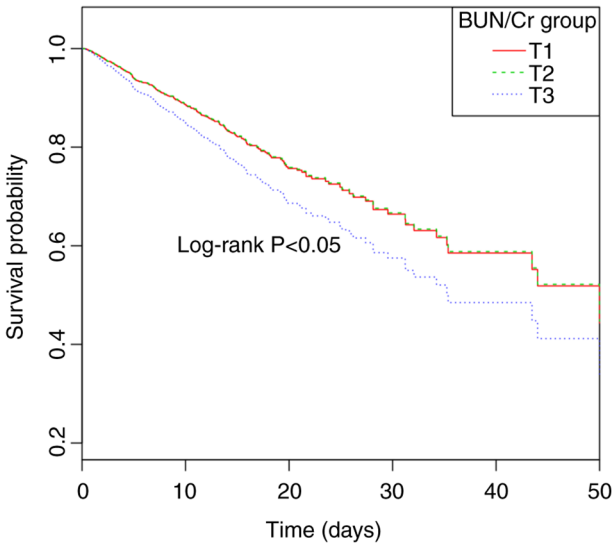

Figure 2. Kaplan-Meier curves of the BUN/Cr ratio for predicting in-hospital mortality with acute myocardial infarction. A high BUN/Cr ratio was significantly associated with a higher mortality than a medium or low BUN/Cr ratio (P<0.05). BUN, blood urea nitrogen; Cr, creatinine; T, tertile.

the BUN/Cr ratio and in-hospital mortality after adjusting for age, sex, ethnicity, BMI, heart rate, HDL, LDL, ALT, AMI group, PCI, CABG, HF, history of diabetes and history of hypertension. Using the two-piecewise linear regression model, the inflection point was calculated as 18. The HR (95% CI) was 1.34 (1.17-1.54) with P<0.001 on the right of the inflection point. However, on the left of the inflection point, the relationship between the BUN/Cr ratio and in-hospital mortality was non-significant (HR, 0.99; 95% CI, 0.91-1.08; P=0.8364; Table III).

Subgroup analyses. The results of the subgroup analyses are presented in Table IV. After adjusting for potential confounders, it was found that the interaction (between the BUN/Cr ratio and AMI group) was statistically significant for the AMI group (P<0.05). However, statistical significance was not observed for age, sex, BMI, history of diabetes, history of hypertension, PCI, CABG, glucose, heart rate, ALT and LDL. Evidence of the BUN/Cr-AMI group being non-linear was also found. The effect of the BUN/Cr ratio on in-hospital mortality differed among patients with different AMI groups. The BUN/Cr ratio was associated with in-hospital mortality (HR, 1.31; 95% CI, 1.19-1.44) in patients with non-STEMI. However, there was no significant relationship between the BUN/Cr ratio and the in-hospital mortality in patients with STEMI. Furthermore, it was observed that the BUN/Cr ratio was associated with in-hospital mortality if the BUN/Cr ratio was ≥18 (P=0.0001).

Discussion

The results of the present study revealed that an elevated BUN/Cr ratio indicated an increased risk of in-hospital death in patients with AMI. Even after adjusting for confounding factors in the multivariate models, the BUN/Cr ratio was associated with adverse outcomes. The findings of the present study

Table II. Association between the BUN/Cr ratio and in-hospital mortality in patients with acute myocardial infarction in different models.

Exposure	Non-adjusted model HR (95% CI)	P-value	Adjusted model I HR (95% CI)	P-value	Adjusted model II HR (95% CI)	P-value
BUN/Cr	1.09 (1.04-1.16)	0.0002	1.06 (1.00-1.11)	0.0447	1.07 (1.00-1.13)	0.0510
BUN/Cr tertiles						
Tertile 1	Reference		Reference		Reference	
Tertile 2	1.02 (0.77-1.34)	0.8974	0.99 (0.74-1.32)	0.9467	1.07 (0.73-1.55)	0.7328
Tertile 3	1.63 (1.28-2.08)	<0.0001	1.35 (1.04-1.75)	0.0220	1.50 (1.08-2.09)	0.0170
P-value for trend		<0.0001		0.0094		0.0077

Models were derived from Cox proportional hazards regression models. Adjusted model I adjusted for: Age, sex and ethnicity. Adjusted model II adjusted for: Age, sex, ethnicity, BMI, heart rate, oxygen saturation, platelets, total protein, acute myocardial infarction category, heart failure, history of diabetes, history of hypertension, percutaneous coronary intervention, and administration of norepinephrine, dopamine and epinephrine. P-value for trend was obtained from the median value of each BUN/Cr tertile as a continuous variable in the models. BUN, blood urea nitrogen; Cr, creatinine; HR, hazard ratio.

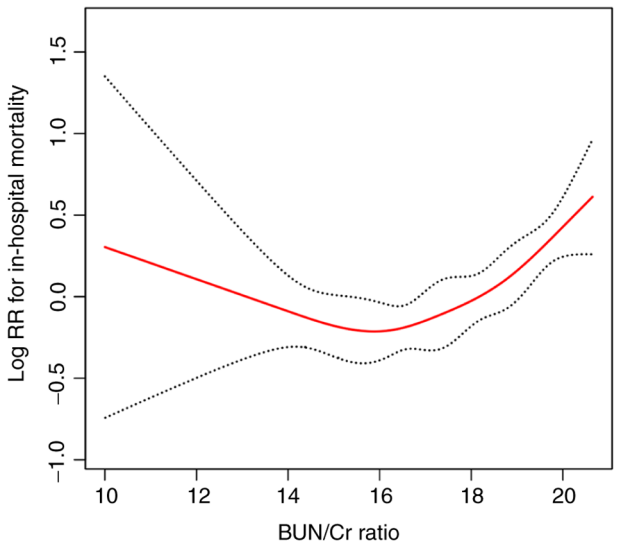

Figure 3. Non-linear relationship between BUN/Cr ratio and in-hospital mortality. There was a non-linear relationship rather than a linear interaction between the BUN/Cr ratio and in-hospital mortality after adjusting for confounding factors. BUN, blood urea nitrogen; Cr, creatinine; RR, relative risk.

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

BUN/Cr ratio inflection point	In-hospital mortalityhazard ratio (95% CI)	P-value
<18	0.99 (0.91-1.08)	0.836
≥18	1.34 (1.17-1.54)	<0.001
Likelihood-ratio test		0.003

The model adjusted for age, sex, ethnicity, BMI, heart rate, high- and low-density lipoproteins, alanine transaminase, acute myocardial infarction category, coronary artery bypass grafting, heart failure, history of diabetes, history of hypertension, and percutaneous coronary intervention. 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 likelihood ratio test. The likelihood ratio test has been widely adopted for assessing the goodness of fit of two competing statistical models based on the ratio of their likelihoods. BUN, blood urea nitrogen; Cr, creatinine.

not only are in agreement with those of the aforementioned previous studies but also demonstrate a non-linear relationship between the BUN/Cr ratio and in-hospital mortality in patients with AMI (1,7). Upon conducting a subgroup analysis, it was found that the BUN/Cr ratio was associated with an increased risk of in-hospital death in critically ill patients with AMI.

BUN is not a specific marker of renal insufficiency. Cr is affected by extra-renal factors, such as muscle mass, sex, age, nutrition and ethnicity (5). Therefore, predictions based on BUN or Cr alone might have limitations. Although estimated glomerular filtration rate (eGFR) improves the assessment of renal function, overestimation and underestimation still exist among patients with a wide range of serum Cr levels (30). Similarly, the serum concentrations of BUN are influenced by several factors (neurohormonal activation, protein intake and catabolic processes) (31). BUN levels reflect persistent and inappropriate renin-angiotensin-aldosterone system and vasopressin activation in HF, but are not necessarily related to a decrease in eGFR. Hence, it is not necessarily a marker of decreased eGFR (32). Therefore, the BUN/Cr ratio has been proposed as a useful parameter to reduce the effect of the aforementioned influencing factors. The BUN/Cr ratio might be a marker for evaluation of the prognosis of patients with AMI, which is more stable and accurate than serum Cr or BUN individually (9,33).

Brisco *et al* (34) also found an association between elevated BUN/Cr ratio upon admission and increased mortality. An elevated BUN/Cr ratio usually indicates serious medical conditions and a poor prognosis in patients with acute kidney injury (AKI) and AHF (7,35). Qian *et al* (1) reported that

Table IV. Effect size of BUN/Cr on in-hospital mortality in prespecified and exploratory subgroups.

Characteristics	No. of participants	Hazard ratio (95% CI)	Subgroup P-value	P-value
BUN/Cr ratio				0.0013
<18	3,462	1.03 (0.93, 1.14)	0.6817	
≥18	2,503	1.44 (1.20, 1.73)	0.0001	
Estimated glomerular filtration rate, ml/min per 1.73 m^2				0.1943
<60	2,098	1.01 (1.00, 1.03)	0.0008	
≥60	3,867	1.03 (1.02, 1.04)	<0.0001	
Sex				0.1901
Female	2,133	0.97 (0.77, 1.22)	0.0607	
Male	3,832	1.19 (0.96, 1.47)	0.0031	
Age, years				0.2092
<65	2,711	1.12 (1.01, 1.20)	0.0183	
≥65	3,067	1.09 (1.01, 1.18)	0.2078	
BMI, kg/m^2				0.5280
<28	2,770	1.12 (1.05, 1.19)	0.0005	
≥28	3,076	1.06 (0.99, 1.15)	0.0981	
Heart failure				0.0522
No	4,465	1.10 (0.91,1.32)	0.0562	
Yes	645	0.75 (0.53.1.05)	0.1089	
History of diabetes				0.3897
No	4,057	1.24 (1.00, 1.53)	<0.0001	
Yes	1,884	1.038 (0.87, 1.35)	0.4147	
History of hypertension				0.6017
No	2,596	1.12 (1.02, 1.17)	0.0025	
Yes	3,345	1.09 (1.02, 1.17)	0.0252	
Coronary artery bypass grafting				0.6173
No	5,199	1.11 (1.05, 1.17)	<0.0001	
Yes	766	1.16(0.91, 1.24)	0.6480	
Percutaneous coronary intervention				0.1418
No	3,788	1.08 (1.02, 1.14)	0.0005	
Yes	2,177	1.20 (1.06, 1.35)	0.0021	
Glucose, mg/dl				0.4315
<128	2,847	1.09 (1.01, 1.17)	0.0407	
≥128	2,858	1.113 (1.05, 1.22)	0.0030	
Acute myocardial infarction group				<0.0001
STEMI	3,010	1.02 (0.97, 1.09)	0.3638	
Non-STEMI	2,955	1.31 (1.19, 1.44)	<0.0001	
Heart rate, beats/min				0.6369
<80	2,806	1.12 (1.04, 1.20)	0.0102	
≥80	3,115	1.09 (1.09, 1.17)	0.0172	
Alanine transaminase, U/l				0.6116
<36	1,585	0.98 (0.78, 1.23)	0.0008	
≥36	1,570	1.06 (0.86, 1.32)	0.4424	
Low density lipoprotein, mmol/l				0.7413
<90	1,119	1.225 (1.06, 1.46)	0.0071	
≥90	1,186	1.31 (1.05, 1.63)	0.0175	

P-values were generated by Cox regression analysis. BUN, blood urea nitrogen; Cr, creatinine; STEMI, ST-segment elevation myocardial infarction.

AHF combined with an elevated BUN/Cr ratio was associated with an increased risk of mortality in patients with AMI. This finding suggested that the BUN/Cr ratio has a predictive value for prognosis in patients with AMI complicated with AHF. Parrinello *et al* (36) found that a BUN/Cr ratio ≥22 was associated with poor survival prognosis in patients with AHF. In addition, Murata *et al* (37) indicated that the BUN/Cr ratio was a factor involved in the treatment and clinical follow-up of patients with AMI, since there was a strong association between a high BUN/Cr ratio and long-term mortality in patients with AMI. The findings of this study are consistent with the present research. In the current study, the BUN/Cr ratio had a predictive value for the prognosis of patients with AMI and the risk was highest in patients with a high BUN/Cr ratio. In further analysis, patients with AMI and HF were excluded, and the results were still consistent. However, Núñez (38) demonstrated that in patients with AMI without AHF, there was no association between the BUN/Cr ratio and prognosis. In the present study, there was no significant relationship between the BUN/Cr ratio and the in-hospital mortality in patients with STEMI. This is consistent with previous research results. However, the BUN/Cr ratio was associated with in-hospital mortality in patients with non-STEMI. The reason may be related to the following aspects: i) Some factors might have affected the baseline BUN/Cr, such as a high protein diet and hepatic insufficiency, and the serum composition is influenced by important extrarenal factors such as muscle mass, sex, age, nutrition and ethnicity; ii) the sample size of the present study was larger and the data might be more representative since the current study investigated patients with AMI, who were enrolled in a multicentre registry and critically ill, and included 50.46% of patients with non-STEMI and 49.54% of patients with STEMI; iii) in-hospital mortality was 8.35% (498/5,965) in the study cohort and the AMI mortality was higher than that in another study (39), which may be related to the severity of the illness. Some patients were too sick to receive standard treatments, including PCI, CABG and medical therapy; and iv) among patients with AMI, pathophysiology, management and outcomes differ between those with STEMI and non-STEMI. Traditionally, patients with non-STEMI have more frequent risk factors and comorbidities, and a greater burden of coronary artery disease (40,41). The present study found that the prevalence of comorbid diseases was higher among patients with a high BUN/Cr ratio, suggesting that comorbid disease events are likely to explain the increased risk of death in these individuals. A higher percentage of patients with HF and a higher average age among those with a high BUN/Cr ratio were also reported.

There is a close bidirectional relationship between the heart and the kidney. HF is a complex syndrome that affects almost all organs and systems of the body. Renal dysfunction is one of the most important comorbidities in patients with chronic HF and is accentuated, or becomes more evident, during episodes of acute HF. This relationship is reflected in cardiorenal syndrome (CRS) (32). There are five types of CRS. CRS type 1 is characterized by the development of AKI and dysfunction in patients with acute cardiac illness (42). Worsening renal function that occurs in patients with acute HF has been classified as CRS type 1. In this setting, worsening renal function is a common finding and is due to complex, multifactorial, and not fully understood processes involving hemodynamic (renal arterial hypoperfusion and renal venous congestion) and non-hemodynamic factors (32). Cardiac function in patients with AMI has a different degree of reduction in the short term (43,44). Thus, the BUN/Cr ratio has a greater guiding value in the clinical treatment of patients with AMI. It is currently widely considered that activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system is associated with adverse prognosis (45). For patients with AMI with complications, a higher BUN/Cr ratio reflects a more active neurohormonal system (32). Being complex and multifactorial, the pathophysiology of renal dysfunction in AMI remains unclear. Nonetheless, an imbalance among abnormal hemodynamic, neurohormonal activation inflammatory responses, intrinsic tubular damage and heterogeneous response to therapeutic interventions has been proposed as the most common pathogenic pathway (32).

The present study has several strengths. To the best of our knowledge, it is 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 the publicly available eICU-CRD (13), which increased the significance of the present 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 the present results. Since the BUN/Cr ratio was the basic index of clinical blood routine, the parameters were simple to collect. These results can be used to support other death indexes and improve the accuracy of prognosis prediction for patients with AMI. Therefore, the BUN/Cr ratio is recommended for use in predicting the in-hospital mortality of AMI, as it is cost-effective and easy to apply.

The Global Registry of Acute Coronary Events (GRACE) risk score was initially established to predict in-hospital mortality in patients with ACS (6) and is currently the guideline-recommended risk model for guiding the management of myocardial infarction (46,47). The present study extracted the in-hospital mortality and AMI data from the eICU-CRD, but could not obtain the GRACE risk score. Therefore, it only compared the predictive value of cTnI with the BUN/Cr ratio for in-hospital mortality in patients with AMI. In future studies, the GRACE risk score will be collected to compare the predictive value of this score with BUN/Cr for in-hospital mortality.

Although the present study is based on a large multicentre critical care database, it still has some limitations. This was a retrospective study derived from an observational study, which cannot definitively establish causality. As this was an observational study, although a multifactor analysis was performed, other confounding factors may still exist. Furthermore, the data were from the United States, and thus, the results may not apply fully to ICUs elsewhere with different practices or resources. In addition, only data from a single BUN/Cr test were available at admission and repeated measures data were not analysed. Different blood collection times would also affect the results of BUN/Cr, which may have resulted in biases in the study results. Furthermore, the present study did not include clinical follow-up data and could not predict the long-term outcomes of these patients with AMI. Finally, data

on the use of intra-aortic balloon pump and left ventricular assist device were not available.

In conclusion, the present findings demonstrated that the BUN/Cr ratio had a strong association with in-hospital mortality in patients with non-STEMI, but not in patients with STEMI. These results may motivate the revision of how the prognosis of patients with AMI should be predicted. Importantly, these findings suggest that the BUN/Cr ratio may be a useful risk stratification factor for critically ill patients with AMI. The effect of the BUN/Cr ratio on in-hospital mortality should be recorded and investigated in future prospective studies.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SH and LG confirm the authenticity of all the raw data. SH, LL and XD conceived the study. SH, NG and LL performed the research. XD, LG, LL, ZZ and QZ analyzed the data. SH, LL and LG wrote the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The establishment and use of this database was approved by the Massachusetts Institute of Technology (Cambridge, MA, USA) and permission was obtained for the original data collection. The database is released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbour provision. The re-identification risk was certified as meeting safe harbour standards by Privacert (HIPAA certification no. 1031219-2). Since all protected health information was de-identified, the requirement for individual patient consent for publication was waived. In addition, they waived the need for informed consent due to the retrospective nature of the study. The study was performed in accordance with the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and regulations.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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