

Prognostic Value of Admission Blood Urea Nitrogen/Creatinine Ratio in Patients with STEMI Undergoing Late Percutaneous Coronary Intervention

Caijuan Dong

First Affiliated Hospital of Xi'an Jiaotong University

Yanbo Xue

First Affiliated Hospital of Xi'an Jiaotong University

Yan Fan

Gansu Provincial Hospital

Ruochen Zhang

First Affiliated Hospital of Xi'an Jiaotong University

Yunfei Feng

First Affiliated Hospital of Xi'an Jiaotong University

Yamei Wang

First Affiliated Hospital of Xi'an Jiaotong University

Puqing Kou

First Affiliated Hospital of Xi'an Jiaotong University

Guoli Li

First Affiliated Hospital of Xi'an Jiaotong University

Aiqun Ma

First Affiliated Hospital of Xi'an Jiaotong University

Tingzhong Wang (✉ tingzhong.wang@xjtu.edu.cn)

First Affiliated Hospital of Xi'an Jiaotong University

Research Article

Keywords: blood urea nitrogen/creatinine ratio, long-term prognosis, ST-segment elevation myocardial infarction, late percutaneous coronary intervention

Posted Date: March 11th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-275679/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Prognostic Value of Admission Blood Urea Nitrogen/Creatinine Ratio in Patients with STEMI Undergoing Late Percutaneous Coronary Intervention

Caijuan Dong¹, Yanbo Xue¹, Yan Fan², Ruochen Zhang¹, Yunfei Feng¹, Yamei Wang¹, Puqing Kou¹, Guoli Li¹, Aiqun Ma^{1,3,4*}, Tingzhong Wang^{1,3,4*}

1. Department of Cardiovascular Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi, P. R. China
2. Department of Cardiovascular Medicine, Gansu Provincial Hospital, Lanzhou, P. R. China
3. Key Laboratory of Molecular Cardiology, Shaanxi Province, P. R. China
4. Key Laboratory of Environment and Genes Related to Diseases (Xi'an Jiaotong University), Ministry of Education, Xi'an, Shaanxi, P. R. China

Short title: BUN/Cr in STEMI patients with late PCI

***Corresponding authors:**

Aiqun Ma, MD, PhD or Tingzhong Wang, PhD

Department of Cardiovascular Medicine,

First Affiliated Hospital of Xi'an Jiaotong University,

No. 277 West Yanta Road,

Xi'an 710061, Shaanxi, P. R. China.

Email: maaiqun1108@126.com (A. M.) or tingzhong.wang@xjtu.edu.cn (T. W.)

Abstract:

Objective: Numerous patients with ST-segment elevation myocardial infarction (STEMI), especially in developing countries, undergo late percutaneous coronary intervention (PCI), defined as time of PCI > 24 hours from symptom onset. This study is aimed to identify the predictive value of admission blood urea nitrogen/creatinine ratio (BUN/Cr) on long-term all-cause mortality and cardiac mortality in STEMI patients receiving late PCI.

Methods: Eligible STEMI patients who received late PCI between 2009 and 2011 were consecutively enrolled. They were classified into two groups based on the median BUN/Cr: low BUN/Cr group and high BUN/Cr group. Patients were followed up by phone or face to face interviews and medical records review. The primary endpoint was defined as all-cause mortality and cardiac mortality.

Results: 780 STEMI patients were enrolled finally. The median BUN/Cr was 14.29. The median follow-up period was 41 months, with 37 all-cause deaths and 25 cardiac deaths. Compared to the low BUN/Cr group, high BUN/Cr group had higher all-cause mortality (6.4% vs. 3.1%, $P=0.029$), and cardiac mortality (6.3% vs. 1.5%, $P<0.001$). The Cox proportional hazard analysis revealed that high BUN/Cr at admission was an independent predictor of long-term cardiac mortality ($P=0.003$), but not of all-cause mortality ($P=0.077$).

Conclusions: High BUN/Cr ratio at admission was an independent predictor of cardiac mortality in STEMI patients receiving late PCI.

Keywords: blood urea nitrogen/creatinine ratio; long-term prognosis; ST-segment elevation myocardial infarction; late percutaneous coronary intervention

Brief Summary: In a retrospective study of STEMI patients receiving late PCI, we found that high BUN/Cr ratio (BUN/Cr>14.29) at admission was an independent predictor of long-term cardiac mortality, but not of all-cause mortality. The study showed that BUN/Cr ratio could be a potential indicator of risk stratification models for STEMI patients undergoing late PCI.

1. Introduction

Acute myocardial infarction (AMI) is one of the leading causes of cardiac death and an eye-catching public health problem in the world. The sooner the ischemic myocardium gets reperfused, the better the cardiac function of victims recovers. Early percutaneous coronary intervention (PCI) or pharmacological reperfusion has been strongly suggested for treating patients with ST-segment elevation myocardial infarction (STEMI) within 12 hours of symptom onset.¹ According to Chinese guideline, PCI is a preferred clinical practice for patients with ongoing ischemia within 12-24 hours of symptom onset, or 3-24 hours after thrombolysis no matter whether the thrombolytic therapy is successful or not. Although the proportion of STEMI patients receiving emergency PCI has remarkably increased, over 45% of the urban and rural patients in China missed the timely reperfusion treatment due to various reasons, such as weak self-awareness and delayed medical system.² These late presenters of STEMI (>24 hours from the initial event) either receive late PCI (time of PCI > 24 hours from symptom onset) or conservative therapy. Fan's study showed that late PCI significantly prevented left ventricular remodeling and reduced the risks of major adverse cardiovascular events, all-cause death, and rehospitalization for heart failure in STEMI patients.³ But there are very few indicators to predict the prognosis of STEMI patients undergoing late PCI. High cystatin C levels was reported to be associated with poor prognosis in STEMI patients undergoing late PCI.⁴ Exploring more indicators for risk stratification can help clinicians to identify high-risk patients early and carry out effective intervention to improve their outcomes.

Both blood urea nitrogen (BUN) and creatinine (Cr), mainly eliminated by the kidney, are waste products of nitrogen-containing substances in the body. Up to now, blood urea nitrogen/creatinine ratio (BUN/Cr) as the predictor of acute ischemic stroke (AIS), gastrointestinal bleeding and acute heart failure (AHF) has been widely studied.⁵⁻⁹ Some studies have found that BUN/Cr can better predict the prognosis of patients with AHF than single BUN or Cr.^{7,9} Admission BUN was an independent predictor of in-hospital mortality and long-term cardiovascular mortality in AHF patients.^{10,11} But its predictive role in AMI is few reported. Doron Aronson's study revealed that elevated BUN and BUN/Cr on admission were independent predictors of long-term mortality in STEMI patients.¹² But in his study, some patients received medical therapy and others underwent reperfusion therapy. Whether the predictive value of BUN/Cr is similar in different therapy groups was not determined. Hao Qian's study evaluated

the predictive value of BUN/Cr in patients with AMI who received emergency PCI. He found that AHF combined with elevated BUN/Cr was associated with an increased risk of mortality in patients with AMI, suggesting that BUN/Cr had a prognostic value in patients with AMI complicated with AHF.¹³ However, to our knowledge, there is no study identifying the predictive power of BUN/Cr in STEMI patients receiving late PCI, which is just the aim of our study.

2. Methods

2.1 Patient selection

This is a retrospective observational study and the study was carried out in compliance with the STROBE guidelines. Eligible patients in the First Affiliated Hospital of Xi'an Jiaotong University in northwest China from January 2009 to December 2011 were enrolled consecutively. The inclusion criteria were as follows: 1. ≥ 18 years of age; 2. diagnosed with STEMI in accordance with 2007 American College of Cardiology Foundation/American Heart Association guidelines;¹⁴ 3. treated with a late PCI (defined as the time of PCI >24 hours from symptom onset); 4. with available urea nitrogen and creatinine at admission. Patients were excluded if they met any of the following criteria: 1. underwent an early PCI; 2. diagnosed with idiopathic cardiomyopathy, congenital heart diseases and valvular heart disease; 3. diagnosed with rheumatic or autoimmune diseases; 4. Significant liver or kidney dysfunction; 5. Malignancy. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University School of Medicine. All patients offered written informed consents. The study design was detailed in Figure 1A.

2.2 Baseline information and laboratory examinations

For all the patients, demographic characteristics, medical history, laboratory measurements, echocardiography findings and angiographic information were obtained from the hospital medical record system. Blood samples for measuring blood counts and serum biomarkers like urea nitrogen, creatinine, were collected within 1 hour of admission as a part of routine clinical care. All the patients underwent color Doppler echocardiography within 72 hours of admission. The estimated glomerular filtration rate (eGFR) was calculated by Simplified Modification of Diet in Renal Disease (MDRD) equation. $eGFR \text{ (mL/min/1.73 m}^2 \text{ of body surface area)} = 186 \times (\text{Serum creatinine}/88.4) - 1.154 \times (\text{Age}) - 0.203 \text{ (}\times 0.742 \text{ for females)}$. The TIMI risk score is a well-known risk stratification for patients with STEMI involving the following variables: age,

presence of diabetes mellitus/hypertension or angina, heart rates, systolic blood pressure, Killip classification, body weight, presence of anterior myocardial infarction or left bundle branch block, and time to treatment. Patients were divided into three groups according to the total score: low risk (0-3 points), moderate risk (4-6 points), and high risk (7-14 points)(more details were seen in Figure 1B).¹⁵

2.3 Follow-up and study endpoints

The primary endpoint was designated to be the long-term all-cause death and cardiac death. The outcome messages were acquired by face to face or telephone interviews and medical record reviews. No interventions were performed during the follow-up and information regarding the outcomes were limited by the researchers.

2.4 Statistical analysis

Continuous variables conformed to a normal distribution were expressed as mean \pm standard deviation (SD) and compared between groups by independent- sample Student's t test, while variables that didn't follow a normal distribution were expressed as the median (interquartile 1, interquartile 3) and the inter-group differences were compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages. The Pearson χ^2 test and the Fisher exact test were used to compare the differences between categorical variables. The optimal cutoff value of BUN/Cr to predict the long-term all-cause mortality was determined by receiver-operator characteristic curve analysis. Survival curves were displayed using the Kaplan-Meier method for long-term all-cause mortality, cardiac mortality and MACE. The differences were tested by the log-rank test. Multivariate Cox regression was used to identify the independent risk factors for long-term all-cause mortality, cardiac mortality and MACE during follow-up and hazard ratios (HR) were presented with their 95% confidence intervals (CI). A two-tailed *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0 (SPSS, Inc., Chicago, IL, USA) and GraphPad prism 5.0 (GraphPad Software, Inc., Cary, NC).

3. Results

3.1 Baseline data of study population

180 patients (18.7%) were excluded due to loss of follow up (Figure1A) . A total of 780 patients were finally enrolled. Based on the median BUN/Cr (14.29), patients were classified into the low BUN/Cr group (BUN/Cr \leq 14.29) and the high BUN/Cr group (BUN/Cr $>$ 14.29).

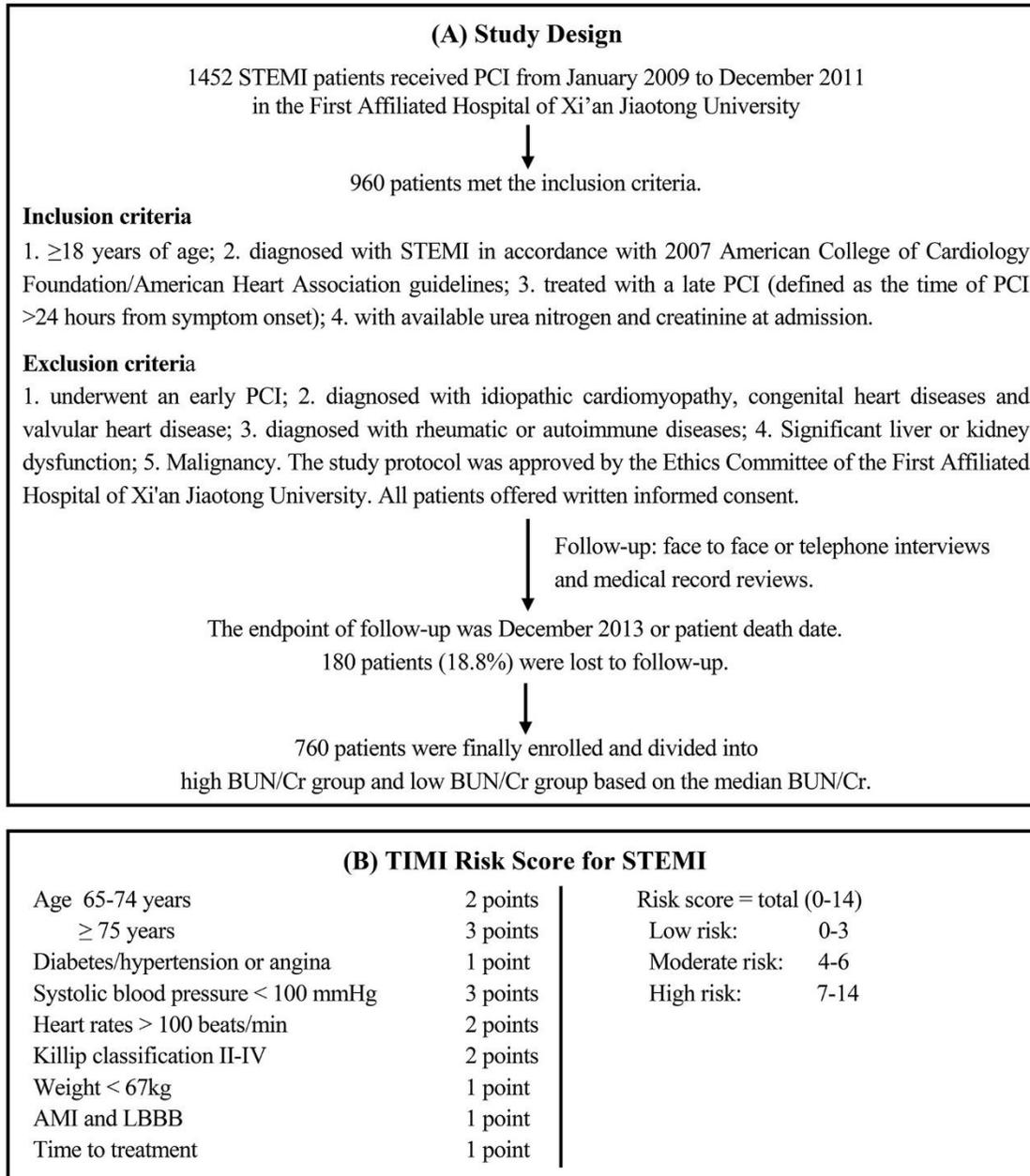


Figure 1. The study design and TIMI risk score for STEMI. BUN/Cr, blood urea nitrogen/creatinine ratio; LBBB, left bundle branch block.

The baseline characteristics for the entire study population were summarized in Table1. The average age of patients was 57.6 years (SD 10.9) and 84.7% of them were male. The patients

with diabetes and hypertension accounted for 13.1% and 42.6% respectively. Compared to the low BUN/Cr group, patients in the high BUN/Cr group had lower blood pressure ($P < 0.001$) at admission and higher rates of diabetes ($P = 0.006$) and hyperlipidemia ($P=0.028$). Gender, age, heart rate, body mass index and the Killip classification showed no difference between the two groups. The high BUN/Cr group was observed to have a higher leukocyte count ($P = 0.001$), higher neutrophil ($P = 0.021$), higher level of serum glucose ($P < 0.001$), higher level of cardiac markers for diagnosing AMI [creatinine kinase ($P < 0.001$), creatine kinase-MB ($P = 0.001$), Troponin I ($P < 0.001$)] and lower eGFR ($P = 0.004$). According to the echocardiography measurement, high BUN/Cr group had a lower left ventricular ejection fraction (LVEF, $P = 0.04$), while other parameters were similar. Angiographic information including the time to PCI from symptom onset, myocardial infarction location, and number of narrowed coronary vessels etc, showed no significant difference.

Table 1. Baseline data of study population

Variable	All (n=780)	Low BUN/Cr group (≤ 14.29 , n=390)	High BUN/Cr group (>14.29 , n=390)	<i>P</i>
Demographic characteristic				
Gender, male (%)	661 (84.7)	330 (84.6)	331 (84.9)	0.921
Age (years)	57.58 \pm 10.96	56.98 \pm 11.24	58.19 \pm 10.68	0.123
Admission examination				
BMI (kg/m ²)	23.87 \pm 2.83	24.02 \pm 2.86	23.71 \pm 2.80	0.128
HR (beats/min)	75.42 \pm 14.39	74.98 \pm 14.37	75.85 \pm 14.41	0.395
SBP (mmHg)	121.51 \pm 19.24	124.25 \pm 20.28	118.77 \pm 17.74	<0.001
DBP (mmHg)	76.71 \pm 12.24	78.37 \pm 12.86	75.04 \pm 11.36	<0.001
History (%)				
Smoking	537 (68.8)	259 (66.4)	278 (71.3)	0.142
Alcohol consumption	259 (33.2)	137 (35.1)	122 (31.3)	0.254
Hypertension	332 (42.6)	170 (43.6)	162 (41.5)	0.562
Diabetes mellitus	102 (13.1)	38 (9.7)	64 (16.4)	0.006
Hyperlipidemia	131 (16.8)	54 (13.8)	77 (19.7)	0.028
Prior revascularization	23 (2.9)	13 (3.3)	10 (2.6)	0.525
Killip classification on admission (%)				0.614
I	462 (59.2)	231 (59.2)	231 (59.2)	
II	247 (31.7)	121 (31.0)	126 (32.3)	
III	52 (6.7)	30 (7.7)	22 (5.6)	
IV	19 (2.4)	8 (2.1)	11 (2.8)	

Laboratory measurements on admission				
Leukocyte (10 ⁹ /L)	8.50±3.52	8.07±2.97	8.92±3.96	0.001
Neutrophil (%)	68.78±13.78	67.64±13.29	69.92±14.18	0.021
Erythrocyte (10 ⁹ /L)	4.28±0.59	4.29±0.57	4.27±0.61	0.709
Hemoglobin (g/L)	134.73±16.39	135.25±16.29	134.22±16.50	0.381
Platelet (10 ⁹ /L)	195.50±71.59	198.57±71.45	192.43±71.68	0.231
TC (mmol/L)	4.02±1.08	3.98±0.99	4.07±1.16	0.221
TG (mmol/L)	1.50 (1.12-2.00)	1.51 (1.14-2.05)	1.47 (1.11-1.99)	0.295
HDL (mmol/L)	1.01±0.26	1.01±0.24	1.02±0.27	0.601
LDL (mmol/L)	2.36±0.88	2.28±0.85	2.44±0.91	0.014
BUN (mmol/L)	5.22±2.08	4.00±1.03	6.44±2.16	<0.001
Cr (μmol/L)	85.85±16.76	87.25±15.63	84.45±17.73	0.019
BUN/Cr	15.11±5.09	11.34±2.05	18.88±4.39	<0.001
eGFR (mL/min/1.73 m ²)	113.99±35.08	117.64±33.42	110.34±36.34	0.004
Glucose (mmol/L)	6.41(5.29-7.99)	6.02(5.09-7.55)	6.66(5.61-8.48)	<0.001
Cystatin C (mg/L)	0.93 (0.78-1.13)	0.93 (0.78-1.13)	0.93 (0.76-1.14)	0.987
Uric acid (μmol/L)	297.70±86.38	295.56±83.66	299.81±88.94	0.491
CK (U/L)	161.15 (74.32-788.09)	122.95 (68.64-519.14)	214.75 (80.04-1065.83)	<0.001
CK-MB (U/L)	21.50 (11.00-67.09)	17.70 (10.42-48.48)	23.87 (11.44-84.66)	0.001
Tropinin I (ng/mL)	1.09 (0.57-3.29)	0.90 (0.50-2.56)	1.40 (0.69-3.83)	<0.001
NT-proBNP (mg/L)	1036.0 (493.05-2201.0)	947.9 (475.9-1955.0)	1119.0 (565.3-2543.0)	0.113
Hs-CRP (mg/L)	7.90 (3.00-25.65)	6.32 (2.70-23.30)	8.70 (3.80-28.35)	0.089
Echocardiography				
LVEDD (mm)	53.53±6.42	53.33±6.19	53.72±6.65	0.397
LVESD (mm)	38.14±7.73	37.74±7.63	38.53±7.81	0.154
LVEDV (mL/m ²)	104.29±24.39	103.85±23.45	104.73±25.31	0.613
LVESV (mL/m ²)	54.64±21.23	53.48±20.84	55.79±21.59	0.130
LVEF (%)	53.67±11.70	54.53±11.54	52.82±11.80	0.040
Angiographic information				
Time to PCI from symptom onset (days)	10.0(7.0-16.0)	10.0(8.0-16.0)	10.0(7.0-16.0)	0.497
Myocardial infarction location (%)				
Anterior/anteroseptal	447 (57.3)	215 (55.1)	232 (59.5)	0.218
Lateral	24 (3.1)	13 (3.3)	11 (2.8)	0.678
Inferior/posterior/right ventricular	362 (46.4)	193 (49.5)	169 (43.3)	0.085
Number of narrowed coronary vessels (%)				
1	215 (27.6)	105 (26.9)	110 (28.2)	0.825
2	268 (34.4)	138 (35.4)	130 (33.3)	
≥3	297 (38.1)	147 (37.7)	150 (38.5)	

Culprit lesion (coronary) (%)				0.228
Right	265 (34.0)	141 (36.2)	124 (31.8)	
LAD	434 (55.6)	210 (53.8)	224 (57.4)	
Left circumflex	72 (9.2)	37 (9.5)	35 (9.0)	
Left main	9 (1.2)	2 (0.5)	7 (1.8)	
TIMI flow grade Pre-PCI (%)				0.554
0	275 (28.6)	114 (29.2)	120 (30.8)	
1	28 (2.9)	11 (2.8)	10 (2.6)	
2	72 (7.5)	23 (5.9)	32 (8.2)	
3	585 (60.9)	242 (62.1)	228 (58.5)	
TIMI risk score				0.108
0-3	297 (38.1)	157 (40.3)	140 (35.9)	
4-6	367 (47.1)	185 (47.4)	182 (46.7)	
7-14	116 (14.9)	48 (12.3)	68 (17.4)	

Data were presented as the mean \pm SD, median (IQR), or n (%). BMI, body mass index; HR, heart rates; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen; Cr, creatinine; BUN/Cr, blood urea nitrogen/creatinine ratio; eGFR, estimated glomerular filtration rate; CK, creatine kinase; NT-proBNP, N terminal pro-brain natriuretic peptide; Hs-CRP, high sensitive C-reactive protein; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

3.2 Follow-up outcomes

The median follow-up period was 41 months. 37 all-cause deaths and 25 cardiac deaths occurred in the 780 patients (Table 2). Compared to the low BUN/Cr group, all-cause mortality (6.4% vs 3.1%, $P = 0.029$) and cardiac mortality (5.4% vs 1.0%, $P = 0.001$) were significantly higher in the high BUN/Cr group (Table 2). The survival curves for all-cause mortality and cardiac mortality were shown in Figure 2, respectively. The survival curves showed that the cumulative survival for all-cause mortality ($\chi^2 = 4.616$, $P = 0.032$) and cardiac mortality ($\chi^2 = 11.580$, $P = 0.001$) were significantly lower in the high BUN/Cr group.

Table 2. Outcomes of study population.

Outcomes	All	Low BUN/Cr group	High BUN/Cr group	<i>P</i>
All-cause death	37 (3.6%)	12 (3.1%)	25(6.4%)	0.029
Cardiac death	25 (2.5%)	4 (1.0%)	21(5.4%)	0.001

Data were presented as n (%). BUN/Cr, blood urea nitrogen/creatinine ratio.

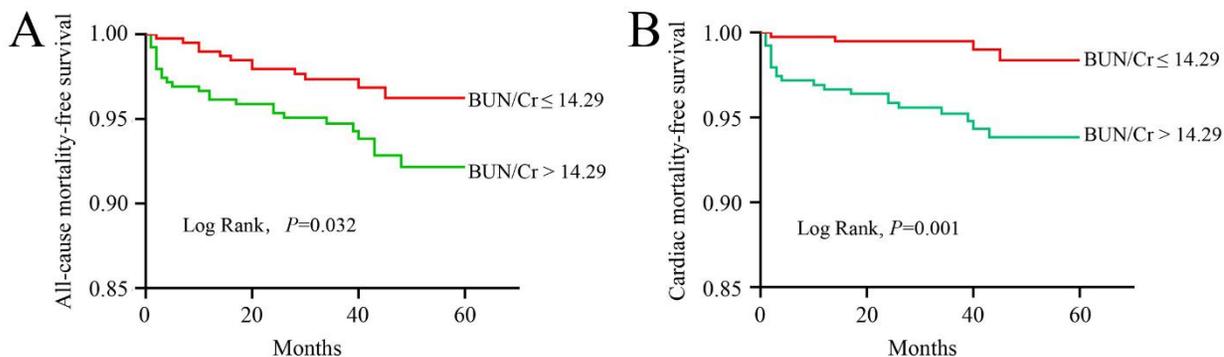


Figure 2. Kaplan-Meier survival curves for long-term all-cause mortality and cardiac mortality.

A. Kaplan-Meier survival curves for long-term all-cause mortality. B. Kaplan-Meier survival curves for long-term cardiac mortality. BUN/Cr, blood urea nitrogen/creatinine ratio.

3.3 Multivariate regression analysis

The Cox regression analysis was applied to determine the independent variables in predicting the risk of all-cause mortality and cardiac mortality. According to the univariate analysis, the high BUN/Cr group had a 2-fold (95% CI: 1.050-4.161, $P = 0.036$) and 5-fold (95% CI: 1.802-15.299, $P = 0.002$) increases in the risk of all-cause death and cardiac death respectively. High BUN/Cr was still an independent predictor of cardiac mortality adjusted by TIMI risk score, neutrophil and left ventricular end-systolic dimension (adjusted HR: 4.967; 95% CI: 1.700-14.512; $P = 0.003$), but not of all-cause mortality adjusted by TIMI risk score, erythrocyte and left ventricular end-systolic dimension ($P = 0.077$) (seen in Table 3).

Table 3. Cox regression analysis of all-cause mortality and cardiac mortality

	Crude HR (95% CI)	<i>P</i>	Adjusted HR (95% CI)	<i>P</i>
All-cause mortality				
Low BUN/Cr	1 (reference)		1 (reference)	
High BUN/Cr	2.090 (1.050-4.161)	0.036	1.870 (0.934-3.743)	0.077
Cardiac mortality				
Low BUN/Cr	1 (reference)		1 (reference)	
High BUN/Cr	5.251 (1.802-15.299)	0.002	4.967 (1.700-14.512)	0.003

BUN/Cr, blood urea nitrogen/creatinine ratio; HR, hazard ratio; CI: confidential interval.

3.4 Killip classification

Killip classification is developed to assess cardiac function of patients with AMI. Patients with Killip I are not complicated by acute heart failure. Killip II-IV respectively represent mild-moderate, severe and extremely severe acute heart failure. Considering that plenty of studies found the level of BUN/Cr was associated with acute heart failure, we evaluated the predictive power of BUN/Cr in non-AHF group (patients with Killip I) and AHF group (patients with Killip II-IV). In the AHF group, high BUN/Cr increased the risk of long-term all-cause death ($P = 0.017$) and cardiac death ($P = 0.011$). But in non-AHF group, elevated BUN/Cr only increased the risk of long-term cardiac death ($P = 0.019$), but not of all-cause death (seen in Table 4). The Kaplan-Meier analysis showed the similar results (Figure 3). The AHF patients' cumulative survival for all-cause mortality ($\chi^2 = 5.454$, $P = 0.020$) and cardiac mortality ($\chi^2 = 6.243$, $P = 0.013$) were significantly lower in the high BUN/Cr group (seen in Figure 3C, D). The non-AHF patients' cumulative survival of cardiac mortality ($\chi^2 = 4.408$, $P = 0.036$) was lower in the high BUN/Cr group, while the cumulative survival of all-cause mortality showed no significant difference ($\chi^2 = 0.815$, $P = 0.367$, Figure 3A, B).

Table 4. Outcomes of AHF patients and non-AHF patients

Outcomes	non-AHF			AHF		
	Low BUN/Cr (n=231)	High BUN/Cr (n=231)	<i>P</i>	Low BUN/Cr (n=159)	High BUN/Cr (n=159)	<i>P</i>
All-cause mortality	9 (3.9%)	13 (5.6%)	0.382	3 (1.9%)	12 (7.5%)	0.017
Cardiac mortality	2 (0.9%)	10 (4.3%)	0.019	2 (1.3%)	11 (6.9%)	0.011

Data were presented as n (%). BUN/Cr, blood urea nitrogen/creatinine ratio.

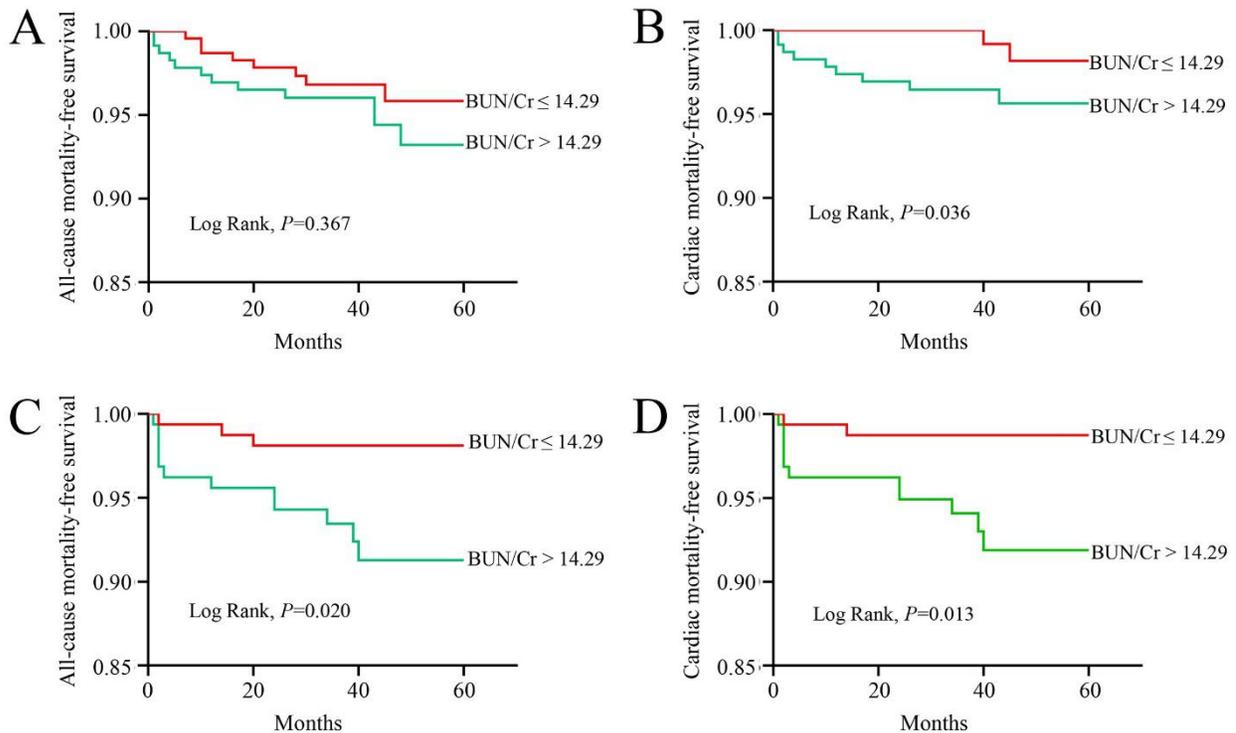


Figure 3. Kaplan-Meier survival curves for long-term all-cause mortality and cardiac mortality in AHF group and non-AHF group. A, B. Kaplan-Meier survival curves for long-term all-cause mortality and cardiac mortality in non-AHF patients. C, D. Kaplan-Meier survival curves for long-term all-cause mortality and cardiac mortality in AHF patients. BUN/Cr, blood urea nitrogen/creatinine ratio.

4. Discussion

Patients with AMI show a great variability in cardiovascular outcomes for their complex clinical characteristics. To identify patients at higher risk and provide better treatment for these patients, a number of risk stratification models have been developed, such as GRACE and TIMI risk stratification model. In developing countries, late presenters of STEMI account for a large proportion and are a heavy burden on medical economy. But up to now, there are very few predictors of the prognosis of STEMI patients undergoing late PCI. Therefore, it is necessary and urgent to explore reliable prognostic indicators for victims receiving late PCI so that to benefit those in higher risk.

The creatinine is mainly produced by a muscle metabolism called creatine, and excreted outside the body by the kidney. The production of creatinine is constant because the muscle mass in human body is relatively stable. Thus, the level of creatinine mainly reflects on renal function. The level of blood urea nitrogen depends on the urea production and renal excretion. Conditions that enhance urea production include high-protein diet, muscle wasting, gastrointestinal bleeding, corticosteroid and tetracyclines therapy etc.¹⁶ Besides, a fall in filtration at glomerulus and a rise in reabsorption at renal tubule can also lead to the increased blood urea nitrogen. The reabsorption of urea nitrogen is a passive process which is associated with the water and sodium reabsorption at the distal nephron under the influence of antidiuretic hormone.¹⁷ It seems the serum urea nitrogen level is more easily affected by extra-renal factors than is the serum creatinine level.¹⁸

In the context of AMI, a variety of factors may impair renal function. These factors include low cardiac output, activation of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) etc. The decrease in renal blood flow as a result of a reduction in effective circulating blood volume, can cause a rise in blood urea nitrogen out of proportion to the rise in serum creatinine.¹⁷ The exact mechanism is not known yet. However, one possible explanation is that renal plasma flow (RPF) declines but glomerular filtration rate (GFR) doesn't change or decrease in proportion, causing the rise of filtration fraction (GFR/RPF). This increase in filtration fraction prevents proteins of the blood existing from the glomerulus to the peritubular capillaries. Accumulating blood proteins increase peritubular capillary colloid osmotic pressure and declined renal blood flow decreases peritubular hydrostatic pressure. The joint effects are in favor of tubular reabsorption of filtered reabsorbable substances. The elevated BUN contributes to both reduced GFR and avid tubular reabsorption. Nevertheless, the serum creatinine may be elevated only moderately with a decrease in renal blood flow. Furthermore, the activation of RAAS and SNS promotes absorption of water and sodium, subsequently giving rise to passive reabsorption of BUN in the renal tubules (Figure 4).^{7,19} It is believed that activation of the RAAS and SNS is associated with adverse prognosis.²⁰ Above all, in the setting of AMI, the elevation of BUN/Cr at admission represents adaptive response to renal hypoperfusion due to low cardiac output and activation of RAAS and SNS rather than intrinsic renal dysfunction, and potentially can be acted as a simple prognostic marker of AMI.

This study revealed that the high BUN/Cr group had a higher long-term mortality and cardiac mortality. After adjusting for those potential confounders such as TIMI risk score, erythrocyte etc, high BUN/Cr was an independent predictor of long-term cardiac mortality in STEMI patients receiving late PCI, but not of all-cause mortality. The exact mechanism of the association between high BUN/Cr and long-term mortality and cardiac mortality has not been totally uncovered. One credible hypothesis is that elevation of BUN/Cr is linked with decreased cardiac output, and activation of RAAS and SNS, which were the indicators of poor prognosis in patients with AMI. The echocardiography finding that high BUN/Cr group had a lower left ventricle ejection fraction further advocates the idea. Considering the established predictive value of BUN/Cr in AHF, patients were divided into non-AHF group (patients with Killip I) and AHF group (patients with Killip II-IV). It was found that high BUN/Cr increased risk of cardiac deaths both in non-AHF group and AHF group, suggesting that high BUN/Cr was a hopeful indicator of poor prognosis for AMI patients, not only limited to those complicated with AHF.

We compared the cutoff value (14.29) of BUN/Cr in our study with that in previous studies. Hao Qian's study identified the median BUN/Cr of 15.32 as the cutoff value and explored the predictive value of BUN/Cr in the long-term prognosis of patients with AMI complicated with AHF^[13]. BUN/Cr >15 is widely recognized as a reference marker for early neurological deterioration and hospital expenses in patients with acute ischemic stroke.²¹⁻²³ BUN/Cr ratio of 35 was adapted to distinguish the upper and lower gastrointestinal bleeding.²⁴ We found that the cutoff value of BUN/Cr to indicate the prognosis of STEMI patients who received late PCI are similar with that in predicting the outcomes of AHF and AIS, but much lower than that to differentiate the location of gastrointestinal bleeding.

The tests of blood urea nitrogen and creatinine are relatively low-cost and are available in any standard hospital laboratory. So, their ratio can be used as simple marker to predict the prognosis of STEMI patients undergoing late PCI, or hopefully enter into the risk stratification models of AMI.

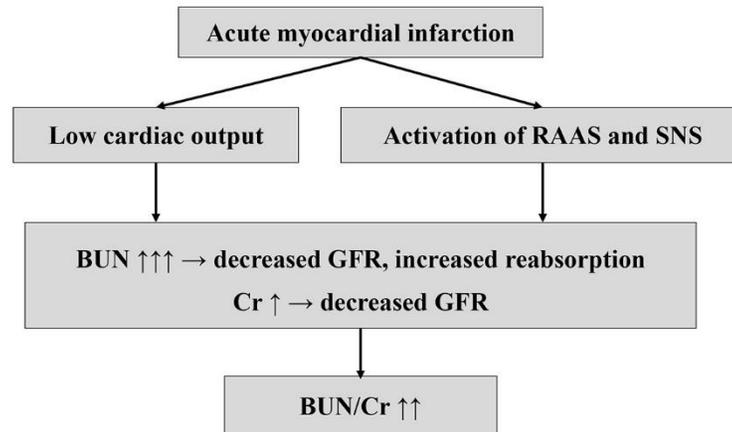


Figure 4. Mechanism of elevated BUN/Cr ratio in patients with AMI. BUN, blood urea nitrogen; Cr, creatinine ratio; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; GFR, glomerular filtration rate.

5. Limitations

First, this study was a single center, retrospective observational study. Our results need to be tested in larger trials with multiple centers and more study population. Second, the BUN/Cr is influenced by non-neurohormonal factors, such as high-protein diet, cachexia, and muscle wasting and the history of diuretic agents, but these factors were not assessed in this study. Third, the results are subject to bias with the high rate of loss to follow-up and other unknown or unmeasured factors.

6. Conclusion

High BUN/Cr ratio at admission increased the risk of long-term all-cause death and cardiac death in STEMI patients receiving late PCI. High BUN/Cr ratio at admission was an independent predictor of long-term cardiac mortality in STEMI patients receiving late PCI, but not of all-cause mortality.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. The

study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University and carried out in compliance with the STROBE guidelines. Because of the retrospective nature of the study, patient consent for inclusion was waived by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University.

Consent for publication

Not applicable.

Availability of Data and Materials

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

Competing interests

The authors declare no potential conflict of interests.

Funding

This work was supported by the Science and Technology Program for Public Wellbeing of China (2012GS610101).

Author's contributions

C.D. drafted the manuscript and contributed to data analysis; Y.X. performed the statistical analysis; Y.F., R.Z., YF.F., Y.W., P.K. and G.L. collected the data and underwent the follow up; A.M. and T.W. conceived and supervised the study.

Acknowledgements

None.

References

1. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2018;39:119-177.

2. Zhang L, Desai NR, Li J, et al. National quality assessment of early clopidogrel therapy in Chinese patients with acute myocardial infarction (AMI) in 2006 and 2011: Insights from the china patient-centered evaluative assessment of cardiac events (PEACE)-retrospective AMI study. *J Am Heart Assoc.* 2015;4: e001906
3. Fan Y, Bai X, Chen Y, et al. Late percutaneous coronary intervention prevents left ventricular remodeling and improves clinical outcomes in patients with ST-elevation myocardial infarction. *Clin Cardiol.* 2015;38:82-91.
4. Chen Y, Fan Y, Men M, et al. High cystatin c levels predict long-term mortality in patients with ST-segment elevation myocardial infarction undergoing late percutaneous coronary intervention: A retrospective study. *Clin Cardiol.* 2019;42:572-578.
5. Ernst AA, Haynes ML, Nick TG, et al. Usefulness of the blood urea nitrogen/creatinine ratio in gastrointestinal bleeding. *Am J Emerg Med.* 1999;17:70-72.
6. Kim H, Lee K, Choi HA, et al. Elevated blood urea nitrogen/creatinine ratio is associated with venous thromboembolism in patients with acute ischemic stroke. *J Korean Neurosurgs S.* 2017;60:620-626.
7. Takaya Y, Yoshihara F, Yokoyama H, et al. Risk stratification of acute kidney injury using the blood urea nitrogen/creatinine ratio in patients with acute decompensated heart failure. *Circ J.* 2015;79:1520-1525.
8. Sujino Y, Nakano S, Tanno J, et al. Clinical implications of the blood urea nitrogen/creatinine ratio in heart failure and their association with haemoconcentration. *ESC Heart Failure.* 2019;6:1274-1282.
9. Otto CM. Heartbeat: Blood urea nitrogen to creatinine ratio predicts outcome in acute heart failure. *Heart.* 2017;103:399-401.
10. Richter B, Sulzgruber P, Koller L, et al. Blood urea nitrogen has additive value beyond estimated glomerular filtration rate for prediction of long-term mortality in patients with acute myocardial infarction. *Eur J Intern Med.* 2019;59:84-90.
11. Horiuchi Y, Aoki J, Tanabe K, et al. A high level of blood urea nitrogen is a significant predictor for in-hospital mortality in patients with acute myocardial infarction. *Int Heart J.* 2018;59:263-271.
12. Aronson D, Hammerman H, Beyar R, et al. Serum blood urea nitrogen and long-term mortality in acute ST-elevation myocardial infarction. *Int J Cardiol.* 2008;127:380-385.

13. Qian H, Tang C, Yan G. Predictive value of blood urea nitrogen/creatinine ratio in the long-term prognosis of patients with acute myocardial infarction complicated with acute heart failure. *Medicine*. 2019;98:e14845.
14. King SB, Smith SC, Hirshfeld JW, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention. *J Am Coll Cardiol*. 2008;51:172-209.
15. Morrow DA, Andrew EMA, Charlesworth A, et al. Infarcting myocardium early II trial substudy. *Circulation*. 2000;102:2031-2037.
16. Weiner ID, Mitch WE, Sands JM. Urea and ammonia metabolism and the control of renal nitrogen excretion. *Clin J Am Soc Nephrol*. 2015;10:1444-1458.
17. Baum N, Dichoso CC. Blood urea nitrogen and serum creatinine. *Urology*. 1975:583-588.
18. Lyman JL. Blood urea nitrogen and creatinine. *Emerg Med Clin North Am*. 1986;4:223-233.
19. Murata A, Kasai T, Matsue Y, et al. Relationship between blood urea nitrogen-to-creatinine ratio at hospital admission and long-term mortality in patients with acute decompensated heart failure. *Heart Vessels*. 2018;33:877-885.
20. Er F, Dahlem KM, Nia AM, et al. Randomized control of sympathetic drive with continuous intravenous esmolol in patients with acute ST-segment elevation myocardial infarction: The beta-blocker therapy in acute myocardial infarction (BEAT-AMI) trial. *JACC Cardiovasc Interv*. 2016;9:231-240.
21. Bhatia K, Mohanty S, Tripathi BK, et al. Predictors of early neurological deterioration in patients with acute ischaemic stroke with special reference to blood urea nitrogen (BUN)/creatinine ratio & urine specific gravity. *Indian J Med Res*. 2015;141:299-307.
22. Schrock JW, Glasenapp M, Drogell K. Elevated blood urea nitrogen/creatinine ratio is associated with poor outcome in patients with ischemic stroke. *Clin Neurol Neurosurg*. 2012;114:881-884.
23. Lin WC, Shih HM, Lin LC. Preliminary prospective study to assess the effect of early blood urea nitrogen/creatinine ratio-based hydration therapy on poststroke infection rate and length of stay in acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2015;24:2720-2727.
24. Zia ZSM, Rimaz S, Shafaghi A, et al. Blood urea nitrogen to creatinine ratio in differentiation of upper and lower gastrointestinal bleedings: a diagnostic accuracy study. *Arch Acad Emerg Med*. 2019;7:e30.

Figures

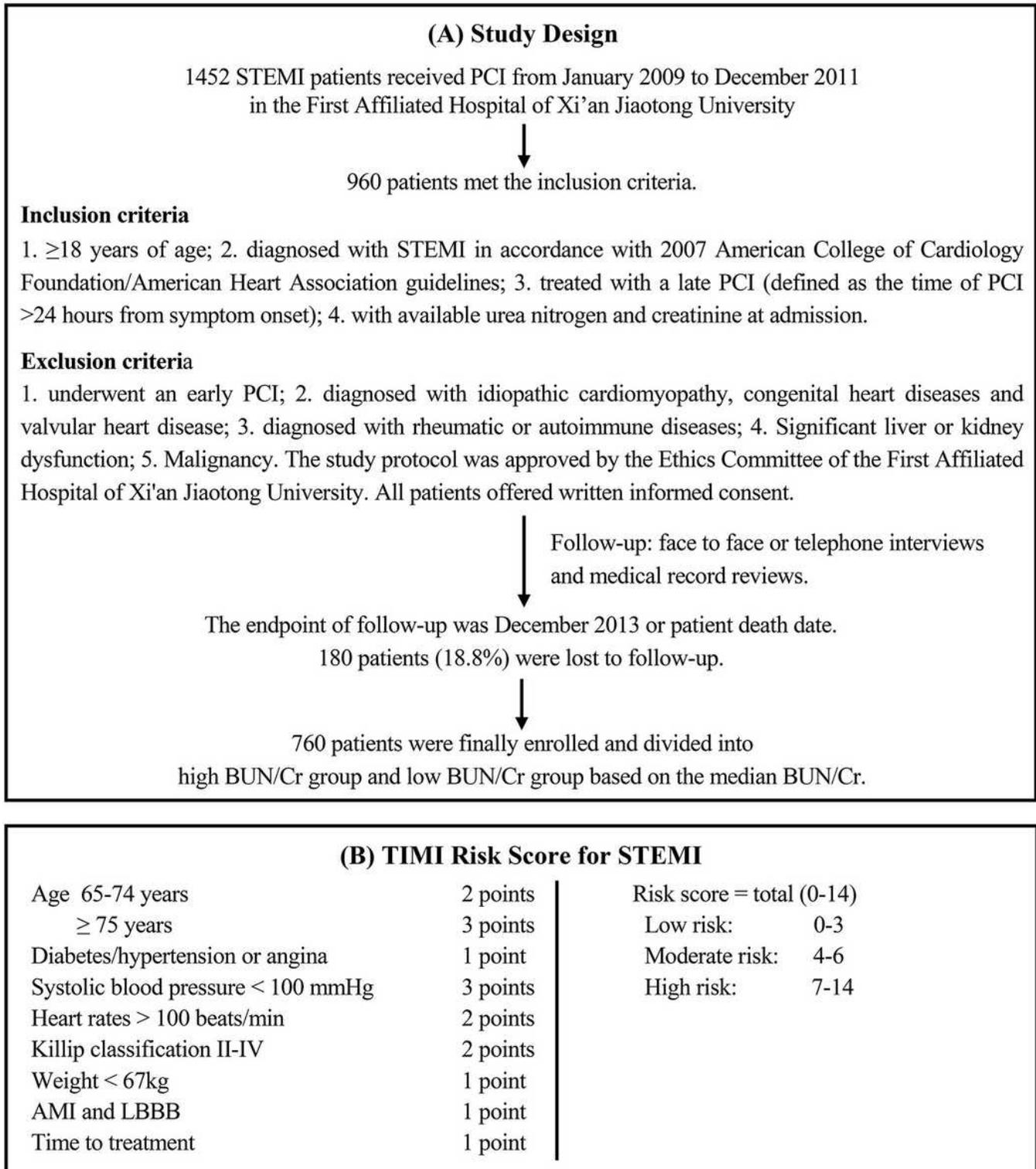


Figure 1

The study design and TIMI risk score for STEMI. BUN/Cr, blood urea nitrogen/creatinine ratio; LBBB, left bundle branch block.

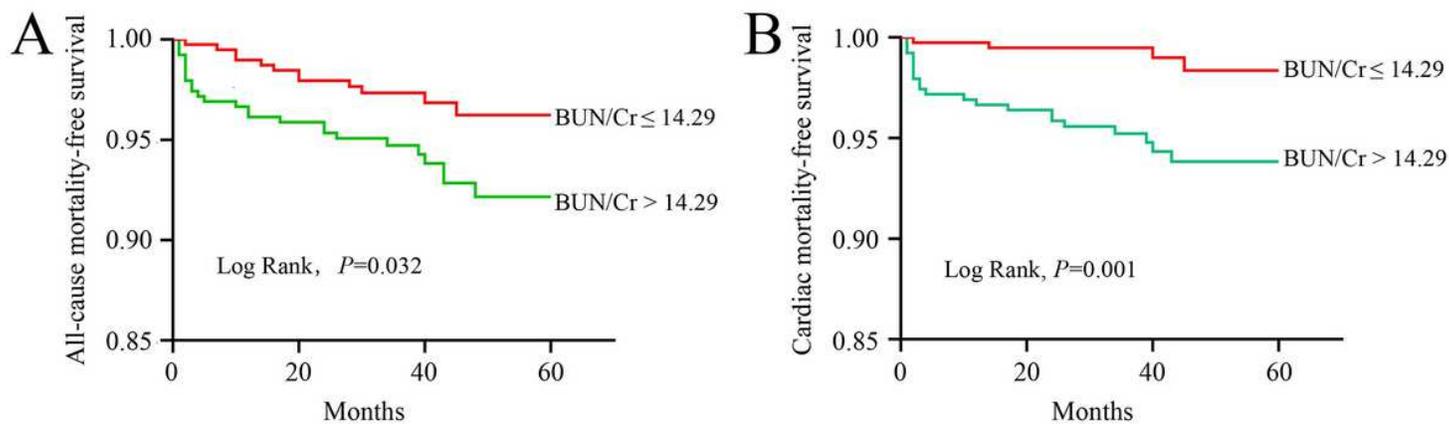


Figure 2

Kaplan-Meier survival curves for long-term all-cause mortality and cardiac mortality. A. Kaplan-Meier survival curves for long-term all-cause mortality. B. Kaplan-Meier survival curves for long-term cardiac mortality. BUN/Cr, blood urea nitrogen/creatinine ratio.

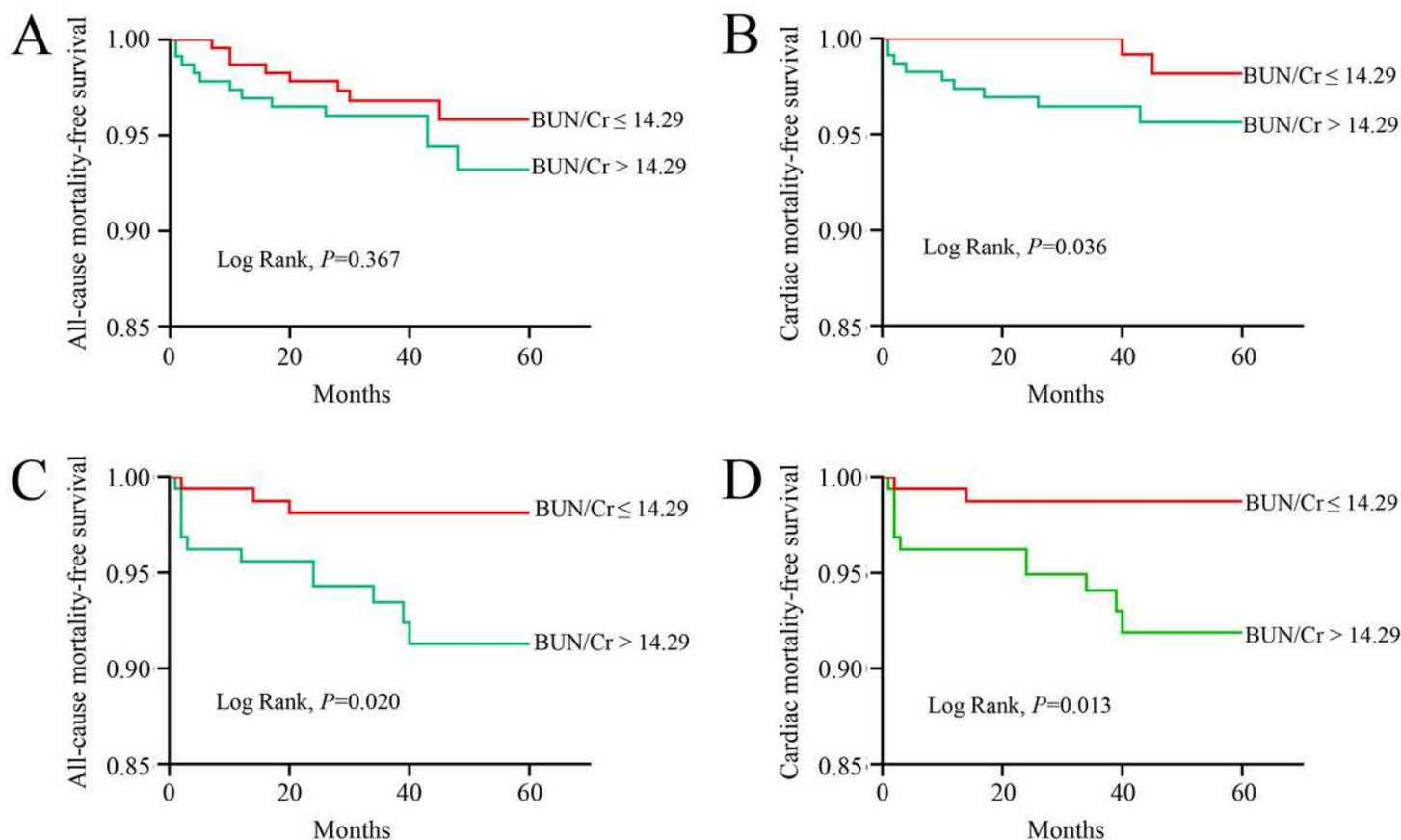


Figure 3

Kaplan-Meier survival curves for long-term all-cause mortality and cardiac mortality in AHF group and non-AHF group. A, B. Kaplan-Meier survival curves for long-term all-cause mortality and cardiac mortality in

non-AHF patients. C, D. Kaplan-Meier survival curves for long-term all-cause mortality and cardiac mortality in AHF patients. BUN/Cr, blood urea nitrogen/creatinineratio.

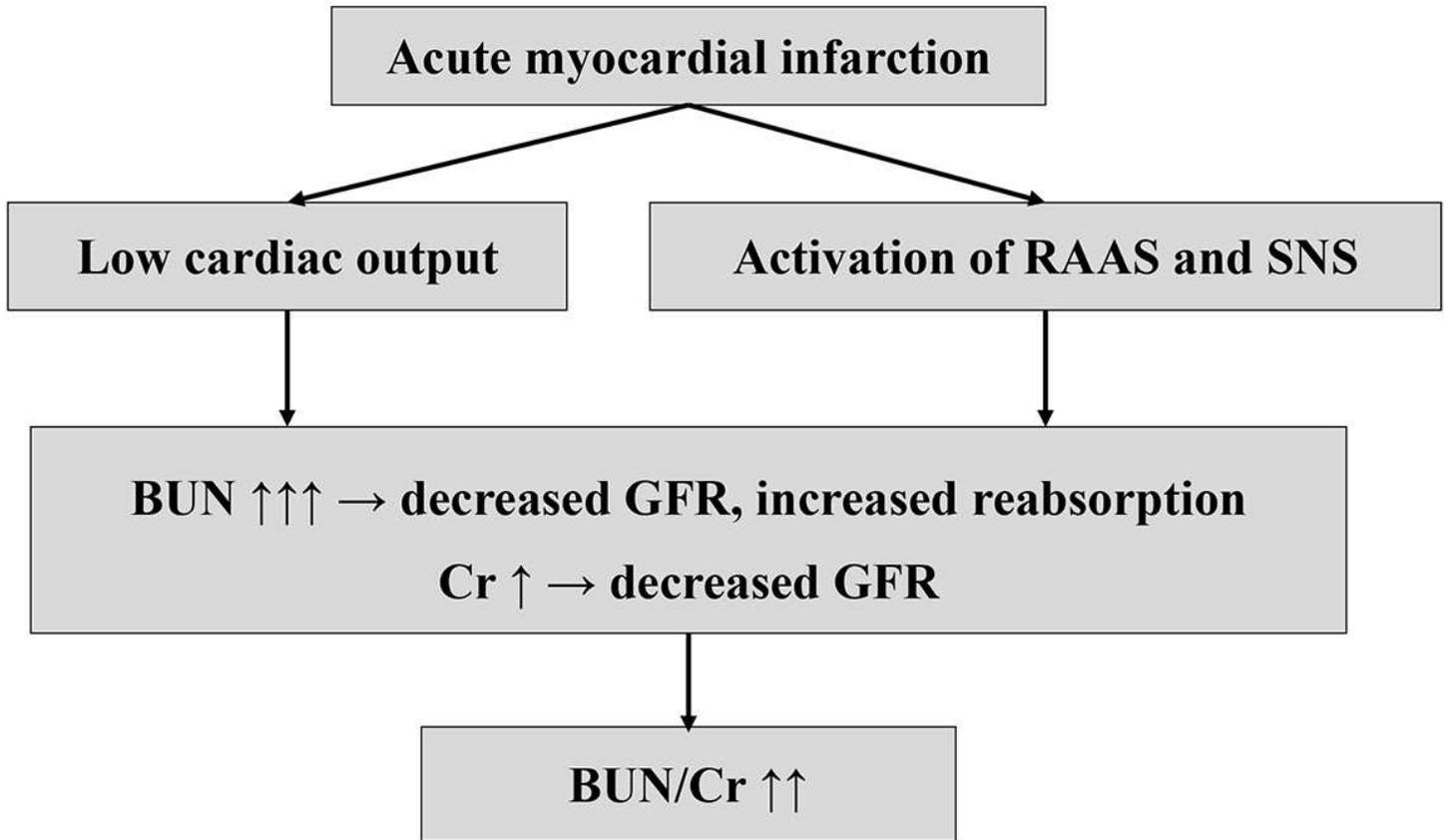


Figure 4

Mechanism of elevated BUN/Cr ratio in patients with AMI. BUN, blood urea nitrogen; Cr, creatinine ratio; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; GFR, glomerular filtration rate.