

Predictive value of blood urea nitrogen/creatinine ratio in the long-term prognosis of patients with acute myocardial infarction complicated with acute heart failure

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Abstract

At present, the long-term prognosis of patients with acute myocardial infarction (AMI) after emergency percutaneous coronary intervention is the focus of attention, and relevant research is actively investigating the risk factors associated with prognosis. Poor prognosis often exists in Patients with AMI complicated with acute heart failure (AHF). In recent years, some studies have found that blood urea nitrogen/creatinine ratio (BUN/Cr) can better predict the prognosis of patients with AHF than single BUN or Cr. The relationship between long-prognosis of patients with AMI, as one of the common causes of AHF, and BUN/Cr is unknown. The main purpose of this study was to determine whether BUN/Cr has a predictive value for long-term prognosis in patients with AMI complicated with AHF.

In this study, 389 consecutive patients with AMI were enrolled. According to AHF and a median BUN/Cr at admission of 15.32, the patients were divided into four groups (non-AHF + low BUN/Cr, non-AHF + high BUN/Cr, AHF + low BUN/Cr, and AHF + high BUN/Cr groups). A 1-year follow-up was implemented, and the study endpoint was defined as all-cause mortality. Predictors associated with 1-year mortality were evaluated using the Cox proportional hazard analysis, and the Kaplan–Meier analysis was used to estimate the survival rates.

AHF occurred in 163 patients (41.9%) during hospital admission and 29 patients died during the 1-year follow-up. The Cox proportional hazard analysis proved an association between the combination of AHF and high BUN/Cr and mortality; however, the association with AHF + low BUN/Cr was not statistically significant.

AHF combined with elevated BUN/Cr is linked with an increased risk of mortality in patients with AMI, which suggests that BUN/Cr has a predictive value for prognosis in patients with AMI complicated with AHF.

Abbreviations: AHF = acute heart failure, AMI = acute myocardial infarction, AVP = arginine vasopressin, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, Cis = confidence intervals, Cr = creatinine, CRS = cardiorenal syndrome, HDL = high-density lipoprotein, HRs = hazard ratios, LVEF = left ventricle election fraction, PCI = percutaneous coronary intervention, RAAS = renin-angiotensin-aldosterone system, ROC = receiver-operating characteristic, SBP = systolic blood pressure, SNS = sympathetic nervous system.

Keywords: acute heart failure, acute myocardial infarction, blood urea nitrogen-to-creatinine ratio, predictors, prognosis

1. Introduction

Acute heart failure (AHF) is one of the most common comorbidities in acute myocardial infarction (AMI) and is

associated with adverse prognosis.^[1,2] Both blood urea nitrogen (BUN) and creatinine (Cr) are metabolic end products of nitrogen-containing substances in the human body. As they are small molecules, they can be freely filtered through the glomerulus. Normally, Cr is hardly reabsorbed in the tubules, while approximately 30% to 40% of BUN is reabsorbed.^[3] Studies have found that the neurohormonal system was involved in mediating this reabsorption process, which might be enhanced in patients with AHF.^[3] Some studies suggest that BUN/Cr, instead of a single BUN or Cr, is associated with the prognosis of patients with AHF.^[4–6] Considering the many primary causes of AHF, AMI is one of them and is the current research focus.^[7] The aim of this study was to investigate the correlation between BUN/Cr and the prognosis of patients with AMI complicated with AHF.

2. Materials and methods

2.1. Study population

This is a prospective observational study. Consecutively, from January 2016 to March 2017, 400 patients with AMI who

Editor: Leonardo Gilardi.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors report no conflicts of interest.

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Medicine (2019) 98:11(e14845)

Received: 3 October 2018 / Received in final form: 14 February 2019 /

Accepted: 18 February 2019

<http://dx.doi.org/10.1097/MD.0000000000014845>

Table 1**Baseline data of study population.**

	non-AHF + low BUN/Cr (n = 134)	non-AHF + high BUN/Cr (n = 92)	AHF + low BUN/Cr (61)	AHF + high BUN/Cr (102)	P
Clinical characteristics					
Age	57.64 ± 12.66	59.68 ± 11.41	66.48 ± 11.86	67.89 ± 11.67	<.001
Male	130 (97.01%)	67 (72.83%)	46 (75.41%)	66 (64.71%)	<.001
BMI	25.01 ± 3.08	24.75 ± 2.99	24.73 ± 3.35	24.36 ± 3.84	.587
SBP	130.31 ± 22.33	129.18 ± 23.36	132.15 ± 26.98	126.29 ± 22.66	.420
DBP	79.25 ± 14.71	78.22 ± 15.68	79.77 ± 17.21	76.62 ± 16.11	.530
HR	80.04 ± 13.45	81.41 ± 17.05	82.21 ± 15.49	85.95 ± 19.33	.049
Smoke	95 (70.90%)	46 (50.00%)	32 (52.46%)	41 (40.20%)	<.001
Co-morbidities					
Hypertension	61 (45.52%)	59 (64.13%)	34 (55.74%)	61 (59.80%)	.030
Diabetes	17 (12.69%)	19 (20.65%)	8 (13.11%)	28 (27.45%)	.020
CAD	3 (2.24%)	2 (2.17%)	2 (3.28%)	1 (0.98%)	.749
AF	4 (2.99%)	4 (4.35%)	4 (6.56%)	10 (9.80%)	.141
CKD	3 (2.24%)	1 (1.09%)	3 (4.92%)	4 (3.92%)	.402
CD	10 (7.46%)	12 (13.04%)	10 (16.39%)	23 (22.55%)	.011
COPD	6 (4.48%)	1 (1.09%)	6 (9.84%)	7 (6.86%)	.086
Laboratory measurements					
Na ⁺	138.96 ± 2.85	137.97 ± 3.28	137.91 ± 3.82	137.5 ± 4.17	.011
Tnl	6.55 (1.38–25.00)	9.39 (2.11–21.90)	19 (5.36–25.00)	18 (3.8–25.00)	.002
BNP	44.1 (10.75–109.00)	53.5 (16.21–147.00)	293 (148.00–434.00)	312 (121.52–618.53)	<.001
Hemoglobin	148 (135–155)	147 (134–159)	140 (125–155)	136 (123–149)	<.001
BUN	11.80 (10.11–13.76)	16.15 (14.33–19.94)	12.92 (10.39–14.61)	18.82 (15.45–24.44)	<.001
Cr	0.98 (0.89–1.07)	0.86 (0.79–0.98)	1.03 (0.89–1.20)	1.00 (0.81–1.21)	<.001
UA	358 (311–422)	311 (262–375)	330 (274–396)	339 (262–406)	.001
ALT	40 (27–54)	40 (26–61)	38 (25–70)	46 (28–85)	.230
AST	133 (68–211)	135.5 (66–199)	137 (84–243)	180 (73–344)	.036
Triglyceride	1.63 (1.22–2.60)	1.59 (1.11–2.07)	1.28 (1.01–2.00)	1.26 (0.91–1.84)	.001
TC	4.49 (3.99–5.15)	4.69 (4.12–5.28)	4.37 (4.05–4.90)	4.32 (3.75–5.04)	.251
HDL	1.02 (0.88–1.16)	1.06 (0.91–1.21)	1.10 (0.96–1.27)	1.11 (0.90–1.29)	.032
LDL	2.83 (2.40–3.39)	2.95 (2.46–3.48)	2.77 (2.37–3.22)	2.76 (2.29–3.28)	.448
Drug history					
Aspirin	21 (15.67%)	23 (25.00%)	21 (34.43%)	38 (37.25%)	.001
ACEI/ARB	18 (13.43%)	17 (18.48%)	12 (19.67%)	17 (16.67%)	.653
β-block	11 (8.21%)	8 (8.70%)	5 (8.20%)	6 (5.88%)	.880
CCB	27 (20.15%)	30 (32.61%)	17 (27.87%)	36 (35.29%)	.053
Cardiac color Doppler ultrasound					
LA	3.82 ± 0.42	3.86 ± 0.49	3.91 ± 0.53	4.00 ± 0.53	.038
LV	4.70 ± 0.41	4.77 ± 0.63	4.88 ± 0.73	4.80 ± 0.49	.159
RA	3.80 ± 0.50	3.79 ± 0.41	3.77 ± 0.59	3.80 ± 0.48	.983
RV	2.32 ± 0.24	2.39 ± 0.39	2.35 ± 0.37	2.27 ± 0.30	.066
EF	0.62 ± 0.09	0.61 ± 0.11	0.55 ± 0.13	0.53 ± 0.13	<.001
GRS	112.28 ± 24.01	114.64 ± 25.17	129.66 ± 26.99	136.96 ± 24.27	<.001

ACEI = angiotensin converting enzyme inhibitors, AF = atrial fibrillation, AHF = acute heart failure, ALT = alanine transaminase, ARB = angiotensin receptor antagonist, AST = aspartate transaminase, BMI = body mass index, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, CAD = coronary artery disease, CCB = calcium channel blocker, CD = cerebrovascular disease, CKD = chronic renal disease, COPD = chronic obstructive pulmonary disease, Cr = creatinine, DBP = Diastolic blood pressure, EF = ejection fraction, GRS = grace risk score HDL = high density lipoprotein, HR = heart rate, LA = left atrium, LDL = low density lipoprotein, LV = left ventricle, RA = right atrium, RV = right ventricle, SBP = systolic blood pressure, TC = total cholesterol, Tnl = troponin I, UA = uric acid.

underwent emergency percutaneous coronary intervention (PCI) at ZhongDa Hospital, affiliated to Southeast University, were included in the study. We excluded 11 patients who did not complete the entire follow-up. Briefly, AMI was diagnosed on the basis of the guidelines of the European Society of Cardiology.^[1] The diagnosis of AHF was based on the 2016 ESC Guidelines and carried out by at least 1 physician above the level of attendance, in accordance with the patient's symptoms, signs, laboratory findings, and cardiac function evaluation.^[7] This study was registered in the Chinese Clinical Trial Registry (Registration No. ChiCTR1800017982) and had been filed with the Ethics Committee of Zhongda Hospital. All the patients provided written informed consent.

2.2. Baseline information and laboratory examinations

For all the subjects, general clinical characteristics, laboratory measurements, and imaging examination results were entered. Clinical data were obtained from the hospital medical record system. Laboratory measurements were performed on admission for all the patients. All the patients underwent color Doppler echocardiography (performed at the Color Ultrasound Room, Department of Cardiology, ZhongDa Hospital) within 72 hours of admission.

2.3. Follow-up and study endpoints

The endpoint of this study was defined as all-cause mortality. A 1-year follow-up was performed through outpatient visits or

Table 2
Factors Related to AHF.

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age > 75	3.129 (1.866–5.248)	<.001	1.806 (0.901–3.620)	.096
Sex	3.093 (1.855–5.159)	<.001	1.344 (0.619–2.915)	.455
AF	2.560 (1.048–6.255)	.039	1.003 (0.342–2.941)	.995
Hemoglobin	0.977 (0.967–0.988)	<.001	0.991 (0.975–1.007)	.267
Culprit artery				
LAD	1 (reference)		1 (reference)	
LCX	0.557 (0.292–1.062)	.076	0.719 (0.301–1.723)	.460
RCA	0.591 (0.377–0.925)	.021	0.662 (0.360–1.219)	.186
EF < 0.50	4.591 (2.720–7.747)	<.001	3.072 (1.615–5.844)	.001
BNP > 100	6.662 (4.093–10.844)	<.001	4.132 (2.357–7.241)	<.001
BUN/Cr > 15.34	2.435 (1.611–3.683)	<.001	1.956 (1.123–3.406)	.018
TFOTEP > 12h	1.453 (0.793–2.663)	.226	–	–
Na ⁺	0.928 (0.875–0.985)	.013	0.991 (0.919–1.069)	.816

AF = atrial fibrillation, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, Cr = creatinine, EF = ejection fraction, LAD = left anterior descending artery, LCX = left circumflex artery, OR = odds ratio, RCA = right coronary artery, TFOTEP = time from onset to emergency PCI.

telephone interviews. Of the 400 patients, 389 completed the 1-year follow-up. No interventions were performed during the follow-up and information regarding the outcomes were obtained by the researchers.

2.4. Data analysis

The 389 subjects were assigned to one of 4 groups according to AHF and a median BUN/Cr of 15.32. Data analysis was performed using SPSS (19.0, International Business Machines Corporation). For quantitative data that followed normal and non-normal distributions, multiple groups were compared using analysis of variance and rank comparison tests, respectively. For categorical variables, the chi-square test was used to compare the composition ratios among the groups. Predictors of 1-year mortality were evaluated using the Cox proportional hazard analysis. Multivariate analysis was respectively performed for indicators, including systolic blood pressure, sex, age, hypertension, and hemoglobin levels, as well as the combination of AHF with BUN/Cr. Hazard ratios (HRs) are presented with their 95% confidence intervals (CIs). The Kaplan–Meier analysis was used to assess the survival rates of the 4 groups. The predictive value of the combination of AHF and BUN/Cr and Grace risk score was assessed using a receiver-operating characteristic (ROC) curve analysis. Statistical significance was defined as a *P* value of <.05.

3. Results

After we excluded 11 patients who did not finish the 1-year follow-up, 389 patients remained in the study. The baseline data of the study population are given in Table 1. The mean age was 62 ± 13 years, and 79% of the patients were male. After the 1-year follow-up, 29 patients died. AHF occurred in 163 patients during hospital stay. According to the combination of AHF and BUN/Cr, the patients were divided into 4 groups as follows: non-AHF + low BUN/Cr (*n* = 134), non-AHF + high BUN/Cr (*n* = 92), AHF + low BUN/Cr (*n* = 61), and AHF + high BUN/Cr (*n* = 102). As shown in Table 1, the AHF + high BUN/Cr was older with lower male ratios, higher prevalence rates of diabetes and cerebrovascular disease, lower hemoglobin level, higher high-density lipoprotein (HDL) level, and lower triglyceride level than the other groups. At the same time, the AHF + high BUN/Cr

group had lower left ventricle ejection fraction (LVEF) and higher Grace risk score (Table 1). As shown in Table 2, AHF was independently related to LVEF of <50% (*P* = .001), brain natriuretic peptide (BNP) level of >100 ng/L; *P* < .001, and higher BUN/Cr (*P* = .018). As shown in Figure 1, which presents the results of the Kaplan–Meier survival curves, the AHF + high BUN/Cr group had a significantly higher 1-year mortality than the other groups (log-rank test, *P* = .002). No statistically significant differences were found among the non-AHF + low BUN/Cr, non-AHF + high BUN/Cr, and AHF + low BUN/Cr groups. Through the COX analysis, we found that compared with the non-AHF + low BUN/Cr group, the AHF + high BUN/Cr group had a significantly higher mortality rate (*P* = .013) after adjustment for sex, age, SBP, heart rate, hypertension, and hemoglobin level, whereas the associations were absent in the non-AHF + high BUN/Cr (*P* = .617) and AHF + low BUN/Cr groups (*P* = .251) (Table 3). The ROC analysis for the

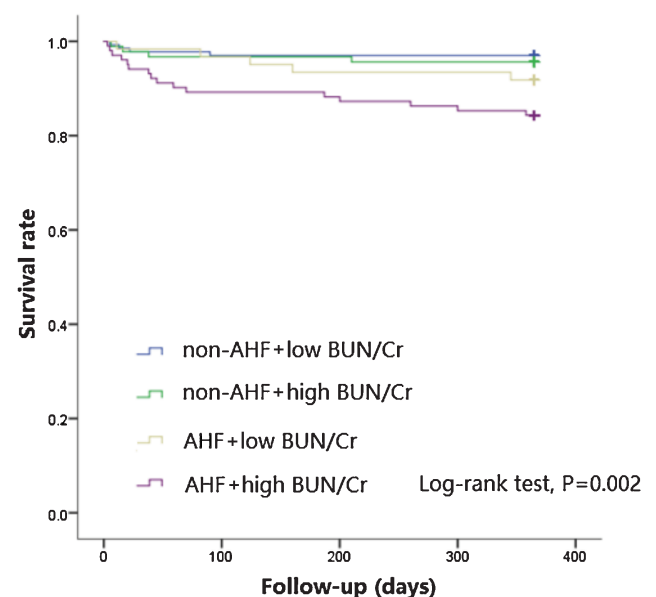


Figure 1. Kaplan–Meier survival curves for one-year follow-up. AHF = acute heart failure, BUN = blood urea nitrogen, Cr = creatinine.

Table 3**Predictive value of BUN/Cr for 1-year Mortality.**

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P
Non-AHF + low BUN/Cr	1 (reference)		1 (reference)	
Non-AHF + high BUN/Cr	1.464 (0.366–5.854)	.590	1.439 (0.346–5.991)	.617
AHF + low BUN/Cr	2.772 (0.744–10.322)	.129	2.191 (0.575–8.348)	.251
AHF + high BUN/Cr	5.57 (1.862–16.663)	.002	4.229 (1.363–13.121)	.013

Adjusted for age, sex, SBP, heart rate, Hypertension, Hemoglobin. AHF=acute heart failure, BUN=blood urea nitrogen, Cr=creatinine, HR=hazard ratio.

combination of AHF and BUN/Cr and Grace risk score, as predictors of prognosis, revealed the following areas under the curve with their 95% CIs: for Grace risk score, 0.707 (0.618–0.795) and for the combination of AHF and BUN/Cr, 0.695 (0.597–0.793) (Fig. 2). The Z-test revealed no statistically significant differences between them in the areas under the curve ($P = .832$, Table 4).

4. Discussion

The kidney and heart have a close bidirectional association that is defined clinically as 5 types of cardiorenal syndrome (CRS).^[8] CRS type 1 is characterized by a rapid deterioration of cardiac function that leads to acute kidney injury.^[8,9] Cardiac function in patients with AMI has different degrees of reduction in the short term.^[1,2] Data showed that the incidence of AHF after AMI is 32.4%.^[10] BUN level, Cr level, and BUN/Cr are currently recognized indicators of renal function.^[9,11–13] Studies have shown that when treating patients with AMI complicated with AHF for diuresis and so on, for patients with reduced BUN/Cr, continuation of decongestion therapy is recommended, even though the Cr level has increased significantly.^[4,14] Therefore, BUN/Cr has a greater guiding value for the clinical treatment of AMI patients. The main finding of this study is that AHF

combined with elevated BUN/Cr was associated with an increased risk of long-term mortality in patients with AMI.^[12,15] In addition, our findings suggest that the predictive value of BUN/Cr combined with AHF for the prognosis of patients with AMI is not weaker than that of the Grace risk score.

Both the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) were activated in patients with AHF, which could promote absorption of water and sodium and cause passive reabsorption of BUN in the renal tubules.^[4,12] Activation of the neurohormonal system could also lead to renal vasoconstriction and decreased glomerular filtration rate and BUN excretion.^[12] Furthermore, insufficient blood volume secondary to low cardiac output stimulates the release of arginine vasopressin (AVP), which can facilitate the reabsorption of BUN in the collecting duct.^[16,17] For the reasons that the Cr was freely filtered through the glomerulus and not reabsorbed and the single BUN had many influencing factors, many studies believe that BUN/Cr is useful for treating AHF patients.^[4] For patients with AMI complicated with AHF, higher BUN/Cr reflects a more active neurohormonal system. It is currently widely believed that activation of the RAAS and SNS systems is associated with adverse prognosis.^[18–21] Yoichi et al reported that BUN/Cr, but not BUN or Cr individually, is linked with an increased risk of mortality in AHF patients.^[4] Gotsman et al also

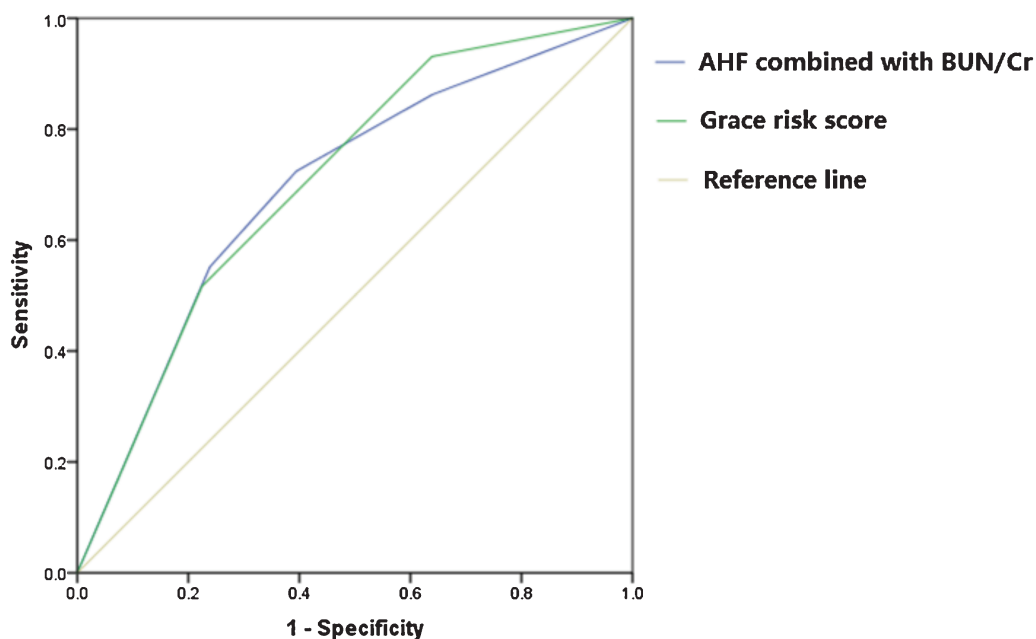


Figure 2. Receiver operating characteristic curves for different indicators to predict long-term mortality for AMI patients. AHF=acute heart failure, BUN=blood urea nitrogen, Cr=creatinine.

Table 4**Comparison of the areas under the ROC curve.**

	AUC	AUC (95%CI)	P	Sensitivity	Specificity
AHF and BUN/Cr	0.695	0.597–0.793	<.001	72.4	60.6
GRS	0.707	0.618–0.795	<.001	51.7	77.5
Z	0.212				
P	.832				

AHF=acute heart failure, AUC=area under curve, BUN=blood urea nitrogen, Cr=creatinine, GRS=grace risk score.

believed that in patients with AHF, admission BUN/Cr was a predictor of worse 1-year and long-term (mean follow-up of 6.5 years) mortality.^[22] Brisco et al also found that a significant association exists between elevated admission BUN/Cr and increased mortality.^[23]

For patients with AMI without AHF, we found no correlation between BUN/Cr and prognosis.^[24] We considered that this might be related to some factors that may have affected the baseline BUN/Cr, such as high protein diet and hepatic insufficiency.^[25] In the analysis of risk factors for the incidence of AHF in patients with AMI, we found that LVEF of <50%, BNP level of >100ng/L, and higher BUN/Cr were significantly associated with the incidence of AHF. LVEF had a significant value for evaluating heart function, and decreased LVEF is closely associated with adverse prognosis. Some studies have suggested that the specific value of elevated BNP level has no significant correlation with prognosis, which needs further study.^[26–28] Our study found that BUN/Cr has a predictive value for the development of AHF in patients with AMI and can be used for risk stratification in patients with AMI.

Studies have shown that the Grace risk score can be used to predict not only in-hospital mortality in patients with AMI but also long-term prognosis. Through an analysis, we found that for patients with AMI, the predictive value of the combination of AHF and BUN/Cr for prognosis is not weaker than that of the Grace risk score. Considering that the Grace risk score is based on a large number of cases, the predicted value of BUN/Cr needs further research to demonstrate. Several studies have previously shown a close association of Na⁺ with heart failure. As shown in this study, Na⁺ levels in non-AHF+high BUN/Cr group and AHF+high BUN/Cr group were lower than those in non-AHF+low BUN/Cr group, while the remaining pair-wise comparisons of Na⁺ levels did not indicate statistically significant differences. Univariate analysis showed a correlation between Na⁺ and the incidence of AHF. However, after multivariate analysis, such a correlation was not present. We postulate that this finding could be due to the larger fluctuations in Na⁺ levels. We intend to conduct a future study using a larger patient population in order to achieve higher accuracy.

The present study had several limitations. First, as this was a single-center clinical study, population limitations may exist in the cases studied. Second, the predictive value of BUN/Cr for long-term outcomes in patients with AMI must be examined in a larger sample size. Third, as this was an observational study, although a multifactor analysis was performed, other confounding factors might still be existing. Furthermore, 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.

5. Conclusion

The combination of AHF with an elevated BUN/Cr admission is linked with an increased risk of mortality in patients with AMI. The predictive value of BUN/Cr for prognosis in patients with AMI is not independent of AHF. In addition, the study also shows that for patients with AMI, the predictive value of the combination of AHF and BUN/Cr for prognosis is not weaker than that of the Grace risk score.

Acknowledgments

This work was supported by Department of Cardiology, Zhongda Hospital in China. We are grateful to Julie Grace (California, USA), for supplying language help.

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