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Original Article

The value of N-terminal pro-brain natriuretic peptide and hs-CRP in predicting acute kidney injury after acute myocardial infarction

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Abstract: Objective: To evaluate the value of combined detection of N-terminal pro-brain natriuretic peptide (NT-pro BNP) and high-sensitivity C-reactive protein (hs-CRP) in predicting acute kidney injury (AKI) after acute myocardial infarction (AMI). Method: We retrospectively analyzed data of 107 patients with AMI admitted to our hospital from May 2020 to May 2021. The patients were assigned into an AKI group (AKIG) (n = 27) and a non-AKI group (NAKIG) (n = 80) according to whether AKI occurred within 1 week after admission. A total of 50 healthy people who underwent physical examination at the same duration were taken as control group (CG). Clinical data, expression of hs-CPR and NT-pro BNP were detected and compared between AKIG and NAKIG. Logistic regression model was applied to analyze risk factors of AKI after AMI, and Pearson linear correlation was used to analyze the correlation of hs-CRP and NT-pro BNP in patients with both AMI and AKI. Receiver operating characteristic (ROC) curve and area under the curve (AUC) were drawn and determined, and predictive value of hs-CRP and NT-pro BNP alone as well as in combination with AKI after AMI was analyzed respectively. Results: Compared with CG, hs-CRP and NT-pro BNP of AKIG and NAKIG were markedly increased (P<0.0001). In AKIG, the levels of uric acid, blood urea nitrogen, serum creatinine (SCr), hs-CRP, NT-pro BNP were higher compared to those in NAKIG, while the estimated glomerular filtration rate (eGFR) was evidently lower than that of NAKIG (P<0.01). Logistic regression model suggested that the use of diuretics, SCr, eGFR, hs-CRP and NT-pro BNP were the risk factors of AKI in patients with AMI (P<0.05). The level of hs-CRP was positively related with NT-pro BNP (P<0.05). ROC curve analysis indicated AUCs of hs-CRP and NT-pro BNP alone as well as in combination were all over 0.8 in predicting the occurrence of AKI after AMI. Conclusion: The increase of hs-CRP and NT-pro BNP linked closely to the occurrence of AKI after AMI, and the combined detection of the two was of high value in predicting the occurrence of AKI among patients with AMI.

Keywords: N-terminal pro-brain natriuretic peptide, hs-CRP, acute myocardial infarction (AMI), acute kidney injury (AKI)

Introduction

According to statistics, the proportion of the elderly in China accounts for over 11.6% of the total population by the year of 2022 [1]. Recent studies have shown that the mortality and morbidity of cardiovascular disease, especially coronary heart disease, are on a yearly rise among the elderly in China [2]. Cardiovascular disease is statistically the highest morbidity and mortality worldwide, and the mortality had risen to 36.6% in 2020 [3]. Acute myocardial infarction (AMI), as a common clinical cardiovascular disease with acute onset and severe condition, is one of the most serious manifestations of coronary artery diseases [4]. Acute kidney injury (AKI) is another common disease secondary to AMI [5]. It was revealed that the incidence of AKI has continued to rise in recent years, and among high-risk groups such as patients diagnosed with AMI, congestive heart failure, sepsis, etc., the incidence of AKI may be as high as 10% to 25% [6]. The study by Cosentino et al. revealed that even mild reversible AKI was of important clinical implications, embracing increased mortality [7]. Therefore, it is of great significance to conduct risk-factor analysis of AKI after the diagnosis of AMI, which is essential for the prevention and treatment of AKI and for the amolioration of patients' life quality and prognosis.

N-terminal pro-brain natriuretic peptide (NT-pro BNP) is a sensitive early marker of cardiac function damage. After hemodialysis, the level of plasma NT-pro BNP would be evidently reduced, suggesting that hypervolemia is a vital factor promoting the secretion of NT-pro BNP [8, 9]. Studies have suggested that abnormal changes of serum BNP and NT-pro BNP concentrations were observed among patients suffering heart failure [10]. Serum high-sensitivity C-reactive protein (hs-CRP), as a plasma C-reactive protein synthesizing in the liver, links closely to the severity of AMI and is considered as a predictor of cardiovascular disease [11, 12]. Correlation between hs-CRP level and AKI after adult cardiac surgery was detected in related study [13]. However, there is no relevant research to verify whether NT-pro BNP and hs-CRP have clinical value in predicting AKI after the diagnosis of AMI.

In this study, the expressions of NT-pro BNP and hs-CRP were analyzed in patients with AMI and with or without AKI, and a predictive model was established through regression model to provide a clinical diagnosis plan.

Methods and materials

Clinical information

A retrospective analysis was conducted on 107 patients with AMI admitted to our hospital from May 2020 to May 2021. Patients were assigned in an AKI group (AKIG) (n = 27) and a non-AKI group (NAKIG) (n = 80) according to whether AKI occurred within 1 week after admission. A total of 50 healthy people underwent physical examination at the same duration were taken as the control group (CG). This study has gained approval from the Medical Ethics Committee of our hospital (2021 Ethics committee approval No. 046), and all patients were informed about the study and signed informed consent.

Inclusion and exclusion criteria

Inclusion criteria: ① Patients met the diagnostic criteria of the 2020 European Society of Cardiology Guidelines for the Management of Non-ST-segment Elevation AMI [14]: 1) typical chest pain with a duration of ≥30 min, 2) accompanied by obvious myocardial ischemia, 3) new ischemic lesions indicated by electrocardiogram examination; 4) with pathological Q waves; 5) with significant myocardial cell activity loss, abnormal local wall activity; 6) with coronary thrombosis. ② Patients with age ≥18 years old; ③ Diagnosis of AKI should be in line with the guidelines "Kidney Disease: Improving Global Outcomes" issued in 2012 [15]; ④ Patients received renal function tests; ⑤ Patients had complete clinical data; ⑥ Patients was conscious; ⑦ Patients had normal cognitive function and an ability to communicate.

Exclusion criteria: ① Patients with malignant tumors; ② Patients with severe damage on liver, heart, brain and other organs; ③ Patients with active bleeding, hematological diseases or a history of immune system; ④ Patients had coronary artery bypass grafting or coronary stent from previous surgeries; ⑤ Patients with severe malnutrition; ⑥ Patients had a recent history of acute or chronic infection; ⑦ Patients who were pregnant.

Clinical data collection

Clinical data of patients were recorded, including age, sex, number of lesions, smoking history, hypertension history, diabetes history, drinking history, use of diuretics and RDW, high-sensitivity C-reactive protein (hs-CRP), NT-pro BNP, high density lipoprotein cholesterol (HDLC), low density lipoprotein cholesterol (LDLC), total cholesterol (TC), uric acid (UA), triglyceride (TG), estimated Glomerular filtration rate (eGFR), blood urea nitrogen (BUN), serum Creatinine (SCr), interventricular septal thickness (IVST), left ventricular ejection fraction (LVEF), left atrial diameter (LAD) and left ventricular end-diastolic diameter (LVEDD).

Biochemical index detection

After the subjects were admitted, 4 mL of fasting venous blood was collected and centrifuged at 1500 rpm for 10 min. The serum was then isolated and stored in a low temperature freezer for later testing. Hs-CRP was determined by immunoturbidimetry (provided by Beijing Ovia Biological Company). Serum NT-proBNP was assayed with electrochemilumi-

Table 1. Comparison of clinical data

Factors	AKIG (n = 27)	Non AKIG (n = 80)	Control Group (n = 50)	P
Age				
≥60 years old	17	45	28	0.808
<60 years old	10	35	22	
Sex				
Male	15	48	30	0.912
Female	12	32	20	
History of Smoking				
YES	15	50	27	0.594
NO	12	30	23	
Hypertension				
YES	20	55	35	0.872
NO	7	25	15	
Diabetes				
YES	13	38	20	0.666
NO	14	42	30	
History of Drinking				
YES	8	20	12	0.855
NO	19	60	38	

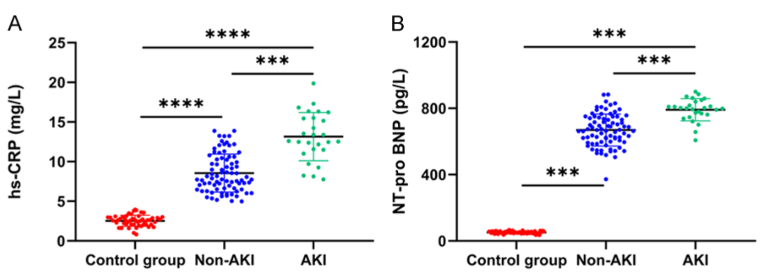

Figure 1. Comparison of serum hs-CRP and NT-pro BNP levels among the three groups. A. Comparison of serum hs-CRP levels among the three groups; B. Comparison of serum NT-pro BNP levels among the three groups. AKI, Acute kidney injury. NT-pro BNP, N-terminal pro-brain natriuretic peptide, hs-CRP, High-sensitivity C-reactive protein, *** means P<0.001, **** means P<0.0001.

nescence immunoassay (provided by Roche, 484246). Serum LDLC, HDLC, TC, TG, UA, BUN, and Scr were measured with Boke bk-400 automatic biochemical analyzer using the manufacturer's original kit, and eGFR was calculated based on the Kidney Disease Improvement Diet Simplified Formula.

Echocardiographic detection

The patient was placed in the left decubitus position, and long axis of the parasternal left ventricle was taken as the view. RLVEDD, IVST, LVEF and LAD were measured by echocardiography (EPIQ 7C Philips). The probe frequency was set to 2.5 Hz, and 3-5 cardiac cycles were selected for each patient. Results of all trials were averaged, and the procedures were done by the same physician.

AKI diagnosis and grouping criteria

AKI diagnostic criteria was referred to the guidelines for AKI diagnosis [16], as follows. The urine output was less than 0.5 mL/(kg·h) for over 6 hours, excluding the reduction of urine output caused by non-AKI factors such as bladder outlet obstruction and reduction of effective bladder capacity. The increase of SCr within 1 week was greater than 1.5 times the baseline value. If one of the above 2 criteria was met, AKI can be diagnosed.

Observation indicator

Main outcome measures: Expression of serum NT-pro BNP and hs-CRP of AKIG and NAKIG before treatment and of CG were compared. Related indicators were compared between AKIG and NAKIG. The value of hs-CRP and NT-pro BNP in predicting the occurrence of AKI after AMI was analyzed.

Secondary outcome measures: Clinical data of the three groups were compared. Logistic regression was used to analyze the risk factors of AKI after AMI, and the correlation between hs-CRP, NT-pro BNP and various indicators was observed.

Statistical analysis

SPSS 22.0 (Beijing Sichuang Weida Information Technology Co., Ltd.) was used for data analysis, and GraphPad 8 (Shenzhen Tianruiqi Software Technology Co., Ltd.) was for figures plotting. Count data were expressed as rate (%) and tested by χ^2 test between two groups.

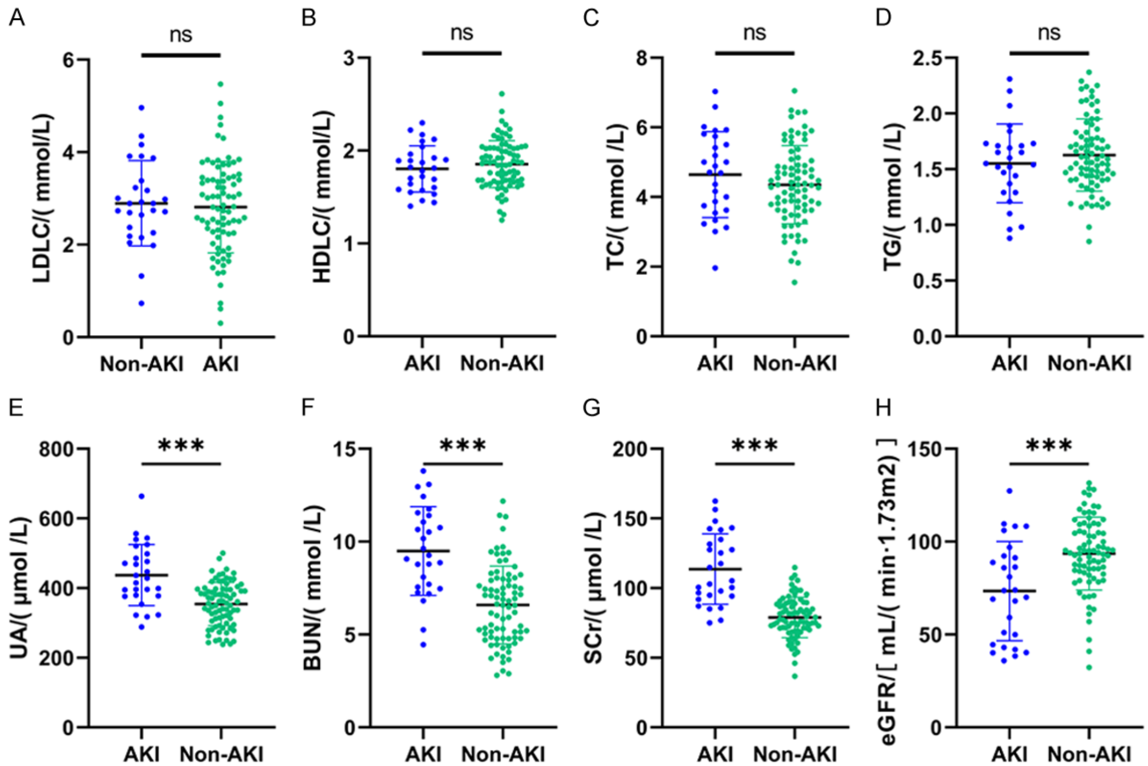

Figure 2. Comparison of biochemical parameters between the two patient groups. A. Comparison of LDLC levels between the two patient groups; B. Comparison of HDLC levels between the two patient groups; C. Comparison of TC levels between the two patient groups; D. Comparison of TG levels between the two patient groups; E. Comparison of UA levels between the two patient groups; F. Comparison of BUN levels between the two patient groups; G. Comparison of SCr levels between the two patient groups; H. Comparison of eGFR levels between the two patient groups. LDLC, Low density lipoprotein cholesterol, HDLC, High density lipoprotein cholesterol, TC, Total cholesterol, TG, Triglyceride, UA, Uric acid, BUN, Blood urea nitrogen, SCr, Serum creatinine, eGFR, Estimated renal Ball filtration rate. nc means no difference between the two groups, P>0.05; *** means P<0.001.

Measurement data (mean ± standard deviation) were compared using nonparametric tests, denoted by Z, and inter-group and intra-group comparison was performed by independent sample t test and paired t test, respectively. Receiver operating characteristic (ROC) curve was applied for diagnostic value analysis in terms of evaluation of predictive power, sensitivity, specificity, etc. Spearman correlation was applied to analyze the relationship between hs-CRP, NT-pro BNP and clinical efficacy, and the risk factors of AKI was analyzed with logistic regression analysis. P<0.05 was considered statistical difference.

Results

Comparison of clinical information

Analysis suggested that no difference existed regarding age, sex, history of smoking, drinking, diabetes and hypertension among the three groups (P>0.05, **Table 1**).

Comparison of hs-CRP and NT-pro BNP expression between patients and normal subjects

Compared with CG, hs-CRP and NT-pro BNP expression in AKIG and NAKIG were both increased markedly (P<0.0001). Further analysis showed that expressions of those two indexes in AKIG were higher than those in NAKIG (**Figure 1**, P<0.001).

Comparison of biochemical indicators

No marked difference was observed in LDLC, HDLC, TC and TG between AKIG and NAKIG (**Figure 2A-E**, P>0.05). Serum levels of UA, BUN and SCr in AKIG were higher than those in NAKIG, and eGFR was comparatively lower in AKIG than that in NAKIG (**Figure 2F-I**, P<0.05).

Comparison of imaging indicators

There was no statistical difference in terms of IVST, LVEDD, LAD and LVEF between the two patient groups (**Figure 3A-D**, P>0.05).

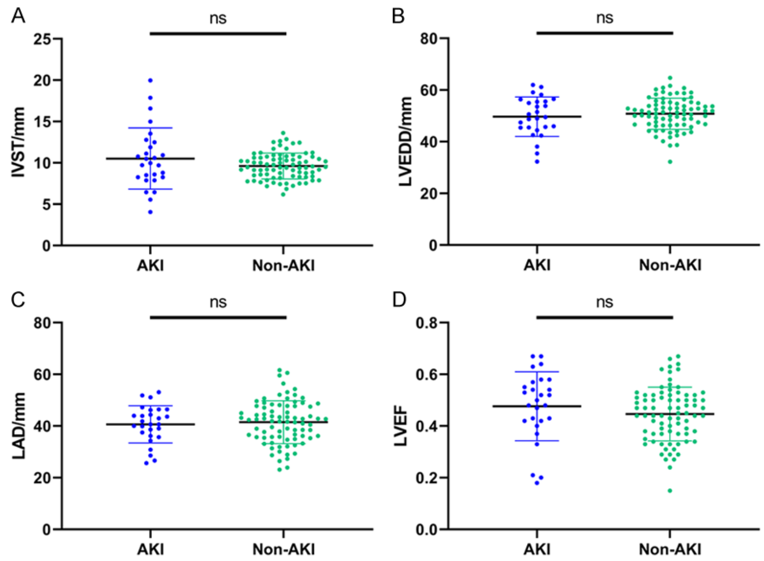

Figure 3. Comparison of imaging indicators between the two groups of patients. A. Comparison of IVST between the two patient groups; B. Comparison of LVEDD between the two patient groups; C. Comparison of LAD between two patient groups; D. Comparison of LVEF between the two patient groups. IVST, Interventricular septal thickness, LVEDD, Left ventricular end-diastolic diameter, LAD, Left atrial diameter, LVEF, Left ventricular ejection fraction. nc means that there is no difference between two groups, P>0.05.

Analysis of clinical data

Further comparison of clinical data suggested that no notable difference was observed in age, sex, history of smoking, drinking, hypertension and diabetes between the two patient groups (P>0.05). However, in AKIG, the number of lesions and the number of patients applying diuretics were more than those in NAKIG (**Table 2**, P<0.01).

Correlation analysis of clinical indicators in patients

Correlation analysis showed that hs-CRP in serum of patients was positively correlated with NT-pro BNP, UA, BUN, SCr and NT-Pro BNP, and negatively correlated with eGFR. However, NT-pro BNP was correlated negatively with eGFR (**Figure 4**, P<0.05).

Analysis of risk factors for AKI in patients with AMI

To identify risk factors for AKI in AMI patients, we collected clinical data from patients and assigned them subsequently (**Table 3**). Multivariate logistic regression analysis showed that SCr, eGFR, hs-CRP and NT-pro BNP were independent risk factors of AKI in patients with AMI (**Table 4**, P<0.05). Then, ROC curves were plotted for meaningful metrics and showed that the AUC of SCr, hs-CRP and NT-pro BNP for predicting the occurrence of AKI in AMI patients was over 0.8. In addition, it was found that AUC of NT-pro BNP + hs-CRP was 0.942, with a sensitivity of 86.30 and a specificity of 88.90, which were higher than those of each index alone, suggesting that the combined of NT-pro BNP and hs-CRP could be taken to predict AKI in patients with AMI (**Figure 5** and **Table 5**).

Discussion

With the ongoing improvement of medical care and quality of life, the population in China has gradually developed into an aging population [17], and the incidence of common diseases among the elderly has also increased [18]. AMI is a common cardiovascular disease among the elderly. Data showed that more than 1 million elderly patients die from AMI in China every year, accounting for 25% of the global AMI deaths [19]. As the incidence of AMI increases gradually, the occurrence of AKI induced by AMI also increased, resulting in a marked rise in mortality [20]. AKI, one of the common complications of AMI, has an incidence of about 15.8% and is considered as an independent risk factor affecting the in-hospital and long-term mortality of patients with AMI [21]. Therefore, it is necessary to find clinical indicators that can effectively predict the occurrence of AKI after AMI, so as to treat the symptoms and improve the prognosis of patients promptly and effectively.

There is a state of high oxidative stress in patients with impaired renal function, and oxidative stress can activate inflammatory factors [22]. Hs-CRP is a non-specific marker of systemic inflammatory response in the acute phase. When the inflammatory response in the body is intensified, a large number of inflamma-

Table 2. Comparison of clinical data of patients

Factors	AKIG (n = 27)	Non AKIG (n = 80)	P
Age			
≥60 years old	17	45	0.541
<60 years old	10	35	
Sex			
Male	15	48	0.684
Female	12	32	
History of Smoking			
YES	15	50	0.522
NO	12	30	
Hypertension			
YES	20	55	0.601
NO	7	25	
Diabetes			
YES	13	38	0.953
NO	14	42	
History of Drinking			
YES	8	20	0.636
NO	19	60	
Number of Lesions			
1	2	34	0.003
2	3	24	
3	12	22	
Use of Diuretics			
YES	12	15	0.008
NO	15	65	

tory factors are secreted in the body, which increases the level of hs-CRP [23]. NT-pro BNP is a common indicator for the diagnosis of heart failure and AMI, and its higher level means larger infarct size [24]. The main excretion route of NT-pro BNP is the kidney. Once the renal function is damaged, it will increase the volume load and the filling of the cardiac cavity, stretch the ventricular myocytes, thereby promoting the synthesis of NT-pro BNP [25]. Besides, NT-pro BNP cannot be excluded after renal function damage, from which the level can be abnormally increased [26]. In this study, we observed a marked increase in expressions of NT-pro BNP and hs-CRP among patients with AMI combined with AKI, which indicates that NT-pro BNP and hs-CRP are indeed involved in the development of AKI in patients with AMI.

The level of eGFR is used to reflect the function of the kidneys [27]. It assesses the kidney function of removing metabolic waste by measuring how many milliliters of blood creatinine can be cleared by the glomerulus per minute (ml/min) [28]. Previous studies found that eGFR was markedly decreased in patients with AKI [29]. In this study, it was found that eGFR showed a downward trend with the increase of hs-CRP and NT-pro BNP, indicating a negative correlation between them, and the two indicators were associated with renal impairment in patients. In the study of Li et al. [30], hs-CRP expression in patients with hypertension and renal impairment was correlated positively with SCr and BUN. In addition, another study reported that hs-CRP and UA showed an upward trend in patients with chronic heart failure after cardiac injury and renal injury [31]. In this study, we have demonostrated that hs-CRP was positively correlated with UA, BUN and SCr through correlation analysis. Also, since UA, BUN and SCr are the diagnostic markers of clinical kidney injury, we believe that CRP plays a vital monitoring role in AKI. In addition, we also analyzed the changes of cardiac function after the onset of the disease in this study. Previous studies have found that up to 20-45% of patients with acute heart failure can develop AKI [32]. In such patients, the decrease of LVEF level, the sharp decrease of cardiac output and stroke volume, the activation of RAAS, inflammatory factors and vasoconstrictor factors, etc., lead to the decrease of blood flow in various organs, especially in the kidney, which is sensitive to ischemia [33]. In this study, we found that there was no difference in LVEDd, ivst, LVEF and LAD between AKI patients and non-AKI patients after AMI. We think this may be due to the small number of samples.

To ascertain risk factors of AKI in patients with AMI, we conducted regression analysis to determine if SCr, eGFR, NT-pro BNP and hs-CRP were independent risk factors of AKI. Through ROC curve analysis, we have shown that AUC of SCr, hs-CRP and NT-pro BNP for predicting the occurrence of AKI was greater than 0.8, which indicated that these three indicators were ideal predictive markers. Earlier studies have determined that the level of SCr elevated evidently after AKI among AMI patients [34]. In the present study, we determined the ability of SCr to predict the occurrence of AKI in patients with AMI by ROC curve. In addition to SCr, the AUC of hs-CRP and NT-pro BNP was also ideal,

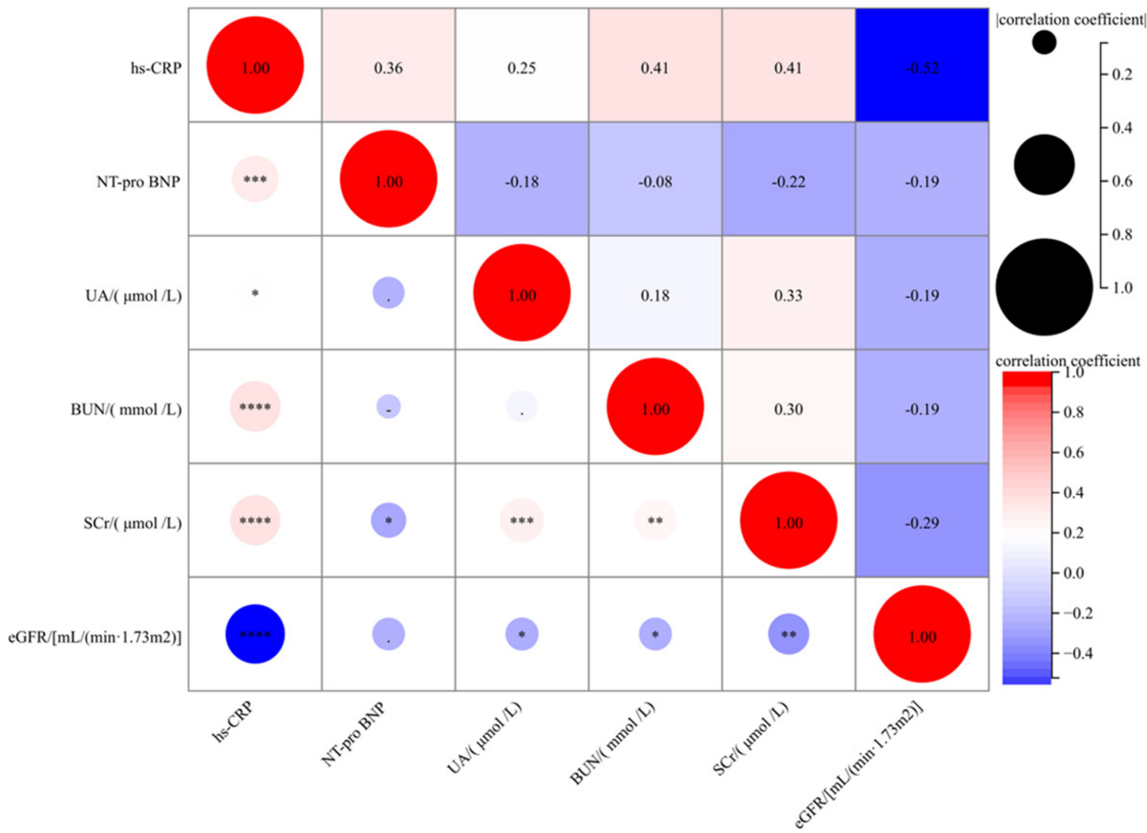

Figure 4. Correlation analysis of clinical indicators. * means P<0.05; ** means P<0.01. UA, Uric acid, BUN, Blood urea nitrogen, SCr, Serum creatinine, eGFR, Estimated glomerular filtration rate. NT-pro BNP, N-terminal pro brain natriuretic peptide, hs-CRP, High-sensitivity C-reactive protein. Red indicates positive correlation; blue indicates negative correlation.

Table 3. Assignments

Factors	Assignments
Number of Lesions	1 lesion = 0, 2 lesions = 1, 3 lesions = 2
Use of Diuretics	YES = 1, NO = 2
UA	>393.32 μmol/L = 1, ≤393.32 μmol/L = 0
BUN	>8.715 mmol/L = 1, ≤8.715 mmol/L = 0
SCr	>94.21 μmol/L = 1, ≤94.21 μmol/L = 0
eGFR	>75.84/[mL/(min·1.73m^2)] = 1, ≤75.84/[mL/(min·1.73m^2)] = 0
NT-pro BNP	>760.14 pg/L = 1, ≤760.14 pg/L = 0
hs-CRP	>11.395 mg/L = 1, ≤11.395 mg/L = 0
Occurrence of AKI	NO = 0, YES = 1

Note: UA, Uric acid, BUN, Blood urea nitrogen, SCr, Serum creatinine, eGFR, Estimated glomerular filtration rate. NT-pro BNP, N-terminal pro brain natriuretic peptide, hs-CRP, High-sensitivity C-reactive protein. AKI, Acute kidney injury. Red indicates positive correlation; blue indicates negative correlation.

and that of NT-pro BNP was second only to that of SCr. Then, ROC curve found that the AUC of the combination of hs-CRP and NT-pro BNP detection was 0.942, which showed an improvement in its specificity compared with single detection of SCr. It was suggested that clinicians can consider observing the levels of hs-CRP and NT-pro BNP when evaluating the condition of patients with AMI and AKI.

This study determined the clinical value of hs-CRP and NT-pro BNP in patients with AMI and

Table 4. Multivariate analysis

Factors	β	SE	χ^2	P	OR	95% CI	
						Floor Level	Upper Limit
Number of Lesions	1.538	0.853	3.246	0.072	4.653	0.874	24.786
Use of Diuretics	2.105	1.691	1.549	0.213	8.205	0.298	225.766
UA	2.639	1.539	2.942	0.086	14.004	0.686	285.778
BUN	2.182	1.479	2.177	0.140	8.868	0.488	161.001
SCr	5.515	1.766	9.750	0.002	248.444	7.794	7919.645
eGFR	-4.372	1.689	6.702	0.010	0.013	0.000	0.346
hs-CRP	4.035	1.632	6.108	0.013	56.523	2.305	1386.015
NT-pro BNP	2.754	1.320	4.354	0.037	15.701	1.182	208.561

Note: UA, Uric acid, BUN, Blood urea nitrogen, SCr, Serum creatinine, eGFR, Estimated glomerular filtration rate. NT-pro BNP, N-terminal pro brain natriuretic peptide, hs-CRP, High-sensitivity C-reactive protein, ROC, Receiver operating characteristic.

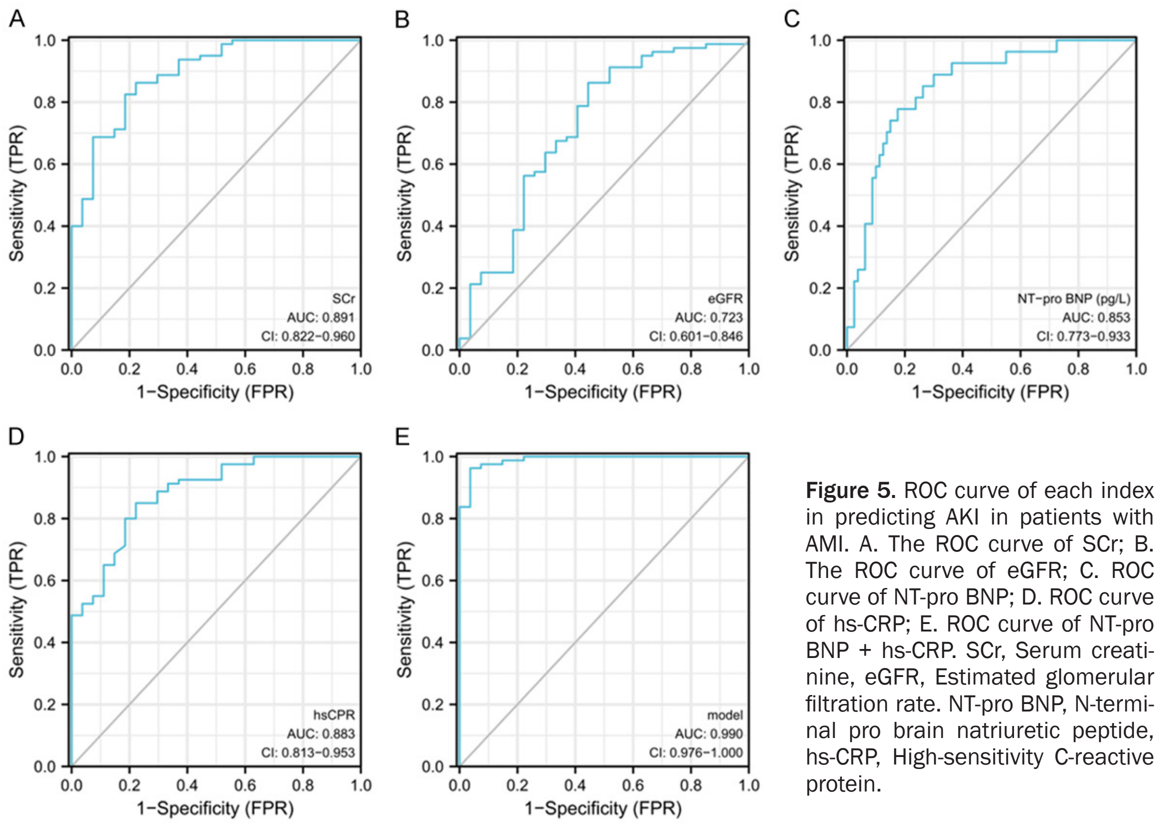

Figure 5. ROC curve of each index in predicting AKI in patients with AMI. A. The ROC curve of SCr; B. The ROC curve of eGFR; C. ROC curve of NT-pro BNP; D. ROC curve of hs-CRP; E. ROC curve of NT-pro BNP + hs-CRP. SCr, Serum creatinine, eGFR, Estimated glomerular filtration rate. NT-pro BNP, N-terminal pro brain natriuretic peptide, hs-CRP, High-sensitivity C-reactive protein.

Table 5. ROC parameter

Predictive Variables	Area under the curve (AUC)	Confidence Interval (CI)	cut-off	Sensitivity	Specificity	Youden Index
SCr	0.891	0.822-0.960	94.21	0.863	0.778	0.640
eGFR	0.723	0.601-0.846	75.84	0.863	0.556	0.418
NT-pro BNP	0.853	0.773-0.933	760.140	0.778	0.825	0.603
hs-CRP	0.846	0.755-0.937	11.395	0.838	0.741	0.578
NT-pro BNP + hs-CRP	0.941	0.897-0.985	0.182	0.950	0.815	0.765

Note: ROC, Receiver operating characteristic, SCr, Serum creatinine, eGFR, Estimated glomerular filtration rate. NT-pro BNP, N-terminal pro brain natriuretic peptide, hs-CRP, High-sensitivity C-reactive protein.

AKI. However, this study still has certain limitations. First of all, follow up study was not conducted to the included patients, so it is unclear whether the patients died after AKI, and whether hs-CRP and NT-pro BNP had an effect on the prognosis of the patients. Secondly, because of the limited sample time and size and the nature of a retrospective study, there might be biases in the results. Therefore, prospective studies with increased sample size and follow up study are needed to refine our conclusions in the future.

In conclusion, increased hs-CRP and NT-pro BNP expression was closely related to the occurrence of AKI after AMI, and the combined detection of the two was of high predictive value for the occurrence of AKI in patients with AMI.

Disclosure of conflict of interest

None.

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