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Article

The Value of Soluble ST2 in Predicting Cardiorenal Syndrome Type 1 in Acute Myocardial Infarction Patients

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Abstract

Objective: To investigate the predictive value of soluble growth stimulation expressed gene 2 (sST2) for the development of Cardiorenal syndrome type 1 (CRS1) in patients with acute myocardial infarction during hospitalization. **Methods**: A retrospective study included 202 patients with acute myocardial infarction, divided into the CRS1 group (n = 61) and the Non-CRS1 group (n = 141) by the CRS1 occurrence. A logistic regression analysis was applied to find independent predictors of the CRS1 occurrence during hospitalization. Receiver operating characteristic (ROC) curves were applied to analyze the predictive values of sST2, N-terminal pro-B type natriuretic peptide (NT-proBNP), and estimated glomerular filtration rate (eGFR). **Result**: The multivariate logistic regression analysis revealed that sST2, NT-proBNP, eGFR, Multivessel coronary artery disease, and diuretic use were independent predictors of the CRS1 occurrence during hospitalization. Application of ROC curve analysis displayed that sST2 had the largest area under the curve (AUC) value of 0.874, sensitivity of 0.770, and specificity of 0.894; sST2, eGFR, and NT-proBNP as combined predictors had an AUC value of 0.908, sensitivity of 0.820, and specificity of 0.908. The ROC curves of sST2 and the combined predictive indices were compared using MedCalc software (version 19.6.3), and no statistically significant difference was found between the two (p = 0.142). The cutoff values of the three indicators were determined by the maximum Youden index. When sST2 $\geq$61.8 ng/mL, eGFR $\leq$80.6 mL/min/1.73 m^2 and NT-proBNP $\geq$1525 pg/mL were classified as abnormal range, it was found that more number of abnormal indicators may be more advantageous of risk stratification in CRS1. **Conclusions**: sST2 can be used as a novel predictor of the CRS1 occurrence in patients with acute myocardial infarction during hospitalization. sST2, eGFR, and NT-proBNP combined may have better predictive value.

Keywords

acute myocardial infarction; cardiorenal syndrome type 1; soluble growth stimulation gene expression protein 2; estimated glomerular filtration rate; N-terminal pro-B-type natriuretic peptide

Introduction

Cardiorenal syndrome (CRS) is characterized as a serious disease of the heart and kidneys whereby dysfunction in one organ may lead to corresponding dysfunction in the other organ. Cardiorenal syndrome type 1 (CRS1) is defined as acute renal impairment caused by the acute deterioration of cardiac function [1]. CRS1 is the most common of the five subtypes of CRS, with the reported incidence ranging from 25% to 33% in patients with acute decompensated heart failure [2]. Acute kidney injury (AKI) and acute heart failure (AHF) are two of most frequent complications in patients with acute myocardial infarction (AMI) during hospitalization. According to Fox CS *et al*. [3], the incidence of CRS1 in patients with AMI during hospitalization was 16%, with mortality increasing with the severity of AKI and reaching 31.8% in patients with severe AKI. As a result, the prognosis with both complications is worse than either one, and patients experiencing more profound deterioration in heart and kidney function frequently encounter a dearth of effective clinical treatment options. This underscores the crucial significance of early detection and intervention [4]. The current research hotspots involve the application of relevant markers to predict the in-hospital morbidity of CRS1 [5], many traditional and novel biomarkers have been studied, such as cystatin C, the urea albumin creatinine ratio, the meanplatelet volume and others. Nevertheless, whether these biomarkers have sufficient prognostic accuracy for early detection of CRS1 remains to be determined. Perhaps the combined predictive value of several biochemical indications may be more substantial [6,7]. Previous studies have confirmed that hemodynamic instability and inflammation activation play important roles in the development of CRS1 in patients with acute heart failure. In patients with AMI, the expression level of ST2 is elevated, which is closely associated with the occurrence and prognosis of heart failure, and also reflects the extent of myocardial injury and inflammation activation. Perhaps soluble growth stimulation expressed gene 2 (sST2) is related to the development of heart failure and CRS1 [8]. There has been limited research into the predictive significance of sST2 for CRS1 [9]. Thus, this study categorized the patients with AMI patients into groups based on whether they experienced CRS1 during their hospital stay. The objective

was to evaluate whether sST2 can server as an independent indicator for early prediction of CRS1 and to assess the efficacy of the combined measurements of sST2, estimated glomerular filtration rate (eGFR) and N-terminal pro-B type natriuretic peptide (NT-proBNP) at admission to predict the occurrence of CRS1.

Methods

Study Population

Data from 202 patients with AMI admitted to the Department of Cardiovascular Medicine, Affiliated Hospital of Nantong University were collected from November 2019 to October 2021.

The inclusion criteria are as follows: (1) The patients enrolled met the diagnostic criteria for STEMI [10] or NSTEMI [11]. (2) All patients received standardized treatment according to current guideline recommendations. (3) Patients enrolled provided informed consent and the study were approved by the ethics committee of the hospital. Exclusion criteria: (1) Patients with renal failure requiring routine hemodialysis and peritoneal dialysis. (2) Creatinine $\geq$442 μmol/L at admission. (3) History of renal transplantation. (4) Deterioration of renal function due to autoimmune system disease, infection and sepsis. (5) Absence of admission data and monitored creatinine values. CRS1 diagnostic criteria: acute heart failure was required to meet Killip classification criteria and cardiac function class II to IV. Acute renal damage has at least one of the following characteristics: (a) Rapid decline in renal function within 48 hours, with an absolute increase in serum creatinine $\geq$26.5 mmol/L; (b) serum creatinine increased to 1.5 times the basal value within 7 days; (c) urine output $<$0.5 mL/(kg/h) for $>$6 h. Baseline renal function level refers to the creatinine value and eGFR at admission. Some patients were discharged with a lower serum creatinine value than at admission, and this value was considered as the baseline level [12]. The eGFR was calculated using the modified equation for renal disease diet in Chinese patients. Acute heart failure occurred first followed by acute kidney injury at any time during hospitalization [13].

Date Collection

The basic clinical parameters were recorded for both groups, including gender, age, systolic blood pressure, diastolic blood pressure and past medical history. Treatment included: (1) Interventional treatment: coronary angiography and coronary stenting [14]. All patients with STEMI underwent primary percutaneous coronary intervention (PCI), which were performed expeditiously within 120 minutes. Among them, 173 patients received treatment within 12 hours of symptom onset, while 14 patients received treatment within 12–48 hours, with 4 patients in the CRS1 group and 10 patients in the non-CRS1 group. In the case of patients with NSTEMI, risk stratification was conducted using the Global Registry of Act Coronary Events (GRACE) Risk Score, and emergency PCI was performed within 24 hours of symptom onset for all patients; recording the contrast dose and the proportion of Multivessel coronary artery disease, intra-aortic balloon pump (IABP), second-generation drug-eluting stents (DES), implatation of two or more DES. (2) Pharmacological treatment: aspirin, clopidogrel, tigretol, statins, angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI), β-blockers and diuretics. Coronary intervention and pharmacological treatment were performed in both groups according to current guide specifications [10, 11]. (3) Experimental data included recordings of sST2, NT-proBNP, high-sensitivity C-reactive protein (hs-CRP), blood urea nitrogen (BUN)/creatinine (Cr) and hemoglobin on admission, as well as serum creatinine values and eGFR on admission and every 48 hours. Cardiac Troponin I (TnI) was measured on admission and every 24 hours and the peak value of TnI was included into the data. Biomarker measurements were performed by the core laboratory of Nantong University Affiliated Hospital. sST2 levels were assays based on a dry immuno-fluorescence quantitative assay (boditech Bio. technology, NanNing, GuangXi, China). NT-proBNP levels were measured by a chemiluminescence enzyme immune assay (Johnson & Johnson Medical Company, New Brunswick, NJ, USA). Serum creatinine concentrations were evaluated using a picric acid method (Beckman Coulter Inc., Brea, CA, USA). (4) Evaluation of cardiac function: the highest Killip classification, left ventricular ejection fraction and left ventricular end diastolic dimension (LVDd) were recorded during hospitalization.

Statistical Analysis

Data statistical analysis was performed using IBM SPSS Statistics 23.0 software (IBM Corp., Armonk, NY, USA). Normality tests were conducted for continuous variables, but we observed that the data followed a non-normal distribution, which were described using median and interquartile range. The Mann-Whitney U test was conducted to compare between groups. Count data were presented as numbers and percentages, and group comparisons were analyzed using the chi-square test. Logistic regression analysis was employed to identify independent risk factors predicting the early occurrence of CRS1, described by odds ratios (ORs) and 95% confidence intervals (CIs). Variables with statistically significant differences in univariate logistic regression analysis were included in the multivariate logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was performed to calculate the area under the curve (AUC) for each independent risk factor and identify valuable predictive indicators. The maximal Youden index was utilized to determine the selected predic-

tor's cutoff values. The impact of the number of abnormal selected indicators on prediction of CRS1 was evaluated using ROC analysis. AUC values were compared pairwise by using the Hanley and McNeil method with MedCalc statistical software version 19.6.3 (MedCalc Software bvba, Mariakerke, Belgium). GraphPad Prism 9 (GraphPad Software, Inc., San Diego, CA, USA) was used to draw images. $p < 0.05$ was considered a statistically significant difference.

Results

Baseline Characteristics and the Prevalence of CRS1

According to the data, 187 had ST elevated myocardial infarction (STEMI), 15 had non-ST elevated myocardial infarction (NSTEMI). In all cases, 99 patients progressed to acute heart failure and 61 progressed to CRS1. 10 patients died during hospitalization, with 7 in the CRS1 group and 3 in the non-CRS1 group.

In our comparative analysis of the two groups, the CRS1 group displayed higher proportions of female patients and a higher prevalence of medical histories including diabetes mellitus, coronary heart disease, chronic kidney disease, atrial fibrillation, and Multivessel coronary artery disease. Additionally, diuretic use was more commonly observed in the CRS1 group, while the utilization of antiplatelet aggregation drugs, ACE-I/ARB/ARNI, β-blockers, and statins was notably lower in comparison to the non-CRS1 group. Importantly, all these differences demonstrated statistically significant. Conversely, there were no statistically significant variations in the proportions of patients with a history of hypertension, hyperlipidemia, stroke, STEMI, as well as the treatment of coronary intervention, second-generation (DES), implantation of two or more DES or IABP between the two groups.

We conducted *t*-tests to assess differences in the values between the two groups, and our results revealed notable distinctions. The results indicate that the CRS1 group exhibited higher values in several pivotal variables compared to the non-CRS1 group. Specifically, the CRS1 group displayed elevated levels in age, sST2, NT-proBNP, hsCRP, BUN/Cr, and Killip classification, all of which achieved statistical significance. In contrast, the CRS1 group exhibited lower values in eGFR and left ventricular ejection fraction (LVEF) when contrasted with the non-CRS1 group, and these differences were also statistically significant. Notably, there were no statistically significant differences observed in contrast agent measures, troponin I levels, left ventricular diastolic diameter (LVDd) values, or systolic and diastolic blood pressure readings between the two groups (Table 1).

Logistic Regression Analysis

On univariate analysis, increased sST2 and NT-proBNP levels and decreased eGFR at admission were significantly associated with CRS1, as were advanced age, female sex, history of diabetes mellitus, coronary artery disease, atrial fibrillation, chronic kidney disease, decreased album, hemoglobin and left ventricular ejection fraction, use of ACE-I/ARB/ARNI, β-blocker andStatins, increased killip classification, hs-CRP, BUN/Cr, percentage of multivessel coronary artery disease and diuretic use.

After multivariable adjustment, sST2 (OR 1.034; 95% CI: 1.015–1.053; $p < 0.001$), NT-proBNP (OR 1.001; 95% CI: 1.0–1.001; $p = 0.014$), and the proportion of Multivessel coronary artery disease (OR 4.594; 95% CI: 1.140–18.513; $p = 0.032$) as well as diuretic use (OR 4.091; 95% CI: 1.073–15.597; $p = 0.039$), eGFR (OR 0.975; 95% CI: 0.952–0.978; $p = 0.041$) at admission could be independent risk factors to predict CRS1 in AMI patients during hospitalization (Table 2).

ROC Curve Analysis

The results of ROC curve analysis revealed that all five independent risk factors significantly predicted the occurrence of CRS1 (AUC: sST2 0.874 $p < 0.001$, NT-proBNP 0.810 $p < 0.001$, eGFR 0.820 $p < 0.001$, Diuretic use 0.668 $p = 0.001$, Multivessel coronary artery disease 0.635 $p = 0.002$). The top three AUC values were sST2, eGFR, and NT-proBNP. Among them, sST2 had the highest AUC value of 0.874 with a sensitivity of 0.770 and specificity of 0.894. We selected sST2, eGFR and NT-proBNP as combined predictors and calculated the AUC value of 0.908, sensitivity of 0.820 and specificity of 0.908, which outperformed individual indicators (Table 3). Then we found that the differences in AUC values between NT-proBNP, eGFR and the combination of these 3 markers were statistically significant (all $p < 0.01$). But there was no significant difference between sST2 and the combined predictors ($p = 0.142$) (Fig. 1).

The Relationship between Number of Abnormal Indicators and the Risk of CRS1

The cutoff values for sST2, NT-proBNP, and eGFR were 61.8 ng/mL, 1525 pg/mL, 80.6 mL/min/1.73 m^2 respectively. We classified sST2 $\geq$61.8 ng/mL, NT-proBNP $\geq$1525 pg/mL and eGFR $\leq$80.6 mL/min/1.73 m^2 as abnormal range (Table 3). The data of ROC curve analysis illustrated that the AUC value was increased significantly with an increased number of abnormal indicators (Table 4 and Fig. 2). When patients presented with three abnormal indicators, the AUC value was 0.746 ($p < 0.001$), with a sensitivity of 0.492 and specificity of 1.0. Compared to the ROC curves that satisfied one or two abnormal indicators, there was a significant difference in the AUC value, with $p = 0.0001$ and $p = 0.0041$, respectively. When the num-

Table 1. Comparison of general information.

	Total number	Non-CRS1 group	CRS1 group	*p* value
	(N = 202)	(N = 141)	(N = 61)	
Sex (female, n %)	51 (25.2)	24 (17.0)	27 (44.3)	<0.001
Age (years)	64.0 (55.0, 76.0)	62.0 (53.0, 71.0)	73.0 (62.0, 84.0)	<0.001
ST-segment elevation myocardial infarction (n, %)	187 (92.6)	133 (94.3)	54 (88.5)	0.149
Hypertension (n, %)	114 (56.4)	75 (53.2)	39 (63.9)	0.157
Diabetes mellitus (n, %)	80 (39.6)	45 (31.9)	35 (57.4)	<0.001
Hyperlipidemia (n, %)	23 (11.4)	16 (11.3)	7 (11.5)	0.979
Coronary artery disease (n, %)	24 (11.9)	11 (7.8)	13 (21.3)	0.006
chronic kidney disease (n, %)	29 (14.4)	11 (7.8)	18 (29.5)	<0.001
Stroke (n, %)	21 (10.4)	11 (7.8)	10 (16.4)	0.66
Atrial fibrillation (n, %)	20 (9.9)	10 (7.1)	10 (16.4)	0.042
Systolic blood pressure (mmHg)	120.0 (110.0, 133.3)	120.0 (110.0, 132.5)	122 (108.0, 135.5)	0.795
Diastolic blood pressure (mmHg)	70.5 (62.0, 80.0)	71.0 (62.5, 79.0)	70 (60.5, 80)	0.363
Killip classification	1 (1, 2)	1 (1, 2)	2 (2, 2)	<0.001
Left ventricular ejection fraction	0.53 (0.46, 0.59)	0.55 (0.48, 0.61)	0.48 (0.42, 0.55)	<0.001
LVDd (mm)	49 (46, 51)	49.0 (45.0, 51.0)	50.0 (47.0, 53.0)	0.099
Coronary intervention (n, %)	190 (94.1)	135 (95.7)	55 (90.2)	0.123
IABP	7 (3.4)	3 (2.1)	4 (6.6)	0.241
Second-generation DES (n, %)	116 (38.7)	76 (37.1)	40 (42.1)	0.405
Implatation of two or more DES	87 (45.8)	56 (41.5)	31 (56.4)	0.062
Multivessel coronary artery disease (n, %)	134 (66.3)	82 (58.2)	52 (85.2)	<0.001
Contrast dose (mL)	100 (80, 130)	100 (80, 120)	100 (80, 145)	0.440
ACE-I/ARB/ARNI (n, %)	111 (55.0)	95 (67.4)	16 (26.2)	<0.001
β-blocker (n, %)	166 (82.2)	125 (88.7)	41 (67.2)	<0.001
diuretics (n, %)	105 (52.0)	59 (41.8)	46 (75.4)	<0.001
Anti-platelet aggregation drugs (n, %)	200 (99.0)	141 (100)	59 (96.7)	0.031
Statins (n, %)	195 (96.5)	140 (99.3)	55 (90.2)	0.001
sST2 (ng/mL)	44.2 (27.8, 74.2)	33.4 (25.3, 48.1)	96.8 (62.8, 118.3)	<0.001
NT-proBNP (pg/mL)	683.0 (147.5, 2332.5)	470.0 (138.0, 1161.0)	4010 (627.0, 8040.0)	<0.001
eGFR (on admission, mL/min/1.73 m^2)	91.2 (70.5, 111.1)	99.8 (82.7, 121.0)	66.1 (48.7, 87.5)	<0.001
BUN/Scr	19.2 (16.8, 24.3)	18.5 (15.6, 22.4)	22.8 (18.9, 26.7)	<0.001
Albumin	40.0 (37.9, 42.9)	40.8 (38.4, 43.3)	39.5 (37.0, 42.4)	0.033
hs-CRP (mg/L)	12.1 (4.2, 38.2)	8.9 (2.8, 26.9)	29.1 (9.5, 107.0)	<0.001
TnI (peak, μg/L)	41.9 (11.3, 80)	40.4 (11.5, 73.1)	50.4 (11.3, 80.0)	0.184
Hemoglobin (g/L)	133.5 (121.8, 146.0)	140.0 (125.5, 147.0)	123.0 (116.0, 132.0)	<0.001
Mortality (n, %)	10 (5.0)	3 (2.1)	7 (11.5)	0.005

Data are given as median [interquartile range], or n (%). CRS1, indicates cardiorenal syndrome type 1; LVDd, Left ventricular end diastolic dimension; ACE-I, indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; sST2, soluble growth stimulation expressed gene 2; NT-proBNP, N-terminal pro-B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; hs-CRP, high-sensitivity C-reactive protein; TnI, cardiac Troponin I; IABP, intra-aortic balloon pump; DES, drug-eluting stents.

ber of abnormal indicators was $\geq$2, the AUC value reached a maximum of 0.827 with a better sensitivity of 0.754 and specificity of 0.901. Compared to the ROC curves of one or two abnormal indices, the difference is statistically significant with $p < 0.0001$.

Discussion

Studies have shown that the occurrence of CRS1 in AMI patients is associated with longer hospital stays and higher in-hospital mortality rates [2]. Therefore, early prediction and intervention the development of CRS1 are particularly important. In our cohort, we found that mortality in the CRS1 group was 5.5 times higher than this in the non-CRS1 group, consistent with previous research. Numerous studies [15] have evaluated various predictive indicators associated with AKI in AMI patients, such as advanced age, female gender, diabetes, chronic renal insufficiency, Killip classification, severity of vascular lesions, and inflammatory markers. We found that these indicators align with the baseline data reflecting renal function and inflamma-

Table 2. Univariate and multivariate logistic regression analysis.

	Univariate analysis	*p* value	Multivariate analysis	*p* value
	OR (95% CI)		OR (95% CI)	
Age	1.074 (1.044, 1.104)	<0.001	0.996 (0.937, 1.058)	0.892
Female, %	3.871 (1.982, 7.561)	<0.001	0.942 (0.196, 4.535)	0.941
Left ventricular ejection fraction	0.001 (0, 0.01)	<0.001	0.181 (0, 171.652)	0.625
Killip classification	4.448 (2.558, 7.737)	<0.001	0.385 (0.133, 1.113)	0.078
sST2	1.051 (1.037, 1.066)	<0.001	1.034 (1.015, 1.053)	<0.001
NT-proBNP	1.001 (1, 1.001)	<0.001	1.001 (1, 1.001)	0.014
eGFR	0.950 (0.935, 0.965)	<0.001	0.965 (0.952, 0.978)	0.041
BUN/Cr	1.070 (1.024, 1.117)	0.002	1.026 (0.941, 1.118)	0.565
Albumin	0.911 (0.844, 0.983)	0.016	0.960 (0.829, 1.112)	0.590
hs-CRP	1.016 (1.009, 1.023)	<0.001	0.996 (0.983, 1.009)	0.553
Hemoglobin	0.953 (0.934, 0.973)	<0.001	0.985 (0.947, 1.025)	0.456
Diabetes mellitus	2.872 (1.547, 5.332)	0.001	1.518 (0.437, 5.275)	0.511
Coronary Artery disease	3.201 (1.343, 7.629)	0.009	1.366 (0.228, 8.195)	0.733
Atrial fibrillation	2.569 (1.009, 6.538)	0.048	1.479 (0.188, 11.658)	0.710
Chronic kidney disease	4.947 (2.167, 11.295)	<0.001	2.515 (0.400, 15.821)	0.326
Multivessel coronary artery disease	4.157 (1.900, 9.094)	<0.001	4.594 (1.140, 18.513)	0.032
ACE-I/ARB/ARNI	0.172 (0.088, 0.337)	<0.001	0.506 (0.144, 1.773)	0.287
β-blocker	0.262 (0.124, 0.553)	<0.001	0.735 (0.170, 3.177)	0.681
Diuretics	4.262 (2.177, 8.346)	<0.001	4.091 (1.073, 15.597)	0.039
Statins	0.065 (0.008, 0.556)	0.013	1.265 (0, 6.552×10^4)	0.966

OR, indicates odds ratio; CI, confidence interval; CRS1, cardiorenal syndrome type 1; sST2, soluble growth stimulation expressed gene 2; NT-proBNP, N-terminal pro-B-type natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; ACE-I, indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor.

Table 3. Receiver operating characteristic curve analysis of sST2, eGFR, NT-proBNP and combined indicators to predict the CRS1 occurrence.

	Optimization boundary	Abnormal proportion (n, %)		AUC	*p* value	95% CI	Sensitivity	Specificity	Maximum Youden index
		Non-CRS1 group	CRS1 group						
sST2	61.8	15 (10.6)	47 (77.0)	0.874	<0.001	0.818~0.931	0.770	0.894	0.664
eGFR	80.6	25 (17.7)	43 (70.5)	0.820	<0.001	0.758~0.882	0.705	0.823	0.528
NT-proBNP	1525	18 (12.8)	44 (72.1)	0.810	<0.001	0.733~0.887	0.721	0.872	0.593
sST2 + eGFR + NT-proBNP				0.908	<0.001	0.859~0.958	0.820	0.908	0.728

The differences in the AUC values between NT-proBNP, eGFR and their combinations were statistically significant, with *p* values of 0.0005 (eGFR *vs.* sST2 + eGFR + NT-proBNP), 0.0007 (NT-proBNP *vs.* sST2 + eGFR + NT-proBNP), but there was no significant difference between sST2 and their combinations, with *p* value of 0.142 (sST2 *vs.* sST2 + eGFR + NT-proBNP). AUC indicates area under the receiver operating characteristic curve; other abbreviations as in Tables 1,2.

tion in our study. Furthermore, there were no significant differences in the proportion of coronary intervention therapy and contrast agent dosage between the CRS1 and non-CRS1 groups, suggesting that the impact of contrast agents on renal function can be ruled out.

ST2, also known as Growth stimulation gene expression protein 2, is a member of the interleukin-1 receptor family. Human ST2 exists in two forms: soluble ST2 (sST2) and transmembrane form ST2 (ST2L) [16,17]. When mechanically stretched, myocardial cells and fibroblasts release a protein called sST2, which is useful for diagnosing acute heart failure and determining risk classification [18,19]. sST2 acts as a decoy receptor that specifically binds to interleukin-33 (IL-33), thereby blocking the IL-33/ST2L pathway. This inhibition suppresses the protective effects of the pathway on the heart, leading to cardiac dysfunction [20–22]. Consequently, it may result in hemodynamic instability and raise the risk of renal impairment. Moreover, IL-33 is definitely a potential mediator of diverse inflammatory diseases and the IL-33/ST2 system

Table 4. Receiver operating characteristic curve analysis of number of abnormal indicators to predict the CRS1 occurrence.

Predictive indicators	AUC	95% CI	*p* value	Sensitivity	Specificity
1	0.520	0.434~0.605	$p = 0.660$	0.131	0.830
2	0.590	0.500~0.679	$p = 0.043$	0.279	0.901
3	0.746	0.661~0.831	$p < 0.001$	0.492	1.000
≥2	0.827	0.757~0.897	$p < 0.001$	0.754	0.901

Cutoff values for abnormal biomarker levels were sST2 ≥61.8 ng/mL, NT-proBNP ≥1525 pg/mL and eGFR ≤80.6 mL/min/1.73 m^2. The abbreviations as in Tables 1,2.

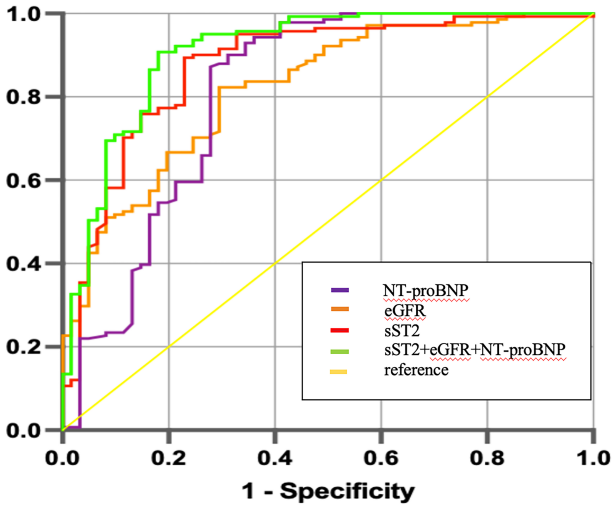

Fig. 1. Receiver operating characteristic curve analysis for the prediction of CRS1 by sST2, eGFR, NT-proBNP and combined indicators. CRS1, cardiorenal syndrome type 1; sST2, soluble growth stimulation expressed gene 2; NT-proBNP, amino-terminal pro–brain natriuretic peptide; eGFR, estimated glomerular filtration rate.

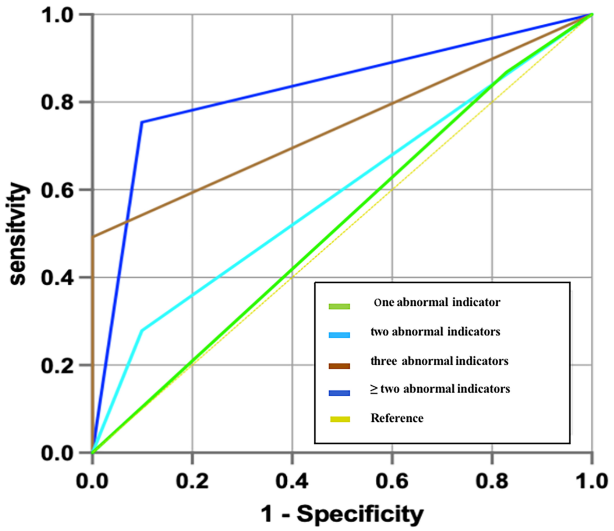

Fig. 2. Receiver operating characteristic curves of the number of abnormal predictors for the CRS1 occurrence. Comparison of AUC values: three abnormal indicators *vs.* one abnormal indicator $p = 0.0001$; three abnormal indicators *vs.* two abnormal indicator $p = 0.0041$; ≥ two abnormal indicators *vs.* one abnormal indicator $p < 0.0001$; ≥ two abnormal indicators *vs.* two abnormal indicator $p < 0.0001$; ≥ two abnormal indicators *vs.* three abnormal indicator $p = 0.1027$.

may take part in the progression of vascular inflammation [23,24]. In the Framingham Heart Study, serum sST2 levels were fond to be associated with age, diabetes, and inflammatory markers [25], which are all considered to be typical risk factors for AKI. This suggests the potential of sST2 in predicting AKI and CRS in acute cardiac events. By using logistic regression analysis, we discovered that sST2 might be utilized as an independent indicator for early prediction of CRS1. Compared to other independent predictors, sST2's AUC area was the largest. Its sensitivity and specificity were superior to NT-proBNP and eGFR. In addition, sST2 is hardly affected by the etiology of heart failure, age, sex, BMI, anemia, and renal function [26]. It can be easily detected by extracting peripheral blood, making it convenient for clinical practice. Hence, sST2 holds greater value compared to other individual independent markers when it comes to forecasting the occurrence of in-hospital CRS1 in patients with AMI.

The mechanisms of CRS1 include: (1) acute myocardial infarction (AMI), which produces acute renal hypoperfusion and then results in acute renal tubular necrosis and CRS1 [27]; (2) the generation of inflammatory factors is stimulated by the activation of the renin-angiotensin system and the sympathetic nervous system, and some research has shown that an increase in the level of inflammatory factors is positively correlated with the deterioration of renal function in ACS patients [28,29]; (3) the incidence and prognosis of CRS1 are related to baseline renal function [12]. Through logistic regression analysis we identified five independent risk factors for predicting the development of CRS1 in AMI patients, sST2, NT-proBNP, and eGFR indicated better discrimination ability, all $p < 0.001$. Furthermore, ROC curve analysis revealed that the three markers have higher diagnostic value, and these three indicators could reflect the relevant factors in the mechanism of CRS1 occurrence. Moreover, we selected these three indicators as joint indicators since they're easy to collect, test at admission, and practice clinically. Diuretic use and Multivessel coronary artery disease are undoubtedly separate risk factors, but on the day of admission, some patients didn't use diuretics, or some patients preferred to receive pharmaco-

logical treatment rather than coronary angiography, making it impossible to evaluate these two factors at this time. As a result, we did not include these two factors. We discovered that the combination's sensitivity and specificity were greater than those of the three separate indexes and its AUC curve area was bigger than that of the three individual indices. Also, we determined that the more number of abnormal indicators, the higher the risk of CRS1. These findings suggest that the predictive value of combined indicators may be superior to individual markers. According to the results of the pairwise comparisons of ROC curves, the predictive value of the combination may be superior to eGFR and NT-proBNP, but there is no discernible advantage over sST2, indirectly indicating that sST2 has better predictive capability of sST2 than other individual indicators.

Conclusions

In summary, in a cohort of 202 patients with AMI in hospital, we discovered that sST2 is a novel predictor of the occurrence of CRS1, and its predictive value is superior to the other individual indicators mentioned in this study. Compared to sST2 alone, the combined detection of sST2, eGFR, and NT-proBNP at admission may have potential advantages in ROC curve analysis, although no significant statistical superiority was observed. However, our study has certain limitations. Firstly, it was a single-center retrospective observational study, and our findings may not be applicable to patients with different definitions of CRS1 or variations in treatment approaches. Secondly, the sample size is small, and the observation period is limited to the duration of hospitalization. Thirdly, some baseline clinical variables may have been overlooked, potentially introducing unmeasured confounding factors that could affect our results. In the future, we can expand the sample size and validate our findings through multicenter prospective studies. Additionally, follow-up of discharged patients can be conducted to observe whether the three markers have predictive value for the occurrence of cardiorenal syndrome outside the hospital.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

YH conceived and designed the study. YH and WZ performed the literature search and data extraction. YH drafted the manuscript. XL provided funding support, participated in the primary conceptualization of the article, and gave suggestion on writing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Ethics Committee of Affiliated Hospital of Nantong University (Research) 2016-052 and written informed consent was obtained from all patients.

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Conflict of Interest

The authors declare no conflict of interest.

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