Original Research

Predictive values of sST2 and IL-33 for heart failure in patients with acute myocardial infarction

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Impact statement

The serum levels of sST2 and IL-33 were significantly enhanced in patients with AMI complicated by HF and could be used as predictive indicators.

Abstract

Timely prediction of the risk of heart failure in acute myocardial infarction patients is critical for better prognosis. This article aims to evaluate the predictive value of serum soluble growth stimulation expressed gene 2 (sST2) and interleukin-33 in patients with acute myocardial infarction complicated by heart failure. A total of 42 healthy controls and 144 acute myocardial infarction patients were recruited in the study. According to Killip cardiac function classification as the basis for concurrent heart failure, they were distributed into non-heart failure group ($n = 76$) and heart failure group ($n = 68$). ELISA was utilized to determine the serum sST2 and interleukin-33 levels, and the diagnostic efficiency was evaluated by receiver operating characteristics curve. sST2 and interleukin-33 levels in patients with acute myocardial infarction were significantly increased when compared with normal healthy controls, and were further enhanced in the heart failure group. With the increased Killip cardiac function classification, interleukin-33 and sST2 levels were gradually elevated. Multivariate analysis indicated that interleukin-33 and sST2 could be used as independent predictors for heart failure combined with acute myocardial infarction.

Keywords: Heart failure, acute myocardial infarction, soluble growth stimulation expressed gene 2, interleukin-33, predictive value

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Introduction

Acute myocardial infarction (AMI) is a common heart disease in cardiology.[1] It refers to the blockage of the coronary arteries, which leads to a sudden decrease in blood flow, myocardial hypoxia, ischemia, necrosis, and complications such as chest pain and arrhythmia.[2] AMI has a rapid onset and disease progression, and it could be life-threatening if not intervened in time.[3] Heart failure (HF) is the ultimate fate of various cardiovascular diseases including AMI.[4] Most AMI patients are accompanied by varying degrees of HF, which triggers major cardiovascular events after treatment.[5] At present, there are many indicators for diagnosing AMI, but there are few reports on the predictive value of AMI with HF.[6] Therefore, the discovery of biomarkers to reflect the predictive indicators of HF patients with AMI could provide a reference for early clinical detection and intervention.

Growth stimulation expressed gene 2 (ST2) is a member of the interleukin receptor 1 family, and its ligand is interleukin (IL)-33.[7] In cardiac fibroblasts, ST2 is expressed during the heart disease or injury and directly participates in cardiac fibrosis and remodeling.[8] ST2 is mainly composed of two subtypes: one is transmembrane ST2 (ST2L), with IL-1 receptor-like structure; the other is soluble ST2 (sST2), with no intracellular receptor or transmembrane domain.[9] In recent years, the IL-33/ST2L signaling pathway has been demonstrated to exhibit cardioprotective effects, such as anti-cardiomyocyte hypertrophy, myocardial fibrosis, and anti-atherosclerosis.[10] sST2 is a myocardial protein induced by mechanical stress, whose secretion increases after being biomechanically stretched.[11] As the degree of HF worsens and the load on the heart increases, the expression of sST2 is further enhanced.[12] sST2 could act as a serum soluble decoy receptor, blocking IL-33-ST2L interaction, thereby inhibiting the cardioprotective effect of IL-33.[13] Therefore, sST2 is a novel biomarker reflecting HF and could be combined with commonly used clinical biomarkers to diagnose and predict the prognosis of HF.[14]However, there is currently no report on the diagnostic value of IL-33/ST2 in AMI with HF. This study aimed to

explore the predictive value of IL-33 and sST2, and to provide new ideas for the therapy and diagnosis of AMI combined with HF.

Materials and methods

Subjects

The study was approved by the Ethics Committee of Cangzhou Central Hospital. A total of 42 healthy controls and 144 AMI patients admitted to Cangzhou Central Hospital from October 2018 to February 2020 were recruited in our study. Age-matched healthy physical examination patients were selected during the same period, whose blood routine, urine routine, liver and kidney function, blood sugar, chest X-ray, and other examinations were all normal. According to Killip cardiac function classification as the basis for concurrent HF, they were distributed into non-HF group ($n = 76$) and HF group ($n = 68$).

Inclusion criteria: 1. Age 18 years or older and less than 80 years old; 2. In accordance with the diagnostic criteria of AMI in the Guidelines for the Diagnosis and Treatment of AMI (acute chest pain occurs within 24 h, ECG examination shows pathological Q waves or ST segment marked elevation, ultrasound examination revealed abnormal segmental motion of the ventricular septum or obvious arterial stenosis or infarction on coronary angiography); 3. No history of HF.

Exclusion criteria: 1. History of acute infection, trauma, or surgery within the past two weeks; 2. Pregnant and lactating women; 3. Malignant tumors; 4. Congenital heart disease; 5. Coarctation pericarditis, aortic dissection, restrictive cardiomyopathy, hypertrophic obstructive cardiomyopathy, valvular disease; 6. Severe liver and kidney dysfunctions; 7. Connective tissue diseases; 8. Complications of diabetes; 9. Severe mental illnesses.

HF diagnostic criteria: sudden dyspnea, chest tightness, orthopedic breathing, breathing rate of 30–50 beats/min, heart rate increase of 15–20 beats/min, wet rales and wheezing could be heard in both lungs, chest X rays showed pulmonary edema and pulmonary congestion, brain natriuretic peptide or B-type brain natriuretic peptide precursor was significantly increased.

ELISA

After admission, 4 mL of total blood was drawn from all subjects to a heparin anti-coagulation tube to stand at room temperature for 1 to 2 h. The serum was separated by centrifuging at 3500 r/min for 10 min, and stored immediately in a refrigerator at −80°C. ELISA was performed according to the human IL-33 and sST2 ELISA kit (Shanghai Westang Bio-Tech Co., Ltd) instructions.

Statistical analysis

Data processing was done by SPSS 18.0. Sample size was determined using PS software (power and sample size collection version 3.0.12). Differences between means of each group, which were divided by the standard deviation to determine the standardized effect size, then using 5% as significance level in one-way ANOVA test and 90% power, the minimum required sample size was calculated. Mean ± standard deviation ($\bar{x} \pm s$) was used for data conforming to normal distribution, and M (P25, P75) was used for data not conforming to normal distribution. The comparison adopts t or F test. Counting data were shown as rate (%), and compared by χ^2 test. Single factor logistic regression was used to analyze the related factors of AMI with HF, and Spearman correlation analysis was used for correlation analysis. The diagnostic efficiency was evaluated by receiver operating characteristics curve (ROC).

Results

Influencing factors of AMI concurrent HF

We collected age, gender, underlying diseases, heart rate, blood pressure, and other general information of all patients at admission, as well as serum biochemical tests. Results showed that age, Killip class, heart rate, left ventricular ejection fraction (LVEF), high-sensitivity C-reactive protein (hs-CRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and creatine kinase-muscle/brain (CK-MB) were the influencing factors of AMI complicated with HF (Table 1).

We found that elder AMI patients exhibited higher risk of concurrent HF ($P = 0.033$). Killip cardiac function classification showed that AMI patients with HF were distributed to class II–IV, but AMI patients without HF were all class I. The LVEF of AMI patients with HF were significantly lower than that of the non-HF group ($P < 0.001$). In addition, serum biochemical experiments showed that the levels of hs-CRP, NT-proBNP, and CK-MB were dramatically increased.

Serum IL-33 and sST2 levels

We found that, compared with normal healthy controls, the serum levels of IL-33 (Figure 1(a)) and sST2 (Figure 1(b)) in patients with AMI were significantly increased, and were further enhanced in the HF group compared to the non-HF group. Spearman's correlation analysis revealed that IL-33 and sST2 levels in the serum of patients with AMI and HF were positively correlated (Figure 1(c)).

The predictive value of IL-33 and sST2 in the prognosis of AMI concurrent HF

The diagnostic efficiency of serum sST2 and IL-33 was expressed through specificity and sensitivity, and the best cut-off value and reliability of the method were analyzed using ROC. We found that the area under the curve (AUC) of IL-33 to predict the prognosis of patients with AMI and HF was 0.8429, the cut off value was 154.4 pg/mL, the sensitivity was 76.47%, and the specificity was 78.95% (Figure 2(a)). The AUC of sST2 predicting the prognosis of AMI patients with HF was 0.7991, the cut off value was 78.79 pg/mL, the sensitivity was 79.41%, and the specificity was 81.58% (Figure 2(b)).

Table 1. Baseline characteristics of patients with and without heart failure (HF) after acute myocardial infarction (AMI) and the healthy controls (HC).

	HC ($n = 42$)	Non-HF ($n = 76$)	HF ($n = 68$)	P value
Age (years)	62.42 ± 8.35	61.49 ± 7.96	69.16 ± 8.29	0.033
Body mass index (kg/m^2)	24.12 ± 2.89	24.82 ± 3.11	25.28 ± 2.93	0.084
Gender				
Male	23 (54.8 %)	44 (57.9 %)	41 (60.3 %)	0.866
Female	19 (45.2 %)	32 (42.1 %)	27 (39.7 %)	
Accompanying disease				
Diabetes	–	18 (23.7 %)	20 (29.4 %)	0.455
Hypertension	–	29 (38.2 %)	31 (45.6 %)	0.400
Hyperlipidemia	–	24 (31.6 %)	25 (36.8 %)	0.598
COPD	–	5 (6.6 %)	5 (7.4 %)	>0.999
Prior stroke	–	6 (7.9 %)	10 (14.7 %)	0.288
Killip class				
Class I	–	76 (100 %)	0	<0.001
Class II	–	0	24 (35.3 %)	
Class III	–	0	28 (41.2 %)	
Class IV	–	0	16 (23.5 %)	
Clinical status				
Heart rate (b.p.m.)	71.67 ± 12.43	77.13 ± 15.71	84.66 ± 17.38	0.025
SBP (mmHg)	109.43 ± 18.47	126.92 ± 24.64	131.54 ± 27.91	0.084
DBP (mmHg)	68.92 ± 17.93	85.16 ± 20.43	94.25 ± 21.76	0.142
Echocardiography				
LVEF (%)	–	54.83 ± 8.92	41.69 ± 7.59	<0.001
LVEDD (mm)	–	4.67 ± 0.86	5.07 ± 0.98	0.265
LVEDV (mL)	–	103.45 ± 28.43	107.66 ± 31.38	0.361
LVESV (mL)	–	46.84 ± 16.94	57.82 ± 19.42	0.096
Laboratory findings				
HDL-C (mmol/L)	1.07 ± 0.38	1.29 ± 0.44	1.41 ± 0.48	0.108
LDL-C (mmol/L)	3.45 ± 0.91	3.15 ± 1.03	2.97 ± 0.93	0.087
TC (mmol/L)	4.06 ± 0.87	3.78 ± 0.91	4.22 ± 0.89	0.336
TG (mmol/L)	1.34 ± 0.41	1.55 ± 0.50	1.72 ± 0.61	0.416
hs-CRP (mg/dL)	3.67 ± 3.16	8.67 ± 4.33	14.61 ± 6.34	<0.001
NT-proBNP (pg/mL)	174.65 ± 85.63	638.47 ± 179.95	1484.93 ± 318.59	<0.001
CK-MB (ng/mL)	34.48 ± 25.13	108.44 ± 69.75	254.324 ± 106.45	<0.001

HF: heart failure; COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; hs-CRP: high-sensitivity C-reactive protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide; CK-MB: creatine kinase-muscle/brain.

Note: The data presented are mean ± SD or n (percentage). P values, HF vs. non-HF. The comparisons of data between the HF and Non-HF groups were done by unpaired Student's t-test followed by Mann–Whitney test or Chi-square test.

Comparison of sST2 and IL-33 levels in patients with different Killip grades

With the increased Killip cardiac function classification, IL-33 (Figure 3(a)) and sST2 (Figure 3(b)) levels were gradually increased, and the differences between class I and II, II and IV were statistically significant. However, no significant difference was observed in sST2 and IL-33 levels between class II and III, and III and IV. Our data suggested that the serum levels of IL-33 and sST2 were reliable for predicting HF, but they were not necessarily effective for accurately predicting the degree of HF.

Analyzing the predictive value of sST2 and IL-33

Through multivariate logistic regression analysis, we evaluated the potential parameters for predicting HF in AMI patients. In Table 2, univariate analysis demonstrated that age, heart rate, Killip class, LVEF, hs-CRP, NT-proBNP, CK-MB, IL-33, and sST2 were statistically significant parameters ($P < 0.05$). Among these parameters, multivariate analysis indicated that LVEF, CK-MB, IL-33, and sST2 could be used as independent predictors for HF after AMI ($P < 0.05$) (Table 2).

Discussion

AMI is a common disease in cardiology emergency.[15,16] The main pathophysiological mechanism of AMI is hypertension and coronary spasm that induce atherosclerotic plaque rupture and thrombosis.[17,18] Such patients are prone to acute HF.[19] One quarter of the approximately two million cardiovascular disease patients in our country has AMI each year, and the incidence of AMI complicated by HF is 32.4%, so early prediction of the risk of HF in AMI patients is very important to improve the prognosis.[20] Early opening of the infarcted blood vessel could save the ischemic myocardium, effectively improve heart function, and reduce the mortality rate.[21] Therefore, to implement timely and effective diagnosis and treatment is the focus of clinicians' attention, and has important value in reducing mortality of HF and other complications.[22,23] Currently, cardiac markers such as BNP and NT-pro BNP are widely used clinically for early diagnosis of HF and prognosis.[24]

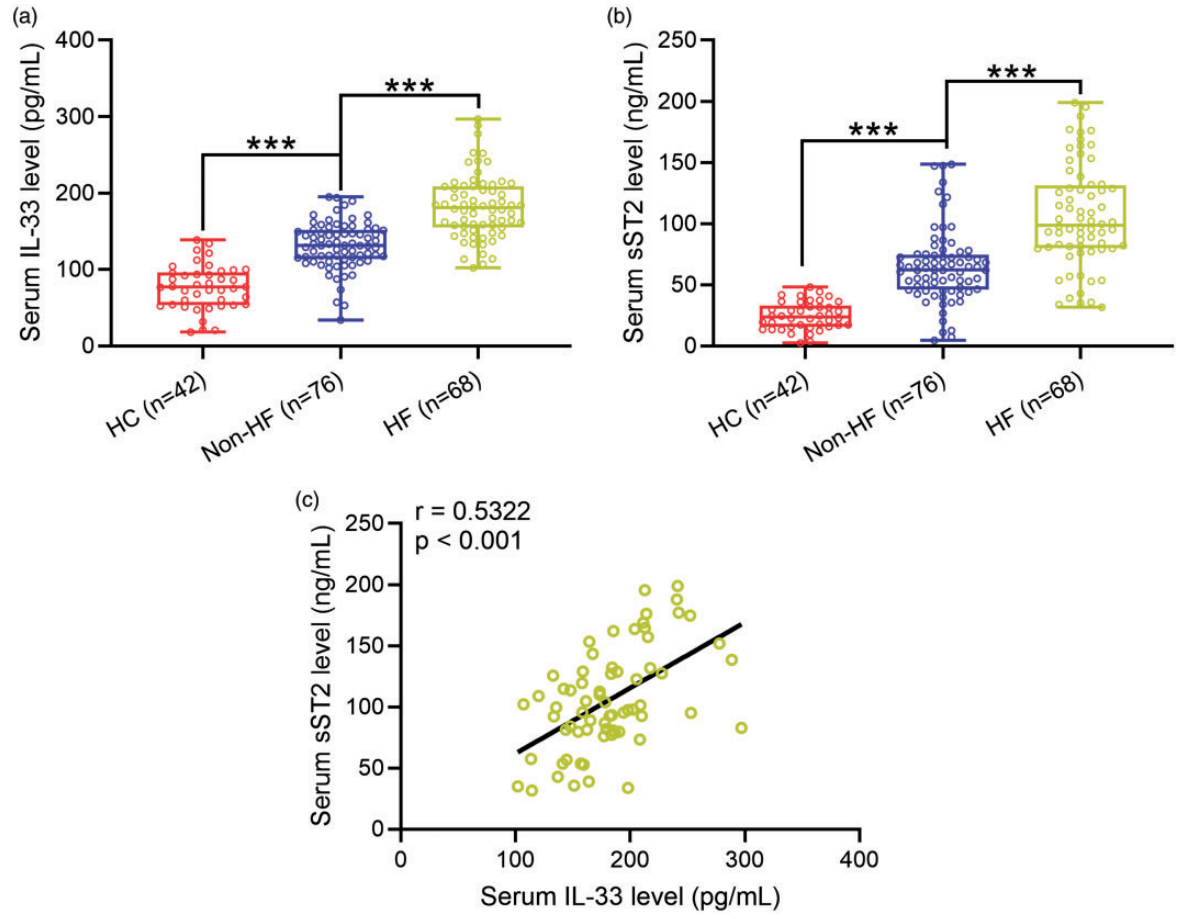

Figure 1. Serum IL-33 (a) and sST2 (b) were detected by ELISA from healthy control (HC, $n = 42$), AMI complicated with HF ($n = 68$), and AMI complicated without HF ($n = 76$). Box plots with all data points were used to present the data. The comparisons were done by one-way ANOVA followed by a Dunn's multiple comparisons test. ***$P < 0.001$. (c) Spearman's correlation analysis was carried out to measure the correlations between IL-33 and sST2 levels in serum from the AMI complicated with HF (HF, $n = 68$). (A color version of this figure is available in the online journal.)

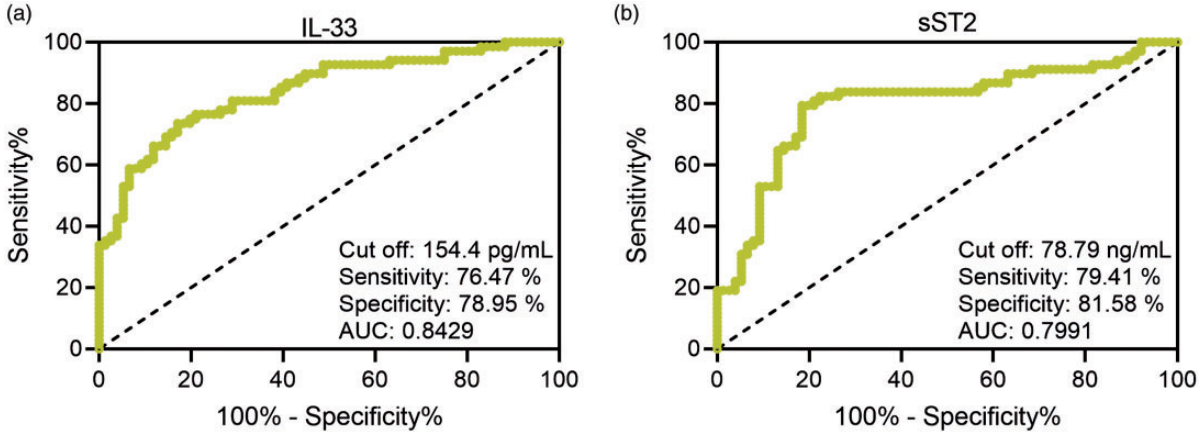

Figure 2. ROC analysis of serum IL-33 (a) and sST2 (b) on HF and non-HF AMI patients. (A color version of this figure is available in the online journal.)

However, due to the limitations of the above indicators, it is necessary to find novel cardiac biomarkers with high specificity and sensitivity, in addition to NT-pro BNP and BNP, to assist in the diagnosis and treatment of HF.

The IL-33/ST2 signaling participates in the communication of fibroblast-cardiomyocyte information in the myocardium, and may become a therapeutic target for the prevention of cardiovascular diseases.[25] Previous studies have shown that when myocardial cells are stimulated by coronary artery ischemia, the expression of ST2 transcript and serum ST2 protein increases.[26] Some clinical research data indicate that the serum ST2 level of AMI

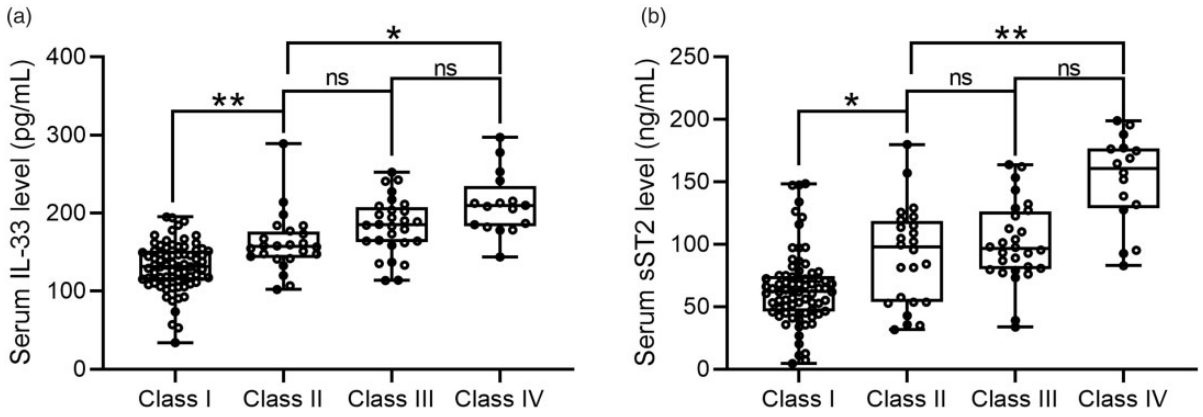

Figure 3. Serum IL-33 (a) and sST2 (b) were detected in the serum from AMI patients with different Killip classifications. Box plots with all data points were used to present the data. The comparisons were done by one-way ANOVA followed by a Dunn's multiple comparisons test. *$P < 0.05$, **$P < 0.01$ and ns means no significance.

Table 2. Univariate and multivariate analysis to predict heart failure (HF) after acute myocardial infarction (AMI).

	Univariate analysis		Multivariate analysis	
Variable	**Odds ratio (95% CI)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
Age (years)	1.16 (1.01–1.26)	0.021	1.03 (0.95–1.08)	0.162
Body mass index (kg/m^2)	1.08 (0.88–1.24)	0.164	–	–
Heart rate (b.p.m.)	1.11 (0.98–1.22)	0.018	1.02 (0.89–1.13)	0.086
SBP (mmHg)	0.96 (0.85–1.04)	0.252	–	–
DBP (mmHg)	1.21 (0.78–1.34)	0.471	–	–
Killip class	1.46 (1.09–2.01)	0.002	0.91 (0.74–1.25)	0.274
LVEF (%)	0.87 (0.64–0.95)	0.003	0.89 (0.81–0.97)	0.019
hs-CRP (mg/dL)	1.07 (0.96–1.21)	0.035	1.14 (0.89–1.37)	0.079
NT-proBNP (pg/mL)	1.26 (1.03–1.38)	0.022	0.96 (0.92–1.04)	0.351
CK-MB (ng/mL)	1.45 (1.08–1.69)	0.004	1.21 (1.04–1.46)	0.017
IL-33 (pg/mL)	1.34 (1.12–1.48)	<0.001	1.18 (1.07–1.32)	0.007
sST2 (ng/mL)	1.29 (1.09–1.47)	0.008	1.31 (1.16–1.55)	<0.001

CI: confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF: left ventricular ejection fraction; hs-CRP: high-sensitivity C-reactive protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide; CK-MB: creatine kinase-muscle/brain; IL-33, interleukin-33; sST2: soluble interleukin-1 receptor-like 1.

patients rises on the first day of onset,[27] and reaches peak around 12 h, which is independently correlated with 30-day mortality. Shampo and other studies found that sST2 increased in 810 patients after thrombolysis of myocardial infarction, especially in patients with new-onset HF or who died within one month.[27] sST2 could predict the one-month clinical endpoint of AMI, which is related to decompensated hemodynamics, and is positively correlated with heart rate, troponin, CRP, BNP, and serum creatinine. Sabatine selected 1239 patients with acute ST-elevation myocardial infarction from the CLARITY-TIM128 clinical trial, and found that patients with elevated sST2 levels exhibited significantly higher risk of cardiovascular events and death from HF.[28] sST2 level could predict the occurrence of cardiovascular death and congestive HF within 30 days of the onset of symptoms, and was independent of traditional clinical risk factors.[29] In the present study, we found that compared with normal healthy controls, the serum levels of sST2 and IL-33 in patients with AMI were remarkably increased, and were further enhanced in the HF group compared to the non-HF group. Consistent with previous research, we confirmed the importance of sST2 and IL-33 in AMI combined with HF.

When cardiomyocytes and fibroblasts of patients with HF are stretched biomechanically, the expression of IL-33 and sST2 increases and participates in the IL-33/ST2 signaling pathway.[30] A large amount of sST2 can inhibit the release of inflammatory factors such as IL-6 and IL-12 and weaken the cardioprotective effect of IL-33 cytokines.[31] As the degree of HF worsens, the load on the heart increases, and the elevated sST2 becomes more significant, so sST2 could be used to predict the adverse outcome of patients with HF. Rehman *et al.*[32] studied 346 patients with acute HF and showed that the level of ST2 was related to the severity of HF, LVEF, creatinine clearance, BNP, NT-pro BNP and CRP, but not related to age or body mass index. Paradoxically, we found that age was one influencing factor of AMI complicated with HF. Studies have found that with increased age, the prevalence of hypertension and old myocardial infarction in AMI patients increases significantly, and the incidence of mechanical complications and arrhythmia is also significantly higher than that of young patients.[33] In addition, the incidence rates of

multivessel diseases and complications in elderly patients are higher than younger patients.[34] These are the reasons for the higher incidence of HF and death during hospitalization in elderly patients. With increased age, the functions of important organs such as the heart and lungs of the elderly further decline, the immune function is low, and complications such as infections are more likely to occur, which also leads to further increased rate of HF and mortality in elderly patients. By conducting cardiac-related multi-parameter analysis of 150 hospitalized patients with acute HF (including ST2, BNP, NT-pro BNP and blood urea nitrogen), Boisot *et al*.[35] found that changes in ST2 levels during hospitalization could predict 90-day mortality, and this effect was independent of BNP or NT-pro BNP. Therefore, serum IL-33/sST2 is a new type of marker that reflects HF, which is different from NYHA heart function classification, LVEF, and BNP. They could be used to assist in the diagnosis and predict the prognosis of HF, and to provide new ideas for the treatment of HF in the future. In this study, we found that with the increased Killip cardiac function classification, IL-33 and sST2 levels were gradually increased. However, there was no significant difference in IL-33 and sST2 levels between class II and class III, and class III and class IV. Our results suggest that IL-33 and sST2 are reliable for predicting HF, but they are not necessarily effective for accurately predicting the degree of HF.

In conclusion, we found that the levels of sST2 and IL-33 in patients with AMI were significantly increased when compared with normal healthy controls, and were further enhanced in the HF group. With the increased Killip cardiac function classification, IL-33 and sST2 levels gradually enhanced. Multivariate analysis indicated that IL-33 and sST2 could be used as independent predictors for HF after AMI.

AUTHORS' CONTRIBUTIONS

Data collection and analysis: JXX, JL, and TG; Study designed and manuscript writing: JXX and TG. All authors approved the final submission.

DECLARATION OF CONFLICTING INTERESTS

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