

Association of Soluble Suppression of Tumorigenicity with No-Reflow Phenomenon and Long-Term Prognosis in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome after Percutaneous Coronary Intervention

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Aims: Soluble suppression of tumorigenicity 2 (sST2) was validated to independently predict prognosis for heart failure (HF) and ST-segment elevation myocardial infarction (STEMI). In this study, we aimed to evaluate the relation between sST2 and coronary artery stenosis, and no-reflow phenomenon and one-year prognosis in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS).

Methods: This prospective study consecutively enrolled 205 patients who were diagnosed with NSTE-ACS and underwent percutaneous coronary intervention (PCI). sST2 was measured for all patients during admission. Patients were divided into two groups based on the optimal cutoff value: sST2 >34.2 ng/ml and sST2 ≤ 34.2 ng/ml groups.

Results: Patients in the sST2 >34.2 ng/ml group was associated with higher Gensini scores and multivessel disease. sST2 had weak predictive value for no-reflow phenomenon (area under the curve [AUC], 0.662; 95% confidence interval [CI], 0.53–0.79; $P=0.015$) with 66.7% sensitivity and 65.2% specificity, and it also had independent predictive value of no-reflow phenomenon after adjusting for confounding factors (odds ratio [OR], 3.802; 95% CI, 1.03–14.11; $P=0.046$). sST2 >34.2 ng/ml had a commendable predictive value for the one-year prognosis (AUC, 0.84; 95% CI, 0.75–0.93; $P<0.001$) with 72% sensitivity and 84% specificity, and it independently predicted one-year major cardiovascular and cerebrovascular events (MACCE) (hazard ratio [HR], 10.22; 95% CI, 4.05–25.7; $P<0.001$).

Conclusion: The sST2 concentration on admission is correlated with the degree of coronary artery stenosis. sST2 can predict both no-reflow and MACCE in patients with NSTE-ACS after PCI and was an independent predictor of MACCE and no-reflow phenomenon.

Key words: Soluble ST2, Non-ST-elevation acute coronary syndrome, Percutaneous coronary intervention, No-reflow phenomenon, Prognosis

Introduction

Acute coronary syndrome (ACS) is a common critical illness in cardiovascular disease and encompasses ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable

angina (UA)¹. With the current technology improvement and new drugs, the prognosis of ACS remains unsatisfactory. Biomarkers (e.g., cardiac troponin I [cTnI] and N-terminal pro-B-type natriuretic peptide [NT-proBNP]) are acknowledged as useful clinical tools². They have the advantage of being convenient and fast detection; therefore, finding

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new and more valuable markers to predict the complication and prognosis of ACS is of great significance.

The suppression of tumorigenicity 2 (ST2) is a novel biomarker in cardiovascular disease and is a member of interleukin (IL)-1 receptor family³. There are two main subtypes of proteins that are encoded by the ST2 gene. One is ST2L, a membrane-bound receptor. When binding to IL-33 ligand, it can promote a T helper 2 (Th2) immune response and protect the heart. The other subtype is soluble suppression of tumorigenicity 2 (sST2), which can bind to IL-33 and block the binding of IL-33 and ST2L, thereby weakening the cardiovascular protection of IL-33/ST2L signaling pathway^{1, 4}. As a mechanical stress-induced myocardial protein, sST2 is expressed from cardiac myocytes, cardiac fibroblasts, and endothelial cells in patients with acute myocardial infarction and heart failure (HF)^{5, 6}. A large amount of sST2 binds to free IL-33 in extracellular fluid, which effectively reduces the binding of ST2L to IL-33 and weakens the protective effect of IL-33 on the myocardium⁶. Previous studies suggested that sST2 is associated with the severity and prognosis of HF⁷⁻⁹. Studies also proved that sST2 is related to no-reflow phenomenon and prognosis in patients with STEMI^{10, 11}. Whether the relationship between sST2 with STEMI is also applicable to patients with NSTEMI-ACS, however, is unclear. To our knowledge, we were the first to investigate the predictive value of sST2 for coronary stenosis, no-reflow phenomenon, and prognosis in patients with NSTEMI-ACS after percutaneous coronary intervention (PCI).

Materials and Methods

In this prospective single-center study, we consecutively included 205 patients who were admitted to the Department of Cardiology of Shengjing Hospital between October 2018 and February 2019, diagnosed as NSTEMI-ACS, and treated with PCI. Overall, 57 patients were diagnosed with NSTEMI, and 148 were diagnosed with UA. This study was approved by the Ethics Committee of Shengjing Hospital (ethics number: 2018PS519K), and all patients signed informed consent. The registration number of this study is ChiCTR1800018952.

All patients were diagnosed according to the criteria of the American College of Cardiology (ACC) or American Heart Association (AHA), which include angina, ST-segment depression, T wave negativity or flattening, and troponin value. Patients with any of the following diseases were excluded: 1) STEMI, 2) asthma, 3) chronic obstructive pulmonary disease, 4) liver and/or kidney dysfunction, and 5) immune and

hematological diseases.

Peripheral venous blood was immediately obtained from all patients during hospital admission. Plasma was separated by centrifuging blood samples at 4000 rpm for 15 minutes and stored at -80°C refrigerator. sST2 was examined by performing Presage[®] ST2 assay (Critical Diagnostics, San Diego, USA). ST2 assay accurately detected plasma ST2 levels in the range of 3.1–200 ng/ml. Routine laboratory parameters were all tested in the Department of Clinical Laboratory by standard assay techniques. Baseline characteristics and angiographic features were collected from the information system of Shengjing Hospital.

All patients received 300 mg aspirin and 300 mg clopidogrel or 180 mg ticagrelor after admission. According to patients' blood pressure, heart rates, and liver and kidney functions, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), and statin were added. Coronary angiography and stent implantation were performed with standard techniques. Thrombolysis in myocardial infarction (TIMI) flow grades were decided by cardiologists who were blinded to the study.

The no-reflow phenomenon was defined as TIMI flow grade of ≤ 2 despite successfully reopening the culprit vessel and lack of mechanical obstructions. TIMI blood flow is defined as follows: grade 0, no antegrade blood flow; grade 1, with antegrade blood flow but cannot fill the distal blood vessels; grade 2, with antegrade blood flow that can fill the distal blood vessels but is significantly slow; and grade 3, with antegrade blood flow that can fill the distal coronary bed quickly and completely.

All patients continued to take drugs following doctors' advice. The primary end point of our study was major cardiovascular and cerebrovascular event (MACCE) during one-year follow-up. MACCE was defined as cardiovascular death, worsening HF (new-onset HF and worsening chronic HF), stroke, and ischemia-driven revascularization. The second end point was all-cause death, worsening HF, stroke, and ischemia-driven revascularization.

Statistical Analysis

The statistical software SPSS 22.0 (SPSS Inc, Chicago, IL, USA) was applied for statistics analysis. If they met the normal distribution, continuous variables were recorded as mean \pm standard deviation (SD), and if they did not meet the normal distribution, they were expressed as median and quartile range. To compare between the two groups, unpaired Student's *t*-test for normal distribution or

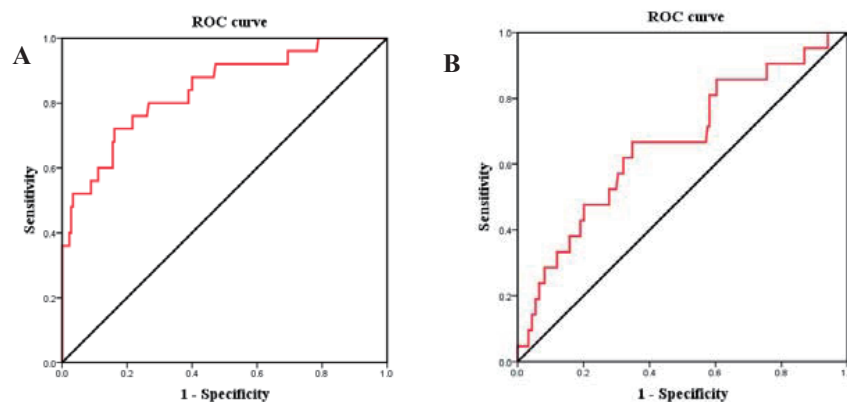


Fig. 1.

A: ROC curve analyses for the correlation of sST2 with MACCE. B: ROC curve analyses for the correlation of sST2 with no-reflow phenomenon.

Mann–Whitney U test for non-normal distribution was adopted. Categorical data was presented as number and percentage and was analyzed using the chi-square test. The receiving operating characteristic (ROC) curve was utilized to analyze the predictive value of sST2 for MACCE and no-reflow phenomenon. Youden' index determined the best cutoffs of sST2. Patients were divided into two groups based on the cutoff value from ROC: sST2 \leq 34.2 ng/ml and sST2 $>$ 34.2 ng/ml groups. The correlation among sST2 and left ventricular ejection fraction (LVEF), NT-pro BNP, cTnI, and Gensini score was calculated by the Spearman rank correlation coefficient. We adopted multivariate logistic regression analysis to identify independent predictors of the no-reflow phenomenon. The Kaplan–Meier survival curves and cox proportional hazard models were used for survival analysis to identify independent predictors of the MACCE. The two-sided P value of $<$ 0.05 was considered statistically significant.

Results

Overall, we recruited 205 patients who were diagnosed with NSTEMI-ACS (143 males and 62 females); their age ranged from 33 to 83. No-reflow phenomenon occurred in a total of 21 (10.2%) patients after PCI. At first, we conducted a ROC curve to evaluate the predictive power of sST2 to predict MACCE. In **Fig. 1A**, the area under the curve (AUC) was 0.84 (95% confidence interval [CI], 0.75–0.93; $P <$ 0.001). The best cutoff value was 34.2 ng/ml, the sensitivity was 72%, and the specificity was 84%.

Table 1 summarizes the baseline characteristics of patients in the sST2 \leq 34.2 and sST2 $>$ 34.2 ng/ml

groups. Patients in the sST2 $>$ 34.2 ng/ml group had higher total cholesterol, white blood cell (WBC), peak cTnI, and NT-proBNP than those in the sST2 \leq 34.2 ng/ml group. The estimated glomerular filtration rate (eGFR) was lower in the sST2 $>$ 34.2 ng/ml group. Compared with the sST2 \leq 34.2 ng/ml group, the sST2 $>$ 34.2 ng/ml group had significantly higher sST2 (42.8 [36.02–52.7] vs. 19.7 [13.68–26.4]; $P <$ 0.001). We also divided patients into single-vessel, two-vessel, and three-vessel lesion group, and it was found that sST2 was statistically different among the three groups (F : 5.163; $P =$ 0.007). Comparison between the two groups revealed that there was statistical difference between the single- and three-vessel lesion groups ($P =$ 0.002). There was no statistical difference in age, gender, medical history, blood pressure, heart rate, creatinine, left ventricular ejection fraction, and platelet counts between the two groups. The angiographic features between the two groups were also compared, as shown in **Table 1**. The multivessel disease and higher Gensini scores were more frequent in the sST2 $>$ 34.2 ng/ml group. Patients in the sST2 $>$ 34.2 ng/ml group have more grades 0–1 initial TIMI flow, and more stents were implanted. We also analyzed the correlation between sST2 and clinical parameters. sST2 is positively correlated with NT-proBNP, peak cTnI, WBC, and Gensini score and negatively correlated with LVEF and initial TIMI flow grade (**Table 2**).

ROC curve analysis was applied to determine the cutoff value of sST2 and predict no-reflow phenomenon (**Fig. 1B**). AUC was 0.662 (95% CI, 0.534–0.79; $P =$ 0.015). The optimal sST2 cutoff value was 27.8 ng/ml, with 66.7% sensitivity and 65.2% specificity. sST2 $>$ 34.2 ng/ml, peak cTnI, initial TIMI flow grade, multivessel disease, and

Table 1. Baseline characteristics and angiographic features

Variables	sST2 ≤ 34.2 ng/ml (n = 157)	sST2 > 34.2 ng/ml (n = 48)	P value
Age, years, mean ± SD	61.13 ± 9.67	63.71 ± 10.02	0.111
Male, n (%)	106 (67.5)	37 (77.1)	0.207
Hypertension, n (%)	65 (41.4)	22 (45.8)	0.587
Diabetes mellitus, n (%)	104 (66.2)	35 (72.9)	0.386
Smoking, n (%)	74 (47.1)	18 (37.5)	0.24
History of stroke/TIA, n (%)	14 (8.9%)	5 (10.4)	0.778
SBP, mmHg, mean ± SD	132.18 ± 18.49	137.08 ± 18.49	0.129
DBP, mmHg, mean ± SD	80.37 ± 11.23	80.35 ± 11.65	0.993
HR, beats/min, mean ± SD	68.81 ± 10.49	71.98 ± 12.19	0.08
Creatinine, μmol/L, mean ± SD	70.14 ± 17.16	77.06 ± 17.16	0.287
eGFR, ml/min/1.73 m ² , mean ± SD	96.31 ± 21.39	86.77 ± 18.26	0.006
TC, mmol/L, mean ± SD	3.89 ± 1.02	4.31 ± 1.05	0.014
LDL-C, mmol/L, mean ± SD	2.36 ± 0.89	2.63 ± 0.95	0.07
HDL-C, mmol/L, mean ± SD	0.94 ± 0.23	1.03 ± 0.35	0.092
WBC counts, × 10 ⁹ /L, mean ± SD	6.31 ± 1.72	7.33 ± 2.29	0.006
Neutrophil counts, × 10 ⁹ /L, mean ± SD	3.9 ± 2.96	3.3 ± 2.23	0.211
Platelet counts, × 10 ⁹ /L, mean ± SD	195.75 ± 45.73	195.25 ± 42.65	0.946
Peak cTnI, μg/L, mean ± SD	0.093 (0.035-0.57)	0.7 (0.115-4.08)	<0.001
NT-pro BNP, pg/mL, mean ± SD	104.2 (46.4-388.7)	400.4 (132.8-848.2)	<0.001
LVEF, %, mean ± SD	62.18 ± 5.53	60.5 ± 4.93	0.066
Medications, n (%)			
Ticagrelor	84 (53.5)	28 (58.3)	0.556
Clopidogrel	73 (46.5)	20 (41.7)	0.556
Beta blocker	148 (94.3)	46 (95.8)	0.665
ACEI/ARB	144 (91.7)	45 (93.8)	0.639
Nicorandil	69 (43.9)	21 (43.8)	0.981
Statin	157 (100)	48 (100)	1
sST2, ng/mL, mean ± SD	19.7 (13.68-26.4)	42.8 (36.02-52.7)	<0.001
Multivessel disease, n (%)	102 (65)	42 (87.5)	0.002
Initial TIMI flow grade, n (%)			<0.001
0-1	13 (8.3)	11 (22.9)	
≥ 2	144 (91.7)	37 (77.1)	
Multistent, n (%)	82 (52.2%)	35 (72.9)	0.01
Gensini Score	34.7 ± 25.09	53.67 ± 24.44	<0.001
No-reflow phenomenon, n (%)	11 (7)	10 (20.8)	0.012

Abbreviations: eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; cTnI, cardiac troponin I; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; sST2: soluble suppression of tumorigenicity 2; WBC:white blood cell; SD, standard deviation

neutrophil counts had predictive values for the no-reflow in univariate logistic regression, and sST2 > 34.2 ng/ml also had independent predictive value from multivariate logistic regression after adjusting peak cTnI and neutrophil counts (Table 3).

All patients completed one-year follow-up. One patient died of acute cerebral infarction, 14 had worsening HF, and 10 had ischemia-driven revascularization (Table 4). According to Kaplan–

Meier curves, the high sST2 concentration (sST2 > 34.2 ng/ml) was strongly related with one-year prognosis, thus worsening HF and ischemia-driven revascularization (Fig. 2). In the univariate cox regression analysis, sST2 > 34.2 ng/ml, NT-proBNP, no-reflow phenomenon, and diabetes mellitus all are statistically significant. From multivariate cox regression analysis, sST2 > 34.2 ng/ml and diabetes mellitus were independent predictors of MACCE

Table 2. Correlation between sST2 and clinical parameters

Variables	Spearman r	P
LVEF	-0.156	0.027
NT-pro BNP	0.339	<0.001
Peak cTnI	0.297	<0.001
White blood cell	0.277	<0.001
Initial TIMI flow grade	-0.27	<0.001
Gensini score	0.352	<0.001

Abbreviations: cTnI, cardiac troponin I; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction; sST2: soluble suppression of tumorigenicity 2; TIMI, thrombolysis in myocardial infarction.

Table 3. Univariate and Multivariate Logistic Regression Analysis for Independent Predictors of no-reflow phenomenon

Variables	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
sST2 > 34.2 ng/ml	3.49 (1.38-8.83)	0.008	3.802 (1.03-14.11)	0.046
eGFR	0.994 (0.97-1.02)	0.595	-	-
Age	1.016 (0.969-1.07)	0.517	-	-
White blood cell	1.116 (0.901-1.38)	0.314	-	-
Peak cTnI	1.06 (1.01-1.113)	0.018	1.06 (0.99-1.12)	0.099
NT-pro BNP	1.0 (0.999-1.001)	0.789	-	-
Gensini score	1.012 (0.996-1.03)	0.143	-	-
Initial TIMI flow grade	0.368 (0.251-0.54)	<0.001	0.434 (0.28-0.68)	<0.001
Diabetes mellitus	2.16 (0.697-6.695)	0.182	-	-
Smoking	1.26 (0.44-3.62)	0.667	-	-
Multivessel disease	0.27 (0.11-0.69)	0.006	0.13 (0.04-0.48)	0.002
LDL-C	0.71 (0.41-1.22)	0.214	-	-
Neutrophil counts	0.71 (0.51-0.997)	0.048	0.93 (0.69-1.25)	0.636

Abbreviations: cTnI, cardiac troponin I; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; sST2: soluble suppression of tumorigenicity 2; TIMI, thrombolysis in myocardial infarction; eGFR, estimated glomerular filtration rate; LDL-C, low density lipoprotein cholesterol OR: odds ratio.

within 1 year after adjusting for LVEF, no-reflow phenomenon, and NT-proBNP (Table 5).

Discussion

In this study, our main findings were as follow: (1) Among the 205 patients with NSTEMI-ACS enrolled in this study, 21 (10.2%) underwent no-reflow phenomenon and 25 (12.2%) developed MACCE. (2) sST2 was weakly related to the degree of coronary artery stenosis, and patients with high level of sST2 had higher Gensini score. (3) sST2 had a great predictive value for the occurrence of adverse outcomes but had a low predictive ability for no-reflow. (4) After the adjustment of confounding variables, sST2 remained independent predictors of MACCE and no-reflow phenomenon.

ST2 was first discovered in 1989 and was considered as an orphan receptor. The specific ligand

IL-33 was discovered in 2005¹²⁾. Its gene sequence and molecular structure are similar to IL-18 and IL-1 β . The effect of IL-33/ST2L pathway on atherosclerosis is mainly achieved by maintaining a balanced Th1/Th2 cell ratio¹³⁾. The combination of ST2L and IL-33 can promote Th2-type immune response and induce the production of Th2-type cytokines such as IL-5, as well as IL-6, thereby slowing the development of atherosclerosis¹⁴⁾. At the same time, it can also reduce Th1 cytokine production. For example, IFN- γ can inhibit the inflammatory response involved in Th1¹⁵⁾. IL-33/ST2L can also exert anti-myocardial hypertrophy and fibrosis by blocking the effects of angiotensin II or epinephrine on the myocardium. Weir *et al.* proposed that sST2 levels at admission in patients with myocardial infarction can predict the recovery of long-term left ventricular function, and it has a correlation with infarcted myocardial volume and cardiac remodeling. Patients

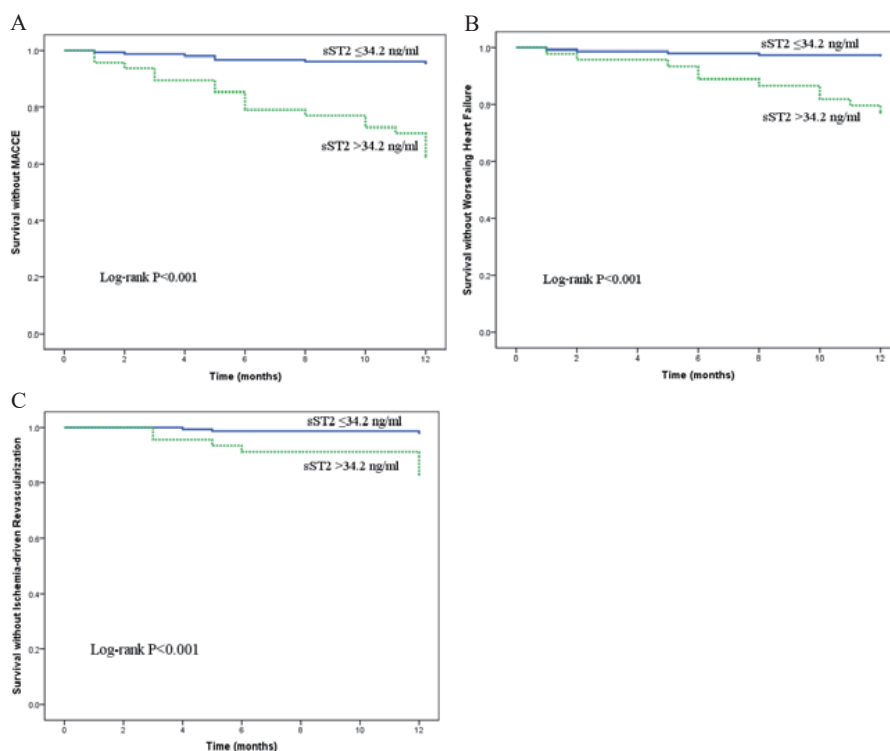
Table 4. Long-term follow-up outcomes

Variables	sST2 \leq 34.2 ng/ml ($n = 157$)	sST2 $>$ 34.2 ng/ml ($n = 48$)	<i>P</i> value
All-cause mortality	0 (0%)	1 (2.1%)	0.234
Cardiovascular mortality	0	0	1
ischemia-driven revascularization	3 (1.9%)	7 (14.6%)	0.002
worsening heart failure	4 (2.5%)	10 (20.8%)	<0.001
MACE	7 (4.5%)	17 (35.4%)	<0.001

Table 5. Predictors of MACCE by Univariate and Multivariate Cox Regression Analysis

Variables	Univariate HR (95% CI)	<i>P</i> value	Multivariate HR (95% CI)	<i>P</i> value
sST2 $>$ 34.2 ng/ml	9.76 (4.1-23.4)	<0.001	10.22 (4.05-25.7)	<0.001
eGFR	0.997 (0.98-1.02)	0.747	-	-
Age	1.04 (0.992-1.08)	0.113	-	-
White blood cell	1.1 (0.92-1.32)	0.287	-	-
Peak cTnI	1.01 (0.95-1.06)	0.824	-	-
NT-pro BNP	1.00 (1.00-1.001)	0.004	1.00 (1.00-1.001)	0.826
Gensini	1.004 (0.99-1.02)	0.561	-	-
No-reflow phenomenon	0.36 (0.15-0.91)	0.031	0.48 (0.17-1.33)	0.158
Diabetes mellitus	0.35 (0.16-0.76)	0.008	0.25 (0.11-0.595)	0.002
Hypertension	0.64 (0.28-1.48)	0.294	-	-
Multivessel disease	1.78 (0.67-4.73)	0.251	-	-
LVEF	0.92 (0.87-0.98)	0.011	0.96 (0.89-1.04)	0.316
Neutrophil counts	0.87 (0.67-1.12)	0.279	-	-

Abbreviations: cTnI, cardiac troponin I; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; sST2: soluble suppression of tumorigenicity 2; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; HR: hazard ratio.

**Fig. 2.** Kaplan–Meier survival curves for the relation between sST2 and MACCE (A), between sST2 and worsening HF (B), and between sST2 and ischemia-driven revascularization (C)

with higher level of ST2 have a severe infarct transmural extent and endocardial extent in the presence of microvascular obstruction¹⁶. The results of another study revealed that the sST2 level in STEMI group was higher than that in NSTEMI, SA, and control groups. The sST2 level in the NSTEMI group was also significantly higher than that in the SA control group. It was observed that the sST2 level in patients with STEMI continued to increase from SA to NSTEMI, to STEMI, indicating that it was related to the development stage and severity of coronary artery disease¹⁷. Therefore, ST2 levels at admission can reflect the degree of inflammatory response, myocardial injury, and myocardial fibrosis in patients developing myocardial infarction.

In our study, it was obvious that the Gensini score of the sST2 >34.2 ng/ml group was significantly higher than that of the sST2 ≤ 34.2 ng/ml group and that sST2 had a weak positive correlation with Gensini score. When we divided patients into 1, 2, and 3 coronary lesions, there was statistically significant difference in sST2 concentration among the three groups. Wang *et al.* concluded that sST2 had a positive correlation with Gensini score ($r=0.29$)¹⁸, and this may be due to the high sST2 level of patients with NSTEMI-ACS, which inhibits the anti-atherosclerotic effect of IL-33, thus leading to the formation of coronary atherosclerosis. However, atherosclerosis is a long-term process, and the level of sST2 before the onset of the disease cannot be known, which requires further monitoring of sST2 in patients with high risk of coronary heart disease to be determined.

No-reflow phenomenon was defined after PCI, and the myocardium is still unable to receive sufficient reperfusion, excluding the reduction of coronary blood flow that is caused by mechanical obstruction. Studies proved that no-reflow, as one of the serious complications after PCI, can aggravate myocardial ischemia, enlarge the area of myocardial infarction, and increase the incidence of HF¹⁹. It was also a predictor of short- and long-term mortality^{20, 21}. Although the exact mechanism of no-reflow was not completely clear at present, researches illustrated that the occurrence of no-reflow may be related to microcirculatory dysfunction, myocardial ischemia-reperfusion injury, distal vascular embolism, and inflammatory cell infiltration²². This was the first study that assessed the relationship between no-reflow phenomenon and sST2 in patients with NSTEMI-ACS. Somuncu *et al.* put forward that sST2 is the independent predictor of no-reflow in patients with STEMI. The cutoff value of sST2 is 11.6 ng/ml with an 82.7% sensitivity and 64.0% specificity and had an

AUC of 0.699 in the ROC curve¹¹. In our study, we revealed that the AUC of 0.662 is similar to 0.699, but the optimal cutoff value was 27.8 ng/ml, which was significantly different from 11.6 ng/ml. This may be related to the different diseases of patients in the two studies. sST2 has predictive value for no-reflow in univariate logistic regression analysis ($P=0.009$). After adjusting for peak cTnI and neutrophil counts, multivariate regression analysis displayed that sST2 > 34.2 ng/ml is also an independent predictor of no-reflow phenomenon. Such experimental results are also consistent with the mechanism of no-reflow. The increase of ST2 indicates the degree of inflammatory response. Severe inflammation likely means that no-reflow will occur.

Recently, ST2 was included in ACC/AHA guidelines as a prognostic marker for patients with HF, which also made this cardiac biomarker being widely used in the clinical setting²³. A meta-analysis of seven studies displayed that sST2 could be applied as a predictor of death in patients with chronic heart failure (CHF), and 35 ng/ml was discovered to be a cutoff value for high incidence of cardiovascular events²⁴. At the same time, the cut point of 35 ng/ml was also written into the guide²³. A multicenter, prospective study on CHF showed that sST2 expression levels are related to HF severity. Patients with elevated sST2 expression levels have significantly increased risk of death and the need for heart transplantation²⁵. In addition, Min-Seok *et al.* also confirmed that BNP was significantly higher in severe renal insufficiency, and sST2 levels did not significantly change in the degree of renal insufficiency compared with BNP levels, so ST2 level was not correlated with the severity of renal function²⁶, suggesting that ST2 has better stability. A large number of studies currently explored the relationship between sST2 and patients with STEMI. Previous researches illustrated that sST2 levels in patients with acute myocardial infarction (AMI) have predictive value for prognosis, especially HF and death, and have complementary effects with NT-proBNP and grace scores^{27, 28}. Sabatine *et al.* demonstrated that, in patients with STEMI, the high level of sST2 was a significant predictor of cardiovascular death and HF independent of NT-proBNP. The combination of ST2 and NT-proBNP can improve risk stratification¹⁰.

However, there are relatively few studies on the relationship between sST2 and patients with NSTEMI-ACS. In MERLIN-TIMI36 study, by observing 4,426 patients with NSTEMI-ACS, patients with sST2 >35 µg/L may be older and male and have diabetes and renal dysfunction. High sST2 levels were significantly associated with 30-day and 1-year risk of

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cardiovascular death/HF but were only weakly related to BNP and troponin²⁹). Eggers *et al.* observed the dynamic changes of sST2 levels in 403 patients with NSTEMI-ACS and concluded that sST2 peaked at 6–17 hours after the onset and then gradually decreased. However, after adjusting for NT-proBNP, sST2 was not the independent predictor of mortality in patients with NSTEMI-ACS within 1 year³⁰). In the results of our study, high-sST2 remains an independent predictor of MACCE in patients with NSTEMI-ACS and had great predictive value (AUC, 0.84). The difference between the two studies may be caused by different measurement times of sST2 and different levels of sST2 used for grouping. In our study, high ST2 was associated with not only increased risk for HF at 1 year but also increased ischemia-driven revascularization risk at 1 year. The cutoff value is 34.2 ng/ml, which is similar to the recommended value of 35 ng/ml in patients with HF; the sensitivity was 72% and specificity 84%. Therefore, whether we can apply 35 ng/ml as the optimal risk stratification for patients with HF and ACS is a direction for further investigation.

Nevertheless, this study has several limitations. This was a single-center study, and the number of patients included was relatively small. In this study, we examined the plasma sST2 levels only for patients with NSTEMI-ACS. It would be better to collect the data in patients with STEMI, stable coronary artery, and control and further compare the levels among those groups. Most importantly, we only detected the ST2 level of patients at the time of admission but did not observe subsequent changes.

Conclusion

This is the first study to explore the relationship between sST2 and the degree of coronary stenosis and the predictive ability of no-reflow phenomenon after PCI in patients with NSTEMI-ACS. Moreover, we concluded that high sST2 at admission is associated with the 1-year prognosis and no-reflow phenomenon. Finally, we believe that 35 ng/ml can be adopted as a recommended value for risk stratification to HF and ACS.

Conflicts of Interest

The authors declared that there was no conflict of interest.

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