CLINICAL STUDY

Soluble ST2 for Prediction of Clinical Outcomes in Patients with ST-Segment Elevation Myocardial Infarction Receiving Primary PCI

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Summary

Soluble suppression of tumorigenicity 2 (sST2), a biomarker representing myocardial fibrosis and inflammation, has been applied in risk stratification of patients with myocardial infarction (MI). However, whether primary PCI (PPCI) will eliminate the predictive value of sST2 in STEMI patients has not been well studied. Here, we conducted a prospective clinical trial to evaluate the correlation between sST2 and prognosis in STEMI patients undergoing PPCI. sST2 levels were measured in 295 STEMI patients (60.2 ± 10.8 years) at admission using a high sensitivity assay. Baseline sST2 levels were significantly associated with heart function, biomarkers of inflammation, and myocardial injury. During a 12-month follow-up, 19 patients had major adverse cardiovascular events (MACEs). Greater sST2 was continuously associated with a higher risk of incident MACEs. Such association remained even after adjusting for other risk factors in a multivariate Cox analysis. A baseline sST2 level in the highest quartile (≥ 58.7 ng/mL) was independently associated with mortality (HR: 5.01, 95%CI: 1.02-16.30, P = 0.048). More incident heart failure was seen in the group with greater sST2, however, the association was not significant after adjustment. Therefore, baseline sST2 may be useful to predict MACEs, especially mortality, in STEMI patients receiving PPCI.

(Int Heart J 2019; 60: 19-26)

Key words: Biomarker, Risk stratification, Prognosis, Revascularization

During the last decade, primary percutaneous coronary intervention (PPCI) has been applied worldwide as an effective treatment for patients with ST-segment elevated myocardial infarction (STEMI). Despite the success, complications like recurrence of myocardial infarction, heart failure, and death in patients after PPCI are haunting clinicians even though they have made great efforts to reduce ischemia time. Other than the procedure itself, the severity of cardiac damage is critical to the prognosis, therefore, it is important to explore biomarkers that can represent the myocardial injury and predict the prognosis of STEMI patients receiving PPCI.

Interleukin (IL)-1 family members participate in multiple pathogenic processes involved in cardiovascular disease, among which IL-33 has been identified to protect myocardiocytes against fibrosis and hypertrophy. Being an important ligand processing the IL-33 signal, suppression of tumorigenicity 2 (ST2) functions via two isoforms. ST2 L, the transmembrane form of ST2, is the receptor of IL-33 and plays a central role in the pathway. Soluble ST2 (sST2), the circulating form of ST2, belongs to the IL-1 receptor-like family, and it is a decoy receptor of IL-33. In response to myocyte stretch, sST2 is released from myocardium and vascular endothelial cells. Massive circulating sST2 neutralizes the protective effects of IL-33. Previous studies have shown that sST2 level is highly associated with poor prognosis in patients with AMI and other cardiovascular diseases.[1-3] Furthermore, sST2 has been reported to be valuable for prediction of clinical outcomes and over-all estimation of cardiac damage for STEMI patients though more clinical data are needed for further support.[4]

Given the limited efforts in risk stratification for STEMI patients receiving PPCI, and the significant association between the baseline sST2 level and major cardiac adverse events (MACEs), we hypothesized that sST2 levels would be associated with prognosis, and might be useful to predict the clinical prognosis in STEMI patients receiving PPCI.

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The study was supported by Wuhan innovational funding (WX16E31), innovational funding in Wuhan Asia Heart Hospital (2015CX3-A05), and grants from Beijing Lisheng Cardiovascular Health Foundation (LSG2014-2015).

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Received for publication January 9, 2018. Revised and accepted April 18, 2018.

Released in advance online on J-STAGE November 20, 2018.

doi: 10.1536/ihj.18-020

Methods

Study design: We conducted this prospective observational study at Wuhan Asia Heart Hospital, Wuhan, China with up to 12-month follow-up. The aim of the study was to evaluate the clinical significance of sST2 in STEMI patients receiving PPCI.

Participants: STEMI patients admitted to the Chest Pain Center of Wuhan Asia Heart Hospital, Wuhan, China between May 2015 and June 2016 were recruited. All patients were diagnosed according to the criteria for STEMI by the American College of Cardiology (ACC) or American Heart Association (AHA):[5] symptoms of myocardial ischemia; persistent electrocardiographic ST elevation; and release of biomarkers of myocardial necrosis. PPCI was performed as soon as possible in those patients who had symptoms within 24 hours and were eligible according to the criteria for myocardial revascularization.[6] PCI procedures were performed according to current guidelines.[7,8] Patients with a history of pulmonary fibrosis, chronic obstructive pulmonary disease, liver and/or kidney dysfunction, autoimmune disease, chronic infection, or tumors were excluded. The Ethics Committee of Wuhan Asia Heart Hospital approved this study. Informed written consent was obtained from patients while recruiting.

Laboratory and clinical assessment: Blood samples were obtained when patients were admitted to the emergency room before PPCI and thereafter according to the study design. Plasma was separated by centrifuging the blood samples at 4000 rpm for 10 minutes. sST2 was analyzed using a US FDA approved high-sensitivity Presage® ST2 assay (Critical Diagnostics, San Diego, CA, USA). The measurement range of the sST2 assay was 3.1 to 200 ng/mL with an intra-assay CV% of 5.1% and inter-assay CV% of 5.2%. All samples with a level of sST2 more than 200 ng/mL were diluted further to provide quantitative results according to the manufacturer's protocol.

Laboratory data at admission included the following: the plasma levels of triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), uric acid (UA), creatinine, high sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), N-terminal pro B-type natriuretic peptide (NT-proBNP), cardiac troponin I (cTnI), D-dimer, and hemoglobin A1c (HbA1C). Peak cTnI was also recorded. These blood tests were analyzed in fresh blood and determined by standard quantitative assay techniques in our Department of Pathology and Clinical Laboratory according to the manufacturer's protocol.

Clinical characteristics were obtained from the medical records and included age, sex, and medical history. Cardiovascular disease assessment variables included evaluation of heart function such as Killip classification and left ventricle ejection factor (LVEF). The location of the infarction and number of affected vessels were also recorded.

Follow-up and primary endpoints: Follow-up was censored at the time of adverse events or lasted until June 2017 when all patients reached 12-month follow-up. The primary endpoints were MACEs, defined as the composite adverse events of all-cause death, heart failure, and non-fatal myocardial infarction (MI).

Statistical analysis: Descriptive statistics such as number of observations were summarized using counts and percentages. Continuous data are reported as the mean ± SD for normally distributed or median with interquartile ranges (IQR) for skewed data. Baseline characteristics were compared with ANOVA or the Krustal-Wallis test for continuous variables depending on the normality of their distributions and with the χ^2 test for categorical variables. Kaplan-Meier survival curves and Cox proportional hazard models were employed for survival analysis and the assessment of risk factors. The Spearman correlation was used to determine the correlations between sST2 and other variables. Receiver operating characteristic (ROC) analysis was performed to determine the predictive efficiency of baseline sST2. Comparison of the area under curve (AUC) between different ROCs was conducted according to the method of Delong, *et al*.[9] A 2-sided *P*-value less than 0.05 was accepted as statistically significant. All statistical analyses were performed using SPSS 21.0 (IBM).

Results

Participant characteristics: We continuously recruited 311 patients at our chest pain center from May 2015 to June 2016. All patients met the diagnostic criteria for STEMI. Six patients were excluded because they were ineligible for PPCI. A total of 305 patients were included in the follow-up, 3 of whom did not continue until completion and 7 were lost during the 12-month follow-up. Therefore, 295 patients were included in the final analysis.

There were 243 males and 52 females and their ages ranged from 32 to 87 years. The range of sST2 at baseline was 6.2 to 559.7 ng/mL. Table I presents the baseline demographic and clinical characteristics of the participants separated by sST2 quartile. Sex, age, and factors of medical history were distributed equally across quartiles. Greater sST2 was associated with longer time of onset to ER time, days in-hospital, and worse heart function. No differences were seen with respect to either infarction location or number of affected vessels among groups. Biomarkers of myocardiocyte damage and inflammation were also positively correlated with baseline sST2 levels as their elevations were significantly associated with greater sST2 across quartiles.

Baseline sST2 and MACEs: A total of 19 patients reached their primary endpoints during the 12-month follow-up in our study. Baseline sST2 levels were associated with MACEs (HR: 1.81, 95%CI: 1.08-2.02, $P < 0.001$), and the independent association remained after being adjusted by other risk factors including age, onset to ER time, Killip classification, LVEF, NT-proBNP, peak cTnI, and hs-CRP (HR: 1.54, 95%CI: 1.07-1.80, $P = 0.018$). When analyzed based on sST2 quartiles, the Kaplan-Meier curves showed more MACEs were observed in the group with the highest interval of sST2 (Figure 1, $P = 0.006$). Table II shows the increase in sST2 was highly associated with adverse events. The risk increased nearly 6-fold from the lowest quartile to the highest quartile of sST2 in unadjusted analysis. After adjustment for

Table I. Basic Characteristics of STEMI Patients Receiving Primary PCI

	sST2 range, ng/mL				*P* value
	Q1 (6.2 - 20.1)	Q2 (20.3 - 32.2)	Q3 (32.3 - 57.2)	Q4 (58.7-559.7)	
Patient number	74	74	74	73	
Age, years	61.5 ± 10.4	58.5 ± 9.5	61.0 ± 11.8	59.7 ± 11.4	0.317
Male	60 (81.1)	67 (90.5)	59 (79.7)	57 (78.1)	0.191
Alcohol	35 (47.3)	42 (56.8)	35 (47.3)	29 (39.7)	0.232
Smoking					0.728
Never	27 (36.5)	21 (28.4)	23 (31.1)	28 (38.4)	
Past	7 (9.5)	3 (4.1)	7 (9.5)	5 (6.8)	
Current	40 (54.1)	50 (67.6)	44 (59.5)	40 (54.8)	
History					
Hypertension	38 (51.4)	41 (55.4)	45 (60.8)	42 (57.5)	0.701
Diabetes	14 (18.9)	16 (21.6)	11 (14.9)	14 (19.2)	0.767
Hyperlipidemia	16 (21.6)	17 (23.0)	13 (17.6)	12 (16.4)	0.712
Stroke	2 (2.7)	2 (2.7)	1 (1.4)	3 (4.1)	0.788
Heart function					
LVEF, %	47.4 ± 3.8	46.3 ± 4.5	45.8 ± 4.8	44.4 ± 4.6	0.002
Killip ≥ II	3 (4.1)	4 (5.4)	11 (14.9)	21 (28.8)	< 0.001
Infarction location					0.766
Anterior	34 (45.9)	38 (51.3)	29 (39.2)	39 (53.4)	
Inferior	35 (47.3)	31 (41.9)	33 (44.6)	31 (42.5)	
No. of affected vessel					0.691
1	18 (24.3)	17 (22.9)	23 (31.1)	17 (23.3)	
2	26 (35.1)	20 (27.0)	20 (27.0)	23 (31.5)	
3	29 (39.2)	36 (48.6)	31 (41.9)	32 (43.8)	
Duration					
Onset to ER, hours	4.0 (1.5 - 8.0)	4.0 (2.0 - 7.0)	6.0 (3.0 - 17.5)	9.0 (5.0 - 14.0)	< 0.001
Hospitalization, days	8.4 ± 3.4	8.6 ± 3.1	8.9 ± 2.5	9.9 ± 4.9	0.007
Biomarkers					
Urea, mmol/L	5.85 ± 1.60	5.88 ± 1.61	6.02 ± 2.07	6.11 ± 2.04	0.980
UA, μmol/L	351.5 ± 95.3	350.0 ± 100.4	354.3 ± 106.5	356.2 ± 110.2	0.960
Crea, μmol/L	77.5 (66.8-87.0)	74.0 (66.0-87.5)	77.0 (67.8-90.0)	71.0 (59.0-88.5)	0.244
TG, mmol/L	1.68 (1.17-2.49)	1.80 (1.29-3.27)	1.56 (1.17-2.31)	1.21 (0.87-1.80)	< 0.001
TC, mmol/L	4.54 (4.06-5.43)	4.93 (4.28-5.80)	5.00 (4.28-5.55)	4.48 (3.93-5.36)	0.057
LDL-C, mmol/L	2.86 (2.40-3.38)	3.13 (2.49-3.70)	3.13 (2.60-3.66)	2.79 (2.48-3.36)	0.147
HDL-C, mmol/L	0.99 (0.84-1.12)	0.97 (0.83-1.14)	1.07 (0.93-1.28)	1.06 (0.91-1.21)	0.016
hs-CRP, mg/L	1.99 (0.73-4.40)	2.54 (1.18-4.29)	3.27 (1.30-8.16)	4.26 (1.78-12.67)	< 0.001
D-dimer, μg/mL	0.24 (0.12-4.83)	0.28 (0.15-3.95)	0.20 (0.11-4.10)	0.27 (0.17-4.97)	0.831
HbA1C, %	5.8 (5.5-6.2)	5.8 (5.6-6.3)	5.9 (5.5-6.4)	5.8 (5.6-6.2)	0.904
IL-6, pg/mL	7.2 (3.6-12.7)	8.1 (4.6-14.0)	9.9 (4.4-29.5)	15.5 (7.4-39.3)	< 0.001
cTnI-adm, ng/mL	1.1 (0.2-4.5)	1.3 (0.2-4.9)	4.4 (0.6-9.7)	7.3 (1.2-17.1)	< 0.001
cTnI-peak, ng/mL	49.3 (14.3-137.6)	68.2 (31.4-143.7)	81.3 (34.9-169.4)	114.5 (53.3-253.1)	< 0.001
NT-proBNP, pg/mL	180.4 (84.8-596.3)	214.2 (68.1-685.4)	626.2 (185.1-1836.3)	817.8 (315.3-2183.0)	< 0.001
sST2, ng/mL	15.2 (13.1-17.8)	25.3 (22.2-27.9)	41.8 (36.1-48.9)	101.3 (78.8-153.9)	< 0.001

Values are mean ± SD, *n* (%), or median (interquartile range). cTnI-adm indicates cardiac troponin I on admission; Crea, creatinine; ER, emergency room; hs-CRP, high sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HbA1C, hemoglobin A1c; IL-6, Interleukin 6; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCI, percutaneous coronary intervention; STEMI, ST-segment elevated myocardial infarction; sST2, soluble suppression of tumorigenicity 2; TG, triglycerides; TC, total cholesterol; and UA, uric acid.

risk factors, the increasing sST2 represented a 2-fold risk of MACEs.

Since a significant difference in the incidence of MACEs was seen between the group with the highest quartile of sST2 and others (Figure 1), we further investigated the details of MACEs using 58.7 ng/mL of sST2 as a cut-off value (Table III). Most MACEs occurred after discharge (n = 15, 78.9%, $P < 0.001$). The incidence of mortality increased significantly as follow-up increased in patients whose baseline sST2 was high (P = 0.001). Moreover, the risk of mortality was significantly greater for patients with higher sST 2 regardless of whether they were in hospital or after discharge. There was no heart failure during hospitalization in our study. Patients with greater sST2 had more heart failure after discharge (P = 0.019). However, the correlation between sST2 and heart failure no longer existed after adjustment by other risk factors. Though MI were seen during follow-up, there was no significant difference between patients with different levels of sST2.

Baseline sST2 and mortality: All-cause death accounted for the majority of major events in MACEs (n = 10, 52.6%). Therefore, we analyzed the predictive value of sST2 for mortality. A total of 11 all-cause deaths were ob-

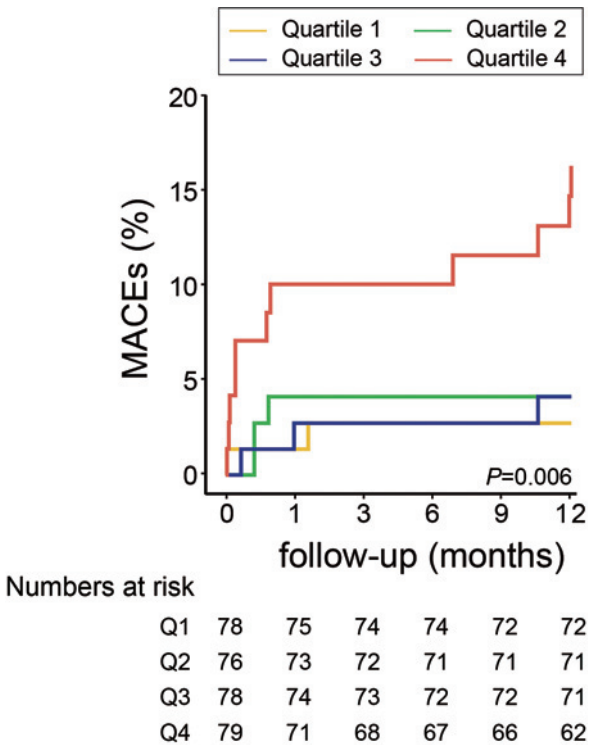

Figure 1. Incidences of MACEs across quartiles. Incidences of MACEs in each group are presented. Highest quartile of sST2 had more adverse events during follow-up compared with the other 3 groups.

served during 12 months of follow-up. Six died from cardiac problems, 3 of which died of an unknown cause. Two patients died from cerebrovascular accidents. Seven deaths occurred in patients with sST2 greater than 58.7 ng/mL (Table III). Notably, the all-cause deaths in patients with sST2 less than 58.7 ng/mL happened after discharge, whereas the mortality of patients with greater sST2 during hospitalization was similar to that after discharge.

When using an sST2 cut-off value of 58.7 ng/mL, a greater sST2, Killip classification, LVEF%, NT-proBNP, and hs-CRP were risk factors for mortality (Table IV). However, the predictive significance remained only for sST2 after adjustment. Patients with a greater sST2 had a 5-fold risk of mortality.

ROC analysis for sST2: sST2 was significantly associated with MACEs, mortality especially, in the study population. We performed ROC curve analysis to evaluate the prognostic efficiency of sST2. Figure 2A presents the ROC curve analysis of sST2 in predicting MACEs. The area under the curve (AUC) was 0.73 (95% CI 0.67-0.78, $P < 0.001$). When applying 58.7 ng/mL as the cut-off value, the sensitivity was 57.9% (95% CI 33.5%-79.7%) and the specificity was 73.9% (95% CI 68.3%-79.0%). As shown in Figure 2B, the predicted probability of predicting mortality yielded an AUC of 0.776 (95% CI 0.724-0.822, $P = 0.0029$). When applying 58.7 ng/mL as the cut-off value, the sensitivity was 70.0% (95% CI 34.8%-93.3%) and the specificity was 77.2% (95% CI 71.9%-81.9%).

No significant differences were seen between sST2

Table II. Predictors of MACEs by Univariate and Multivariate Cox Analysis

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
sST2	-	-	0.006	-	-	0.035
Q1 (6.2-20.1, ng/mL)	reference	-	-	reference	-	-
Q2 (20.3-32.2, ng/mL)	1.51	0.25-9.02	0.153	1.44	0.72-6.57	0.222
Q3 (32.3-57.2, ng/mL)	1.50	0.25-8.97	0.258	1.29	0.60-5.23	0.530
Q4 (58.7-559.7, ng/mL)	5.91	1.31-26.65	< 0.001	2.23	1.20-6.78	0.001
Age	1.07	1.02-1.12	0.005	1.04	0.98-1.08	0.161
Sex	1.24	0.41-3.73	0.706	0.81	0.21-2.32	0.558
Time from onset to ER	1.01	0.99-1.01	0.399	1.01	0.98-1.02	0.476
Hospitalization days	1.04	0.96-1.14	0.339	-	-	-
Infarction location	0.99	0.37-2.30	0.867	-	-	-
Number of affected vessels	1.16	0.65-2.08	0.617	-	-	-
Hypertension	1.09	0.78-1.71	0.431	-	-	-
Diabetes	1.04	0.93-1.77	0.160	-	-	-
Killip classification	2.28	1.63-3.18	< 0.001	1.57	0.76-2.29	0.223
LVEF	0.83	0.76-0.90	< 0.001	0.93	0.78-0.99	0.041
NT-proBNP	1.01	1.00-1.03	< 0.001	1.00	0.99-1.01	0.236
cTnI-adm	0.99	0.97-1.02	0.780	-	-	-
cTnI-peak	1.01	1.00-1.01	0.048	1.00	0.99-1.01	0.797
hs-CRP	1.01	1.01-1.02	0.002	1.00	0.99-1.01	0.901
IL-6	0.99	0.99-1.01	0.795	-	-	-

CI indicates confidential interval; cTnI-adm, cardiac troponin I on admission; ER, emergency room; hs-CRP, high sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IL-6, Interleukin 6; LVEF, left ventricular ejection fraction; MACEs, major adverse cardiac events; NT-proBNP, N-terminal pro B-type natriuretic peptide; and sST2, soluble suppression of tumorigenicity 2.

Table III. Incidence of MACEs

	sST2 < 58.7 ng/mL (n = 222)	sST2 ≥ 58.7 ng/mL (n = 73)	P value
MACEs			
Total	8 (3.6)	11 (15.1)	< 0.001
In-hospital	1 (0.5)	3 (4.1)	0.019
After-discharge	7 (3.1)	8 (11.0)	0.008
All-cause death			
Total	3 (1.4)	7 (9.6)	0.001
In-hospital	0 (0.0)	3 (4.1)	0.002
After-discharge	3 (1.4)	4 (5.5)	0.044
Heart failure			
Total	1 (0.5)	3 (4.1)	0.019
In-hospital	0 (0.0)	0 (0.0)	-
After-discharge	1 (0.5)	3 (4.1)	0.019
Non-fatal MI			
Total	4 (1.8)	1 (1.4)	0.801
In-hospital	1 (0.5)	0 (0.0)	0.566
After-discharge	3 (1.4)	1 (1.4)	0.985

MACEs indicates major adverse cardiac events; MI, myocardial infarction; and sST2, soluble suppression of tumorigenicity 2.

Table IV. Predictors of Mortality by Univariate and Multivariate Cox Analysis

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
sST2 ≥ 58.7 ng/mL	1.01	1.01-1.10	0.001	5.01	1.02-16.30	0.048
Age	1.05	0.98-1.12	0.113	1.04	0.96-1.11	0.154
Sex	1.16	0.26-5.44	0.856	0.89	0.15-4.76	0.827
Time from onset to ER	1.00	0.99-1.01	0.174	1.01	0.99-1.01	0.286
Hospitalization days	1.01	0.96-1.02	0.147	-	-	-
Infarction location	0.99	0.24-3.02	0.806	-	-	-
Number of affected vessels	1.27	0.55-2.95	0.582	-	-	-
Hypertension	1.77	0.73-2.68	0.690	-	-	-
Diabetes	1.04	0.71-2.90	0.339	-	-	-
Killip classification	2.61	1.68-4.06	< 0.001	1.26	0.61-2.29	0.639
LVEF	0.81	0.72-0.91	0.001	0.86	0.64-1.09	0.188
NT-proBNP	0.84	0.73-0.96	< 0.001	1.00	0.88-1.10	0.810
cTnI-adm	1.00	0.97-1.02	0.840	-	-	-
cTnI-peak	1.01	0.98-1.12	0.069	1.00	0.99-1.01	0.734
hs-CRP	1.01	1.00-1.01	< 0.001	1.01	0.98-1.02	0.073
IL-6	0.99	0.97-1.03	0.874	-	-	-

CI indicates confidential interval; cTnI-adm, cardiac troponin I on admission; ER, emergency room; hs-CRP, high sensitivity C-reactive protein; HR, hazard ratio; IL-6, Interleukin 6; LVEF, left ventricular ejection fraction; MACEs, major adverse cardiac events; NT-proBNP, N-terminal pro B-type natriuretic peptide; and sST2, soluble suppression of tumorigenicity 2.

and other markers when ROC curve analysis was employed for other risk factors that were associated with MACEs and mortality. Though sST2 ≥ 58.7 ng/mL had the highest specificity numerically, it failed to show a statistical improvement in predicting MACEs and mortality when compared with other markers. In addition, adding sST2 did not improve the prognostic efficiency of other markers.

Discussion

Here we report a prospective clinical trial of sST2 for prediction of clinical outcomes in STEMI patients receiving PPCI. Our study shows baseline sST2 levels predicted the incidence of MACEs in these patients during a 12-month follow-up. Increased sST2 levels were associated with an increasing risk of MACEs. Specifically, the cut-off value of 58.7 ng/mL for sST2 identified the patients at high risk of MACEs, even after adjustment for other risk factors. Furthermore, baseline sST2 ≥ 58.7 ng/mL predicted mortality with a sensitivity of 70.0% and a specificity of 77.2% using a US FDA approved high sensitivity assay. There were no significant differences in overall predictive efficiency between sST2 and other markers. Adding sST2 to other markers did not improve their prognostic efficiency either.

In the era of PCI, it is usually recommended that STEMI patients receive PPCI. However, adverse clinical

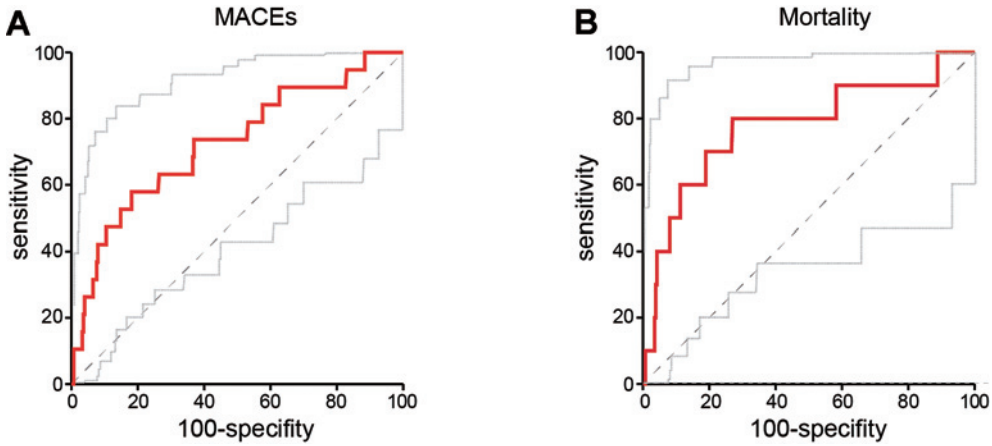

Figure 2. sST2 ROC curve analyses for MACEs and mortality. **A:** ST2 ROC curve analyses for MACEs. AUC 0.725, *P* = 0.0008, 95% CI 0.670-0.775. **B:** ST2 ROC curve analyses for mortality. AUC 0.776, *P* = 0.0029, 95% CI 0.724-0.822. Red line represents the ROC curve, and grey lines represent the 95% confidence intervals. MACEs indicates major adverse cardiovascular events; ROC, receiver operating characteristic; AUC, area under the curve; and CI, confidence interval.

outcomes such as death, heart failure, and others are still seen in patients after PPCI.[10] Other than the operation performance, STEMI patients with different age, cardiac function, and different health conditions present different risks of adverse outcomes before any treatment. Early risk stratification is required for an overall estimation and preventative therapeutic strategies thereafter even though the application of PPCI has reduced mortality by nearly 50%.[11] Being a member of the superfamily of IL-1 receptors, ST2L, the transmembrane form of ST2, binds with IL-33 to reduce the fibrosis and hypertrophy of tissue when overloaded. sST2, the soluble form of ST2, acts as a decoy receptor to decreased beneficial effect from IL-33/ST2L signaling by binding free IL-33. After Weinberg and colleagues first reported that sST2 increased in patients after MI,[12] studies found that released sST2 also participated in the processes of myocardial fibrosis and inflammation.[13,14] Thereafter, sST2 has been widely used in risk stratification for cardiovascular disease. Shimpo, *et al*. first reported sST2 predicted clinical outcomes in patients with acute myocardial infarction,[15] and a subsequent recommendation by guidelines that sST2 can be used for risk stratification and prognostication in patients with heart failure further emphasized its application.[16] Studies observed that sST2 not only added more comprehensive value to existed biomarkers for risk evaluation, but also predicted death and heart failure independently in STEMI patients.[17,18]

The revascularization from PPCI reduces the myocardial damage caused by ischemia in STEMI patients, whereas whether traditional biomarkers retain their predictive power for patients after PPCI remains unclear. Recently, two research groups have been focusing on the application of sST2 in patients undergoing PPCI. Wang and colleagues found the serum level of ST2 was an independent risk factor for MACEs in 1-year follow-up, and was positively correlated with the Gensini score.[19] Another study carried out by Yu and colleagues observed 38 MACCEs in 323 STEMI patients undergoing PPCI during 1-year follow-up.[20] Serum sST2 at baseline also predicted 1-year MACCE independently. Higher sST2 combined with higher NT-proBNP was associated with worst prognosis. The present study obtained similar conclusions that baseline sST2 levels were associated with MACEs in STEMI patients receiving PPCI. Baseline sST2 significantly predicted mortality after adjustment and such significance did not remain when applied to heart failure, which is in agreement with other studies reporting that sST2 is highly associated with mortality in STEMI patients.[21] In addition, we assessed the prognostic efficiency of sST2 using a US FDA approved high sensitivity assay in our study. Among all the markers significantly associated with clinical outcomes, sST2 ≥ 58.7 ng/mL provided the highest specificity in predicting either MACEs or mortality in the present study. A previous study from our group also observed 56.68 ng/mL of sST2 predicted MACEs within 30 days for STEMI patients.[22] The US FDA approved high sensitivity sST2 assay suggests that a cut-off value of 35 ng/mL will differentiate patients with cardiovascular disease at high risk of all-cause mortality. No specific cut-off value has yet been suggested for STEMI patients. Therefore, a cut-off of sST2 around 57 ng/mL may identify STEMI patients who are at high risk of MACEs with increased prognostic specificity even though they underwent PPCI. However, our study did not observe a significant improvement in adding sST2 to other markers. Further studies may focus on the application of this specific cut-off of sST2 in practice and provide more suggestions on combination of different markers.

Being a promising biomarker for risk stratification for STEMI patients, sST2 has more advantages other than the significant association between elevated levels and fibrosis and myocardial injury as follows: first, it is less affected by GFR. Second, the biological variability of sST2 is low. Third, sST2 levels respond well to the effective treatment.[23] Here, our study adds more evidence to the application of sST2 as a new predictive biomarker for the prognostication of adverse events in STEMI patients re-

ceiving PPCI. However, there are still several limitations: firstly, more male patients were included in our study due to the continuous recruitment of participants, which may lead to an unselected bias on gender. Secondly, only 12-month follow-up was performed in our study, which may need to be extended for further evaluation. Thirdly, there were only 295 patients included in our final analysis, which may eliminate some statistical significance due to the small number of participants.

In conclusion, the present study not only observed baseline sST2 presented myocardial injury and predicted MACEs independently, especially mortality, in patients receiving PPCI, but also showed that sST2 provided prognostic efficiency that was similar to other markers, and a cut-off value of 58.7 ng/mL identified the patients at greater risk of MACEs with the highest specificity. Since no previous studies have offered a prognostic cut-off value for sST2 in predicting MACEs in STEMI patients receiving PPCI in clinical practice, our study suggests an overall evaluation of cardiac damage based on a cut-off value of 58.7 ng/mL for sST2 will provide more confidence to physicians as well as better risk stratification to the patients.

Disclosures

Clinical trial: NCT02830217
Conflicts of interest: None.

References

1. Zhang K, Zhang XC, Mi YH, *et al*. Predicting value of serum soluble ST2 and interleukin-33 for risk stratification and prognosis in patients with acute myocardial infarction. Chin Med J (Engl) 2013; 126: 3628-31.
2. Chen C, Qu X, Gao Z, *et al*. Soluble ST2 in patients with nonvalvular atrial fibrillation and prediction of heart failure. Int Heart J 2018; 59: 58-63.
3. Xu SD, Su GH, Lu YX, *et al*. Elevated soluble ST2 and depression increased the risk of all-cause mortality and hospitalization in patients with heart failure. Int Heart J 2014; 55: 445-50.
4. Jenkins WS, Roger VL, Jaffe AS, *et al*. Prognostic value of soluble ST2 after myocardial infarction: A community perspective. Am J Med 2017; 130: 1112.e9-1112.e15.
5. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, *et al*. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013; 61: e78-140.
6. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, *et al*. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014; 35: 2541-619.
7. Kolh P, Windecker S, Alfonso F, *et al*; European Society of Cardiology Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, *et al*; Task Force on Myocardial Revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery; European Association of Percutaneous Cardiovascular Interventions. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur J Cardiothorac Surg 2014; 46: 517-92.
8. Endorsed by the Latin American Society of Interventional Cardiology; PCI WRITING COMMITTEE, Levine GN, Bates ER, Blankenship JC, *et al*; STEMI WRITING COMMITTEE, O'Gara PT, Kushner FG, Ascheim DD, *et al*; ACC/AHA TASK FORCE MEMBERS, Halperin JL, Levine GN, Anderson JL, *et al*. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial Infarction: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv 2016; 87: 1001-19.
9. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44: 837-45.
10. Laukkanen JA, Kunutsor SK, Niemela M, *et al*. All-cause mortality and major cardiovascular outcomes comparing percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: a meta-analysis of short-term and long-term randomised trials. Open Heart 2017; 4: e000638.
11. Puymirat E, Simon T, Steg PG, *et al*. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. JAMA 2012; 308: 998-1006.
12. Weinberg EO, Shimpo M, De Keulenaer GW, *et al*. Expression and regulation of ST2, an interleukin-1 receptor family member, in cardiomyocytes and myocardial infarction. Circulation 2002; 106: 2961-6.
13. Seki K, Sanada S, Kudinova AY, *et al*. Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarction through ST2 signaling. Circ Heart Fail 2009; 2: 684-91.
14. Sanchez-Mas J, Lax A, Asensio-Lopez Mdel C, *et al*. Modulation of IL-33/ST2 system in postinfarction heart failure: correlation with cardiac remodelling markers. Eur J Clin Invest 2014; 44: 643-51.
15. Shimpo M, Morrow DA, Weinberg EO, *et al*. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. Circulation 2004; 109: 2186-90.
16. Yancy CW, Jessup M, Bozkurt B, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013; 128: 1810-52.
17. O'Donoghue ML, Morrow DA, Cannon CP, *et al*. Multimarker risk stratification in patients with acute myocardial infarction. J Am Heart Assoc 2016; 5: e002586.
18. Sabatine MS, Morrow DA, Higgins LJ, *et al*. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation 2008; 117: 1936-44.
19. Wang YP, Wang JH, Wang XL, *et al*. Roles of ST2, IL-33 and BNP in predicting major adverse cardiovascular events in acute myocardial infarction after percutaneous coronary intervention. J Cell Mol Med 2017; 21: 2677-84.

20. Yu J, Oh PC, Kim M, *et al*. Improved early risk stratification of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention using a combination of serum soluble ST2 and NT-proBNP. PLoS One 2017; 12: e0182829.
21. Marino R, Magrini L, Orsini F, *et al*. Comparison between soluble ST2 and high-sensitivity troponin I in predicting short-term mortality for patients presenting to the emergency department with chest pain. Ann Lab Med 2017; 37: 137-46.
22. He L, Peng J, Zheng X, Liu CW, Su X. Correlation study between serum soluble ST2 level and the early clinical prognosis in patients with acute ST-elevation myocardial infarction. Chin Circ J 2017; 32: 41-5.
23. Díez J, Bayes-Genis A. Compelling benefit of soluble suppression of tumorigenicity-2 in post-myocardial infarction estimation of risk: The time is right for its routine use in the clinic. J Am Heart Assoc 2017; 6: e007665.