BMC Cardiovascular Disorders

RESEARCH

Open Access

Soluble suppression of tumorigenicity 2 associated with microvascular obstruction in patients with ST-segment elevation myocardial infarction

Xinjia Du[1†], Jiahua Liu[1†], Jingfang Zhou[1], Yanfei Ren[1], Nauman Gul[1], Lei Chen[2*] and Yuan Lu[1*]

Abstract

Background Microvascular obstruction (MVO) develops in approximately 50% of patients with ST-segment elevation myocardial infarction (STEMI) after undergoing percutaneous coronary intervention (PCI). MVO is strongly linked to inflammation, myocardial fibrosis, and adverse clinical outcomes. Soluble suppression of tumorigenicity 2 (sST2) serves as a biomarker for inflammation and myocardial fibrosis. Yet, the correlation between sST2 and MVO in STEMI patients has not been fully elucidated. This study attempts to evaluate the association between sST2 levels and MVO in STEMI patients following pPCI.

Methods In this retrospective study, 315 STEMI patients who underwent pPCI at the Affiliated Hospital of Xuzhou Medical University between June 2018 and August 2023 were included. Cardiac magnetic resonance imaging (CMR) was used to assess the characteristics of myocardial infarction and microvascular obstruction (MVO), while sST2 levels were measured upon admission.

Results The median time for completion of CMR after hospitalization was 5 (4, 6) days. Multivariate regression analysis showed that sST2 (OR 1.01, 95% CI 1.01–1.02, $p < 0.001$), peak high-sensitivity troponin T (OR 2.40, 95% CI 1.66–3.47, $p < 0.001$), peak high-C-reactive protein (OR 1.01, 95% CI 1.01–1.02, $p < 0.001$), left ventricular ejection fraction (OR 0.93, 95% CI 0.89– 0.98, $p = 0.009$) and age (OR 1.03, 95% CI 1.01– 1.05, $p = 0.042$)were independently associated with MVO.

Conclusion sST2 is associated with MVO after pPCI in STEMI patients. Incorporating soluble ST2 (sST2) into the risk model for MVO leads to significant improvement.

Keywords Microvascular obstruction, Soluble suppression of tumorigenicity 2, Myocardial infarction, Cardiovascular magnetic resonance

[†]Xinjia Du and Jiahua Liu contributed equally to this work.

*Correspondence:
Lei Chen
drleichen@tongji.edu.cn

Yuan Lu
drluyuan329@163.com
[1]Department of Cardiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China
[2]Department of Cardiology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China

The advantages and limitations of this paper

Advantages This is the first study to investigate the association between sST2 and MVO in patients with STEMI. The key findings of this study are as follows: First, sST2 was significantly correlated with MVO in STEMI patients; Second, incorporating sST2 into risk models significantly enhances their predictive capacity for MVO. This study suggests that ST2 can optimize hazard stratification, which provides a new insight into MVO. Therefore, sST2 may serve as a useful biomarker for identifying MVO after pPCI, allowing early identification of high-risk patients and optimizing risk stratification to improve long-term outcomes.

Limitations First, as a single-center retrospective study, this study suffers from unavoidable bias. We look forward to more subsequent optimization protocols to improve this study of ours. However, we adjusted these parameters in multi-factor regression analysis to reflect the situation of these people in the real world to some extent, because people with MVO normally have different ages. Furthermore, the limited sample size may restrict the applicability of the results. Therefore, future larger multicenter cohort studies are necessary to repeatedly validate these results. Third, since the study population exclusively consists of STEMI patients, the conclusions may not be directly applicable to other populations. Lastly, the exact pathological mechanisms by which sST2 contributes to MVO formation remain unclear and warrant further investigation through basic research. However, this study found correlations between sST2 and high-sensitivity C-reactive protein (hs-CRP) and extracellular volume (ECV), which somewhat validate the rationale and feasibility of this study.

Introduction

ST-segment elevation myocardial infarction (STEMI) stands out as one of the most severe forms of acute cardiovascular illness, often accompanied by high mortality rates and severe complications [1]. The incidence of microvascular obstruction (MVO) after primary percutaneous coronary intervention (pPCI) in STEMI patients can reach as high as 50%[(2)]. Mechanistically, a study has suggested that MVO is related to reperfusion injury, microthrombosis, endothelial cell damage, tissue edema, and inflammatory responses [2]. The occurrence of MVO can lead to left ventricular dysfunction, adverse left ventricular remodeling, and myocardial fibrosis, and it has been proven to be an independent predictor of major adverse cardiovascular events (MACE) in STEMI patients [3]. Therefore, identifying more risk factors associated with MVO will help in the early identification of high-risk patients, optimized risk stratification, and improved prognosis for STEMI patients.

Soluble suppression of tumorigenicity 2 (sST2) belongs to the interleukin-1 (IL-1) receptor family. After myocardial injury, the levels of sST2, acting as a decoy receptor for interleukin-33 (IL-33), are significantly elevated. Increased levels of sST2 can competitively bind to IL-33, thus blocking the cardioprotective effects of the IL-33/ST2L pathway and promoting both inflammatory responses and myocardial fibrosis [4]. The European Society of Cardiology has indicated that sST2, as a new generation biomarker, can be used for risk stratification, prognosis, and treatment guidance in heart failure [5]. sST2 exhibits low biological variability and a single threshold for detection, unaffected by renal function, age, body mass index (BMI), or other factors. Compared to N-terminal pro-B-type natriuretic peptide (NT-pro BNP), sST2 provides more consistent results compared to NT-pro BNP [6]. sST2 has been proven to be related to myocardial fibrosis, ventricular remodeling, heart failure, and new-onset atrial fibrillation in STEMI patients [4, 7–9]. In addition, a recent study showed that higher sST2 levels are closely related to the occurrence of no-reflow (TIMI ≤ 2) and poor prognosis in STEMI patients after pPCI [10]. However, the relationship between sST2 and MVO in STEMI patients remains unclear. This study aims to assess the correlation between sST2 and MVO in STEMI patients after pPCI.

Materials and methods

Study population

This single-center retrospective study consecutively included STEMI [11] patients who underwent pPCI at the Affiliated Hospital of Xuzhou Medical University between June 2018 and August 2023. All STEMI patients received aspirin and ticagrelor before surgery according to guidelines [11]. Inclusion criteria: aged > 18 years, successful pPCI within 12 h of symptom onset (TIMI ≥ 2), sST2 was measured upon admission, complete cardiac magnetic resonance imaging (CMR) during hospitalization. Exclusion criteria: estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2, malignant tumors or inflammatory diseases, previous myocardial infarction, prior heart failure, poor CMR quality or incomplete sequences. The requirement for signed written consent was waived owing to no risk to the patient in accordance with the relevant IRB regulatory guidelines. The Ethics Committee of Xuzhou Medical University Affiliated Hospital approved this study. The inclusion and exclusion criteria are shown in Fig. 1.

Clinical data collection

Patient data were collected from the hospital's medical record system, including height, weight, age, systolic and diastolic blood pressure, heart rate, smoking history, past medical history (hypertension, diabetes, stroke), and

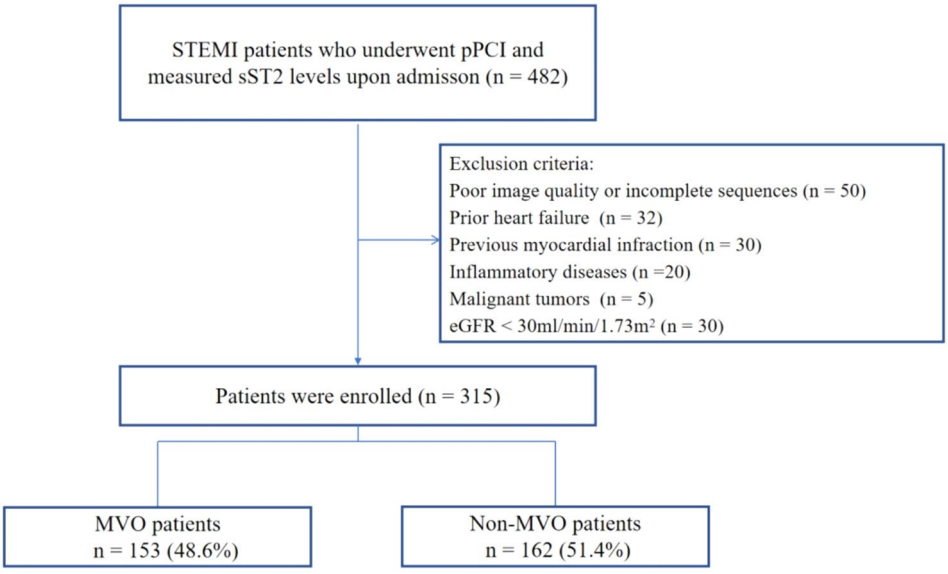

Fig. 1 Study flowchart

medications (statins, beta-blockers, ACEIs, ARBs, antiplatelet). During hospitalization, multiple blood tests were conducted, and the peak levels of high-sensitivity C-reactive protein (hs-CRP), high-sensitivity troponin T (hs-TnT), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were documented. sST2 levels were measured upon admission for all patients. sST2 was evaluated utilizing an immunoassay kit (provided by Springbio, Guangzhou, China) according to the protocol. The infarct-related artery (IRA) and coronary flow grade (TIMI) were documented based on the results of the coronary angiography.

Cardiac MRI-related parameters

Each patient underwent a CMR examination at a median of 5 days (IQR 4, 6) post-admission. The patients were supine, and images were obtained under the breath-hold using a digital stream(dS) anterior phased-array surface coil and an integrated dS posterior spine matrix coil. The standardized imaging protocol was implemented according to the current recommendations [12]. The parameters were as follows: slice thickness 7 mm; echo time (TE)1.4 ms; repetition time (TR) 2.8 ms; field of view (FoV) 300×300 mm, matrix 280×240). Modification as a standard imaging protocol, cine images on short axes covering the LV (10–12 slices) were collected after the administration of gadolinium-based contrast agent (0.1 mmol/kg), and delay enhanced images (Late Gadolinium Enhancement; LGE) were obtained after 10–15 min.

The CMR images were processed with CVI42 (version 5.13.5, Circle Cardiovascular Imaging, Canada). In late gadolinium enhancement (LGE) images, the endocardial and epicardial contours were manually outlined. In CMR-LGE images, areas with a signal intensity greater than five standard deviations above normal myocardium were defined as the LGE region. MVO was defined as a dark area surrounded by the constantly visible hyperintensity zone and located at the same position within the cardiac wall on each SSFP image during the complete cardiac cycle. MVO mass was expressed as a percentage of total LV mass. Extracellular volume (ECV) was calculated using T1 mapping. Endocardial, epicardial, and blood pool contours were traced, and average relaxation times were measured, avoiding the edges and papillary muscles. The formula used to calculate ECV: ECV = (1−HCT) × (1/myocardial enhanced T1−1/myocardial native T1)/ (1/blood pool–enhanced T1−1/blood pool native T1)(Fig. 2).

Statistical analysis

Statistical analysis was conducted using SPSS version 26.0 (Inc, Chicago, IL, USA) and R 4.1.2 (https://cran.r-project.org). The Kolmogorov-Smirnov test was used to evaluate the normality of data distribution. Continuous variables following a normal distribution were represented as mean ± standard deviation and assessed using the Student's t-test. Non-normally distributed continuous variables were expressed as median (Q1, Q3) and subjected to analysis using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and analyzed using the chi-square test. Spearman's correlation analysis was used to assess the correlation between sST2 and related continuous variables. All variables were analyzed using univariate logistic regression, and variables with $P<0.1$ in univariate regression were included in multivariate logistic regression to identify independent

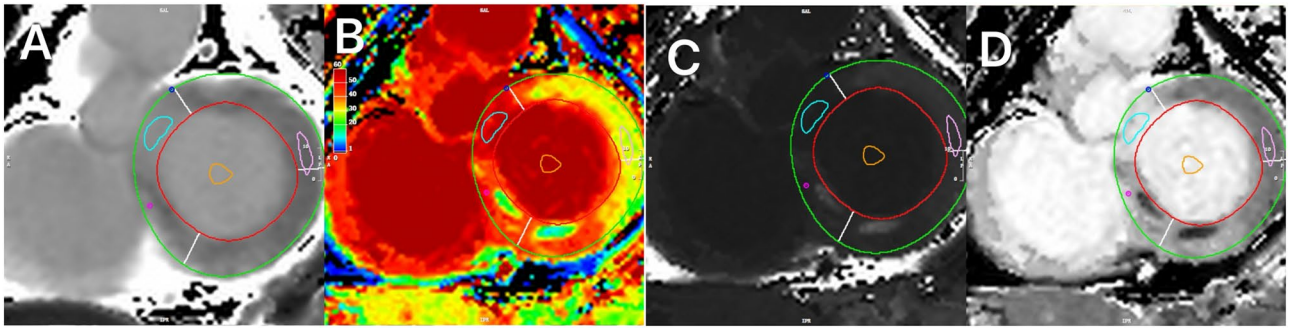

Fig. 2 Extracellular volume (ECV) acquisition. (**A**) Native T1 map; (**B**) generated ECV images; (**C**) enhanced T1 map; (**D**) the distribution coefficient λ that generates the image; circles indicate different regions

predictors of MVO. Restricted cubic splines(RCS) were used to explore the dose-response relationship between sST2 and MVO. Receiver operating characteristic (ROC) curves were used to evaluate the sensitivity and specificity of sST2 in predicting MVO. Comparisons of the AUC (area under the curve) of combined variables were performed using the Delong test.

Results

Baseline data comparison between groups

As shown in Table 1, the laboratory findings indicated that compared to the Non-MVO group, the MVO group had significantly higher levels of hs-TnT, NT-proBNP, hs-CRP, age and sST2, with statistically significant differences ($P<0.05$). Significant differences were observed in cardiovascular angiographic indicators when pre-TIMI≤1 ($p=0.003$) was considered. In terms of CMR indicators, there were significant differences observed in LV mass, LV end-diastolic volume index (LVEDVi), LV end-systolic volume index (LVESVi), and left ventricular ejection fraction (LVEF) ($p<0.05$).

Correlation between sST2 and other indicators

In Table 2, Spearman correlation analysis was utilized to evaluate the relationship between sST2 and other variables. The results indicated that sST2 was significantly correlated with several known predictors of MVO, including moderate correlations with hs-TnT and ECV ($n=219$), weak correlations with hs-CRP, NT-proBNP, LVEF, TIMI≤1, LV-mass, LVEDVi, and LVESVi.

Logistic regression analysis results

According to Table 3, univariate logistic regression analysis revealed that MVO was significantly correlated with LVEF, Pre-TIMI, Peak hs-TnT, sST2, age, NT-proBNP, Peak hs-CRP, LV-mass, LVEDVi, and LVESVi ($p<0.05$). Subsequently, variables with $P<0.1$ were included in a stepwise forward multivariate logistic regression analysis, and the results showed that age, Peak hs-TnT, Peak hs-CRP, LVEF, and sST2 were independent predictors of MVO ($p<0.001$).

ROC curve analysis

ROC curves based on multivariate logistic regression analysis results showed that sST2, Peak hs-CRP, age, LVEF and Peak hsTnT had significant predictive value for MVO (as shown in Fig. 3 and Table 4). The sensitivity and specificity of sST2 in predicting MVO were 0.497 and 0.901. The sensitivity and specificity of peak hsTnT were 0.712 and 0.741, The sensitivity and specificity of age in predicting MVO were 0.425 and 0.716, The sensitivity and specificity of Peak hs-CRP in predicting MVO were 0.765 and 0.525, The sensitivity and specificity of LVEF in predicting MVO were 0.804 and 0.469, respectively. As shown in Fig. 4, adding sST2 to the conventional model (Peak hs-TnT+Peak hs-CRP+LVEF+age) (AUC=0.804) significantly improved the predictive value of the traditional model. The AUC of the new model was 0.847, with sensitivity and specificity of 0.876 and 0.698. The AUC of the two models is significantly different, and the prediction ability of the new model is better than that of the traditional model, and the difference is statistically significant. (z=2.719, $p=0.007$). The dose-response relationship between sST2 and MVO was shown in Fig. 5. A nonlinear dose-response relationship was initially observed between sST2 and MVO (p for nonlinear=0.023). However, after asjusting Peak hs-TnT, Peak hs-CRP, age, LVEF and, a linear dose-response relationship between sST2 and MVO (p for nonlinearity=0.249) was identified, indicating that the risk of MVO rises with higher levels of sST2.

Discussion

To the best of our knowledge, this is the inaugural study examining the connection between sST2 and MVO in patients diagnosed with STEMI. The main discoveries of this research are as follows: Firstly, sST2 was significantly correlated with MVO in STEMI patients; Secondly, the

Table 1 Baseline data comparison between groups

Variables	Non MVO (*n* = 162)	MVO (*n* = 153)	*P*
Age, (years)	55.94 ± 11.83	59.73 ± 11.21	0.004
BMI, (kg/m^2)	26.01 ± 3.41	26.69 ± 3.64	0.089
Systolic blood pressure, (mm/Hg)	127.36 ± 20.64	126.90 ± 18.27	0.835
Diastolic blood pressure, (mm/Hg)	79.64 ± 13.10	80.20 ± 12.52	0.702
Heart rate, (times/min)	78.19 ± 12.37	78.96 ± 13.14	0.590
Peak hsTnT, (ng/L)	2259.50 (1049.50, 3736.25)	6323.00 (3229.00, 10000.00)	<0.001
Peak NTproBNP, (pg/mL)	1095.37 (638.47, 1923.33)	1430.00 (914.80, 2445.88)	0.002
Peak hs-CRP, (mg/L)	19.30 (8.27, 40.98)	38.30 (21.40, 77.30)	<0.001
TC, (mmol/L)	1.71 ± 1.16	1.78 ± 1.51	0.660
TG, (mmol/L)	4.35 ± 1.09	4.31 ± 1.05	0.690
LDL-C, (mmol/L)	2.80 ± 1.19	2.80 ± 0.91	0.946
HDL-C, (mmol/L)	0.96 ± 0.23	0.96 ± 0.29	0.939
eGFR, (mL/min/1.73 m^2)	107.80 ± 16.08	106.55 ± 14.95	0.475
LVEF, (%)	54.22 ± 6.68	50.42 ± 6.15	<0.001
sST2,(ng/ml)	37.31 (23.49, 53.25)	78.63 (40.59, 150.95)	<0.001
Male, n(%)	146 (90.12)	131 (85.62)	0.22
Smoking, n(%)	85 (52.47)	88 (57.52)	0.368
Hypertension, n(%)	77 (47.53)	76 (49.67)	0.704
Diabetes, n(%)	26 (16.05)	18 (11.76)	0.273
Stroke, n(%)	13 (8.02)	19 (12.42)	0.197
Killip class ≥ 2, n(%)	19 (11.73)	17 (11.11)	0.863
IRA-LCX, n(%)	19 (11.73)	24 (15.69)	0.307
IRA-LAD, n(%)	75 (46.30)	66 (43.14)	0.573
IRA-RCA, n(%)	68 (41.98)	63 (41.18)	0.886
Proximal segment occlusion, n(%)	108 (66.67)	113 (73.86)	0.163
Pre-TIMI ≤ 1, n(%)	119 (73.46)	133 (86.93)	0.003
Stent number, n(%)	0.96 ± 0.55	0.94 ± 0.52	0.795
Post-procedural TIMI = 2, n(%)	2 (1.23)	5 (3.27)	0.400
Stent number = 0, n(%)	28 (17.28)	25 (16.34)	0.823
Stent number = 1, n(%)	113 (69.75)	112 (73.20)	0.498
Stent number = 2, n(%)	21 (12.96)	16 (10.46)	0.490
LV-mass, (g)	104.41 ± 28.75	112.74 ± 31.43	0.015
LVEDV, (ml)	135.85 ± 37.52	149.40 ± 43.19	0.003
LVESV, (ml)	73.25 ± 28.53	90.40 ± 36.02	<0.001
Statins, n(%)	157 (96.91)	146 (95.42)	0.49
Sacubitril Sodium Tablets/ACEI/ARB, n(%)	84 (51.85)	86 (56.21)	0.438
β-blockers, n(%)	137 (84.57)	133 (86.93)	0.55
Spirolactone, n(%)	4 (2.47)	7 (4.58)	0.309
Antiplatelet drug, n(%)	162 (100)	153 (100)	1

BMI = body mass index; LAD = left atrium dimension; LVEF = left ventricular ejection fraction; TC = Serum total cholesterol; TG = Serum triglyceride; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; NT-proBNP = N-terminal pro B-type natriuretic peptide; hsTnT = high-sensitivity troponin T; peak hs-CRP = peak high sensitivity c-reactive protein; eGFR = estimated glomerular filtration rate; MVO = microvascular obstruction; hs-CRP, highly sensitive C-reactive protein; LCX = left circumflex branch; LAD = left anterior descending branch; RCA = right coronary artery; TIMI = thrombolysis in myocardial infarction; LV-mass = left ventricular mass; LVEDV = left ventricular end-diastolicvolume; LVESV = left ventricular end-systolicvolume; sST2 = soluble growth stimulator gene 2 protein; ARB = angiotensin II receptor antagonist; ACEI = angiotensin-converting enzyme inhibitors

Table 2 Correlation between sST2 and predictive indicators of MVO

Parameter	Correlation Coefficient (*r*)	*p*-value
peak hsTnT, (ng/L)	0.327	< 0.001
Peak NT-proBNP, (pg/mL)	0.163	0.004
LVEF, (%)	-0.119	0.035
ECV	0.446	< 0.001
hs-CRP, (mg/L)	0.174	0.002
Pre-TIMI ≤ 1	0.143	0.011
LV-mass, (g)	0.104	0.066
LVEDV, (ml)	0.196	< 0.001
LVESV, (ml)	0.274	< 0.001

hsTnT = high-sensitivity troponin T; NT-proBNP = N-terminal pro B-type natriuretic peptide; LVEF = left ventricular ejection fraction; TIMI = thrombolysis in myocardial infarction; LV-mass = left ventricular mass; LVEDV = left ventricular end-diastolicvolume; Extracellular volume (ECV), LVESV = left ventricular end-systolicvolume

addition of sST2 to risk models significantly improves their ability to predict MVO.

Although the prognosis of STEMI patients has significantly improved due to the widespread use of pPCI in recent decades, studies have shown that approximately 50% of STEMI patients still experience MVO after pPCI [13]. A large body of literature indicates that MVO leads to adverse left ventricular remodeling, myocardial fibrosis, and poor outcomes for STEMI patients [7, 14]. Formation of MVO is strongly associated with heightened inflammatory activation and myocardial fibrosis. In recent times, sST2 has emerged as a promising inflammatory and myocardial fibrosis biomarker, which has been proven to predict mortality in various cardiovascular diseases, including acute heart failure, chronic heart failure,

Table 3 Logistic regression analysis

Variables	Univariate Logistic Regression Analysis		Multivariate Logistic Regression Analysis	
	P	OR (95%CI)	P	OR (95%CI)
Age, (years)	0.004	1.03 (1.01 ~ 1.05)	0.042	1.03 (1.01 ~ 1.05)
BMI, (kg/m^2)	0.091	1.06 (0.99 ~ 1.13)	0.226	1.05 (0.97 ~ 1.14)
Systolic blood pressure, (mm/Hg)	0.835	1.00 (0.99 ~ 1.01)		
Diastolic blood pressure, (mm/Hg)	0.701	1.00 (0.99 ~ 1.02)		
Heart rate, (Times/min)	0.589	1.00 (0.99 ~ 1.02)		
PeakhsTnT, (ng/L)	< 0.001	3.16 (2.32 ~ 4.31)	< 0.001	2.40 (1.66 ~ 3.47)
PeakNTproBNP, (pg/mL)	0.004	1.47 (1.13 ~ 1.91)	0.007	0.72 (0.50 ~ 1.04)
TC, (mmol/L)	0.659	1.04 (0.88 ~ 1.23)		
TG, (mmol/L)	0.689	0.96 (0.78 ~ 1.18)		
LDL-C, (mmol/L)	0.964	1.00 (0.82 ~ 1.24)		
HDL-C, (mmol/L)	0.939	0.97 (0.42 ~ 2.25)		
Fasting blood glucose, (mmol/L)	0.098	0.89 (0.77 ~ 1.02)		
Peak hs-CRP, (mg/L)	< 0.001	1.02 (1.01 ~ 1.02)	0.025	1.01 (1.01 ~ 1.02)
eGFR, (mL/min/1.73 m^2)	0.474	0.99 (0.98 ~ 1.01)		
LVEF, (%)	< 0.001	0.91(0.88 ~ 0.95)	0.009	0.93 (0.89 ~ 0.98)
Proximal segment occlusion, n(%)	0.164	1.41 (0.87 ~ 2.30)		
Stent number, n (%)	0.795	0.95 (0.62 ~ 1.43)		
Stent number, *n* = 0(%)	0.823	0.93 (0.52 ~ 1.69)		
Stent number, *n* = 1(%)	0.498	1.18 (0.73 ~ 1.93))		
Stent number, *n* = 2(%)	0.491	0.78 (0.39 ~ 1.57)		
IRA-LAD, n(%)	0.573	0.88 (0.56 ~ 1.37)		
Pre-TIMI ≤ 1, n(%)	0.003	2.40 (1.34 ~ 4.31)	0.188	1.63 (0.79 ~ 3.38)
Post-procedural TIMI = 2, n(%)	0.239	2.70 (0.52 ~ 14.14)		
Stroke, n(%)	0.2	1.63 (0.77 ~ 3.42)		
Male, n(%)	0.222	0.65 (0.33 ~ 1.30)		
Hypertension, n(%)	0.704	1.09 (0.70 ~ 1.70)		
Smoking, n(%)	0.368	1.23 (0.79 ~ 1.91)		
Diabetes, n(%)	0.275	0.70 (0.37 ~ 1.33)		
Killip class ≥ 2, n(%)	0.863	0.94 (0.47 ~ 1.89)		
sST2, (ng/ml)	< 0.001	1.02 (1.01 ~ 1.02)	< 0.001	1.01(1.01 ~ 1.02)
LV-mass, (g)	0.016	1.01 (1.01 ~ 1.02)	0.565	1.00 (0.99 ~ 1.02)
LVEDV, (ml)	0.004	1.01 (1.01 ~ 1.01)	0.418	0.99 (0.98 ~ 1.01)
LVESV, (ml)	< 0.001	1.02 (1.01 ~ 1.03)	0.386	1.01 (0.99 ~ 1.03)

BMI = body mass index; LAD = left atrium dimension; LVEF = left ventricular ejection fraction; TC = Serum total cholesterol; TG = Serum triglyceride; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; NT-proBNP = N-terminal pro B-type natriuretic peptide; hsTnT = high-sensitivity troponin T; peak-hsCRP = peak high sensitivity c-reactive protein; eGFR = estimated glomerular filtration rate; MVO = microvascular obstruction; hs-CRP, highly sensitive C-reactive protein; LCX = left circumflex branch; LAD = left anterior descending branch; RCA = right coronary artery; TIMI = thrombolysis in myocardial infarction; LV-mass = left ventricular mass; LVEDV = left ventricular end-diastolicvolume; LVESV = left ventricular end-systolicvolume; sST2 = soluble growth stimulator gene 2 protein

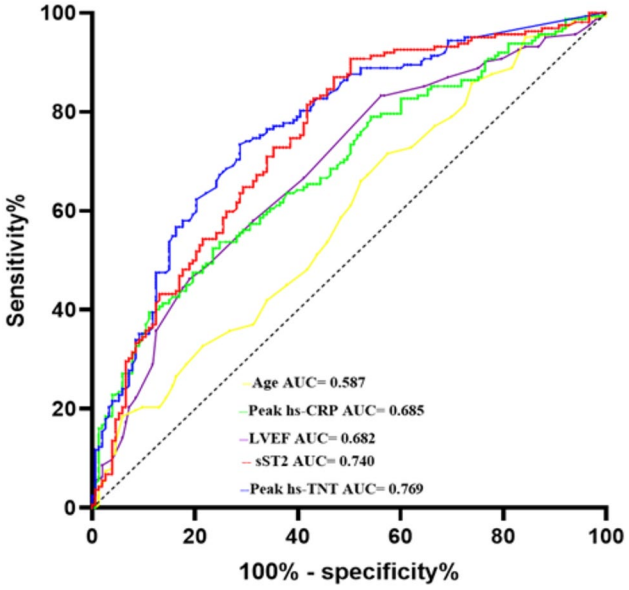

Fig. 3 Receiver operating characteristic analysis (ROC) for identifying MVO. sST2 = Soluble Suppression of Tumorigenicity 2; peak hs-TNT = Peak high-sensitivity troponin T; peak hs-CRP = peak high sensitivity c-reactive protein; LVEF = left ventricular ejection fraction

and STEMI [15–17]. ST2 is a member of the interleukin (IL-1) receptor family, with two main forms associated with cardiovascular diseases: ST2L and sST2. The IL-33/ST2L signaling pathway has protective effects against inflammation and myocardial fibrosis. Myocardial injury in STEMI patients leads to an elevation in blood levels of sST2, which competitively binds to IL-33 and prevents it from interacting with ST2L. This process inhibits the defense mechanisms, inducing inflammation and myocardial fibrosis [4, 16]. In this study, we found that sST2 is significantly associated with MVO after pPCI in STEMI patients. Although the exact mechanisms remain unclear, several potential explanations exist. First, sST2 has been shown to play a role in the release of pro-inflammatory cytokines by macrophages, which may trigger an inflammatory response and the production of reactive oxygen species after STEMI, leading to no-reflow, myocardial dysfunction, and myocardial fibrosis, further increasing sST2 levels [4, 18, 19]. Second, sST2 may activate interleukin-6 (IL-6) to promote inflammation, leading to increased levels of tumor necrosis factor-α (TNF-α) and hs-CRP. This inflammatory response may cause

Table 4 ROC curve analysis

	AUC	95% CI	*P*	Cut-off	Sensitivity	Specificity
sST2	0.744	0.690–0.799	< 0.001	88.105	0.497	0.901
Peak hs-TNT	0.769	0.716–0.821	< 0.001	3528.5	0.712	0.741
Age	0.587	0.524–0.649	0.008	63.5	0.425	0.716
Peak hs- crp	0.685	0.627–0.744	< 0.001	20.25	0.765	0.525
LVEF	0.682	0.625–0.741	< 0.001	54.16	0.804	0.469

sST2 = souble growth gene 2 protein; hsTnT = high-sensitivity troponin T; LVEF = left ventricular ejection fraction; peak hs-crp = peak high sensitivity c-reactive protein; ROC = receiver operating characteristic; AUC = area under the curve; CI = confidence interval

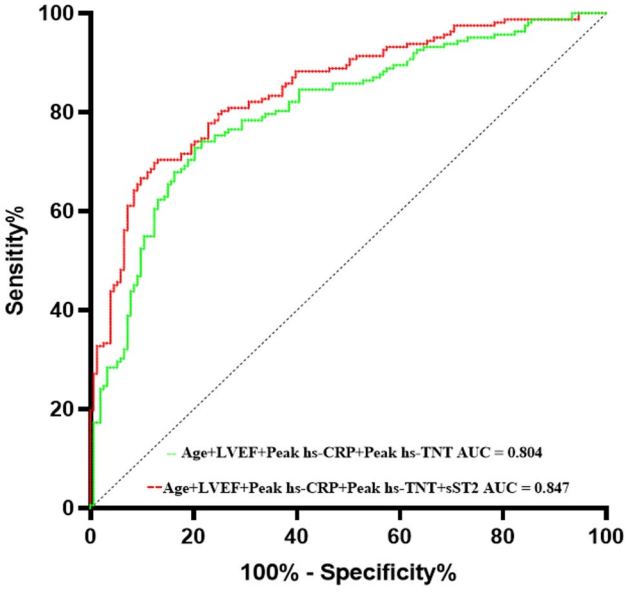

Fig. 4 Receiver operating characteristic analysis (ROC) of combined parameters for identifying MVO. sST2 = Soluble Suppression of Tumorigenicity 2; Peak hs-TNT = peak high-sensitivity troponin T; Peak hs-CRP = peak high sensitivity c-reactive protein; LVEF = left ventricular ejection fraction

endothelial damage, creating a vicious cycle of inflammation and contributing to MVO formation [4, 18]. Third, sST2 can predict adverse left ventricular remodeling, inflammation, and myocardial fibrosis, processes in which inflammation and myocardial fibrosis play key roles in the formation of MVO [18, 20]. Finally, Mustafa Umut Somuncu et al. demonstrated that sST2 is an independent predictor of postoperative absence of refluxation (TIMI 0,1,2) in STEMI patients [10]. No reflow is closely related to MVO, so this may further explain the correlation between sST2 and MVO. Additionally, we found sST2 was significantly correlated with LVEF, Pre-TIMI, Peak hs-TnT, sST2, age, NT-proBNP, Peak hs-CRP, LV-mass, LVEDVi, and LVESVi. These markers have all been shown to be associated with MVO risk, partially explaining the results of this study. Interestingly, we also found a correlation between sST2 and ECV and hs-CRP. What is known is that ECV and hs-CRP are recognized markers of myocardial fibrosis and inflammatory response [21, 22], respectively. This further explains the results of this study (see Table 2).

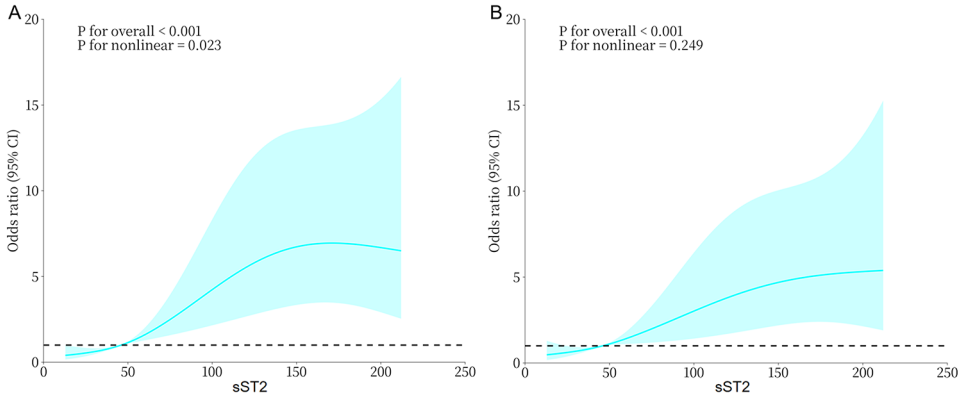

Fig. 5 Dose-response relationship between sST2 and MVO in patients with STEMI. (**A**) unadjusted dose-response relationship between sST2 and MVO; (**B**) adjusted dose-response relationship between sST2 and MVO

Both age, Peak hs-TNT, Peak hs-CRP and LVEF have been demonstrated to be related to MVO [23, 24]. This study aligns with these findings, confirming that age, Peak hs-CRP, Peak hs-TNT and LVEF are independent predictors of MVO. Moreover, tincorporating sST2 into a model that already includes age, Peak hs-CRP, Peak hs-TNT and LVEF markedly improves the predictive ability for MVO. Our study suggests that ST2 can optimize hazard stratification, which provides a new insight into MVO. Therefore, sST2 may serve as a useful biomarker for identifying MVO after pPCI, allowing early identification of high-risk patients and optimizing risk stratification to improve long-term outcomes.

Limitations

First, as a single-center retrospective study, this study suffers from unavoidable bias. We look forward to more subsequent optimization protocols to improve this study of ours. However, we adjusted these parameters in multifactor regression analysis to reflect the situation of these people in the real world to some extent, because people with MVO normally have different ages. Furthermore, the limited sample size may restrict the applicability of the results. Therefore, future larger multicenter cohort studies are necessary to repeatedly validate these results. Third, since the study population exclusively consists of STEMI patients, the conclusions may not be directly applicable to other populations. Lastly, the exact pathological mechanisms by which sST2 contributes to MVO formation remain unclear and warrant further investigation through basic research. However, this study found correlations between sST2 and high-sensitivity C-reactive protein (hs-CRP) and extracellular volume (ECV), which somewhat validate the rationale and feasibility of this study.

Conclusion

sST2 is significantly associated with MVO in STEMI patients following pPCI. Including sST2 in the risk model for MVO could greatly enhance its predictive accuracy.

Acknowledgements
Not applicable.

Author contributions
Xinjia Du: Writing -original draft. Jiahua Liu: Data curation. Jingfang Zhou: Data curation. Yanfei Ren: Data curation. Yixuan Wu: Data curation. Lei Chen: Writing–review & editing. Yuan Lu: Writing–review & editing.

Funding
This work was partly supported by China Postdoctoral Science Foundation funded project, the 68th batch of surface projects (No. M681738) and Jiangsu Provincial Health Commission Medical Research Project (No. M2021046).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The requirement for signed written consent was waived owing to no risk to the patient in accordance with the relevant IRB regulatory guidelines. This study was approved by the Ethics Committee of Xuzhou Medical University Affiliated Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

Received: 10 October 2024 / Accepted: 21 November 2024
Published online: 30 November 2024

References

1. Shaya GE, Leucker TM, Jones SR, Martin SS, Toth PP. Coronary heart disease risk: low-density lipoprotein and beyond. Trends Cardiovasc Med. 2022;32(4):181–94.
2. de Waha S, Patel MR, Granger CB, Ohman EM, Maehara A, Eitel I, et al. Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. Eur Heart J. 2017;38(47):3502–10.
3. Germain S, Bochaton T, Lassus J, Paccalet A, Derimay F, Rioufol G et al. Association of myocardial hemorrhage and persistent microvascular obstruction

with circulating inflammatory biomarkers in STEMI patients. PLoS ONE. 2021;16(1).
4. Gerber Y, Weston SA, Enriquez-Sarano M, Jaffe AS, Manemann SM, Jiang R et al. Contemporary risk stratification after myocardial infarction in the community: performance of scores and Incremental Value of Soluble suppression of Tumorigenicity-2. J Am Heart Association. 2017;6(10).
5. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147–e239.
6. Januzzi JL, Mebazaa A, Di Somma S. ST2 and prognosis in acutely decompensated heart failure: the International ST2 Consensus Panel. Am J Cardiol. 2015;115(7 Suppl):B26–31.
7. Broch K, Ueland T, Nymo SH, Kjekshus J, Hulthe J, Muntendam P, et al. Soluble ST2 is associated with adverse outcome in patients with heart failure of ischaemic aetiology. Eur J Heart Fail. 2014;14(3):268–77.
8. Aldous SJ, Richards AM, Troughton R, Than M. ST2 has diagnostic and prognostic utility for all-cause mortality and heart failure in patients presenting to the Emergency Department with chest Pain. J Card Fail. 2012;18(4):304–10.
9. Zhao T-t, Pan T-j, Yang Y-b, Pei X-y, Wang Y. Association of soluble suppression of tumorigenicity 2 protein with new-onset atrial fibrillation in patients with acute ST-segment elevation myocardial infarction undergoing primary PCI. Front Cardiovasc Med. 2023;10.
10. Somuncu MU, Akgun T, Cakır MO, Akgul F, Serbest NG, Karakurt H, et al. The elevated Soluble ST2 predicts No-Reflow Phenomenon in ST-Elevation myocardial infarction undergoing primary percutaneous coronary intervention. J Atheroscler Thromb. 2019;26(11):970–8.
11. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. Eur Heart J. 2008;29(23):2909–45.
12. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, Captur G, Francois CJ, Jerosch-Herold M et al. Reference ranges (normal values) for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. J Cardiovasc Magn Reson. 2020;22(1).
13. Zhao J, Cheng W, Dai Y, Li Y, Feng Y, Tan Y et al. Excessive accumulation of epicardial adipose tissue promotes microvascular obstruction formation after myocardial ischemia/reperfusion through modulating macrophages polarization. Cardiovasc Diabetol. 2024;23(1).
14. Bière L, Garcia G, Guillou S, Larcher F, Furber A, Willoteaux S, et al. ST2 as a predictor of late ventricular remodeling after myocardial infarction. Int J Cardiol. 2018;259:40–2.
15. Tymińska A, Kapłon-Cieślicka A, Ozierański K, Budnik M, Wancerz A, Sypień P, et al. Association of Galectin-3 and Soluble ST2, and their changes, with Echocardiographic Parameters and Development of Heart Failure after ST-Segment Elevation myocardial infarction. Dis Markers. 2019;2019:1–12.
16. Dudek M, Kałużna-Oleksy M, Migaj J, Straburzyńska-Migaj E. Clinical value of soluble ST2 in cardiology. Adv Clin Experimental Med. 2020;29(10):1205–10.
17. Metra M, Tomasoni D, Adamo M, Bayes-Genis A, Filippatos G, Abdelhamid M, et al. Worsening of chronic heart failure: definition, epidemiology, management and prevention. A clinical consensus statement by the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2023;25(6):776–91.
18. Wang YP, Wang JH, Wang XL, Liu JY, Jiang FY, Huang XL, et al. Roles ofST2,IL-33 andBNPin predicting major adverse cardiovascular events in acute myocardial infarction after percutaneous coronary intervention. J Cell Mol Med. 2017;21(11):2677–84.
19. Călburean P-A, Lupu S, Huțanu A, Oprica M, Opriș DR, Stan A et al. Natriuretic peptides and soluble ST2 improves echocardiographic diagnosis of elevated left ventricular filling pressures. Sci Rep. 2024;14(1).
20. Gruzdeva O, Dyleva Y, Uchasova E, Akbasheva O, Karetnikova V, Kashtalap V, et al. Biological markers and cardiac remodelling following the myocardial infarction. Aging. 2019;11(11):3523-35.
21. Erik B, Schelbert SMT, CGM, WJC, JEL, AJB PK et al. Myocardial extravascular extracellular volume fraction measurement by gadolinium cardiovascular magnetic resonance in humans: slow infusion versus bolus. 2011, 13:16.
22. Takahashi T, Anzai T, Kaneko H, Mano Y, Anzai A, Nagai T, et al. Increased C-reactive protein expression exacerbates left ventricular dysfunction and remodeling after myocardial infarction. Am J Physiol Heart Circ Physiol. 2010;299(6):H1795–804.
23. Younger JF, Plein S, Barth J, Ridgway JP, Ball SG, Greenwood JP. Troponin-I concentration 72 h after myocardial infarction correlates with infarct size and presence of microvascular obstruction. Heart. 2006;93(12):1547–51.
24. Wu KC. CMR of microvascular obstruction and hemorrhage in myocardial infarction. 2012;14:68.

Publisher's note