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Prediction of myocardial ischemia–reperfusion injury post-PCI: role of sST2 levels in STEMI patients

Wenjing Che[1*], Yubin Jin[1], Shumin Chang[1], Yihan Sun[1], Aijie Hou[1*] and Chengfu Wang[1]

Abstract

Background Myocardial ischemia–reperfusion injury (MIRI) after ST-segment elevation myocardial infarction (STEMI) significantly impacts clinical outcomes. However, only a few studies have examined its clinical predictors and prognostic biomarkers.

Methods Patients with STEMI who received percutaneous coronary intervention (PCI) at Liaoning Provincial People's Hospital between 2020 and 2021 were enrolled in the study. Based on a thorough evaluation of clinical features, which included data obtained from intraoperative angiography and inpatient monitoring, patients were divided into the MIRI group and the non-MIRI group. Upon admission, serum solube growth stimulation expressed gene 2 protein (sST2) levels were assessed, and follow-up examinations were conducted for the patients.

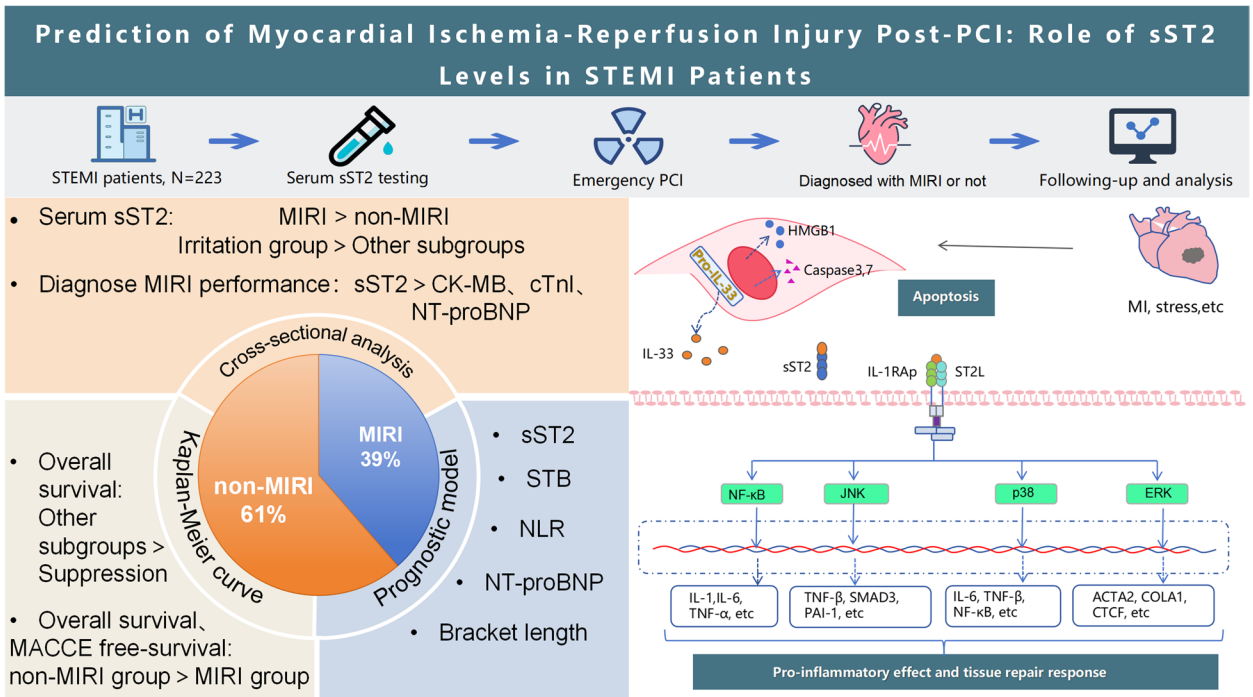
Results Patients with MIRI who were admitted to the hospital present elevated serum sST2 levels ($P < 0.001$). Serum sST2 was recognized as a standalone risk factor contributing to the occurrence of MIRI in STEMI patients who are undergoing PCI ($P < 0.001$). Throughout the follow-up duration, 37 (17.0%) patients encountered major adverse cardiovascular and cerebrovascular incidents (MACCEs), which included eight (3.6%) deaths from all causes. The Kaplan–Meier assessment revealed that individuals in the MIRI group had an unfavorable prognosis (all log-rank $P < 0.05$). Both univariable and multivariable Cox regression models were established using MIRI patients as the study cohort. The findings indicated that sST2 levels exceeding 68.98 ng/mL served as one of independent risk factors for predicting MACCEs (all $P < 0.001$). The model was evaluated using the C-index, AUC, calibration plot, and Decision Curve Analysis (DCA) curve.

Conclusion Elevated levels of serum sST2 may accurately predict the onset of MIRI following PCI in STEMI patients. Specifically, a serum sST2 concentration > 68.98 ng/mL is a prominent independent risk predictor for overall mortality and MACCE in individuals experiencing MIRI.

Keywords Myocardial infarction, Acute ST-segment elevation, Soluble growth-stimulated expressed gene 2 protein, Myocardial ischemia–reperfusion injury, Reperfusion

*Correspondence:
Wenjing Che
cwj2123209052@163.com
Aijie Hou
1758624242@qq.com

Graphical Abstract



Introduction

ST-segment elevation myocardial infarction (STEMI) is associated with high levels of morbidity and mortality, along with a difficult prognosis. The mortality rate in hospitals for patients experiencing STEMI is around 4–21% [1]. The most effective method for reducing myocardial necrosis in the ischemic myocardium and improving long-term outcomes is early reperfusion (< 90 min) [2]. Although reperfusion restores the oxygen supply to heart muscle cells, it also damages heart muscle cells through a process known as myocardial ischemia–reperfusion injury (MIRI) [3]. Post-PCI MIRI reduces its clinical benefits and long-term efficacy; therefore, the increasing incidence of complications associated with MIRI prognosis is a serious problem that needs to be solved [4]. Soluble growth stimulation expressed gene 2 protein (sST2) participates in various immune responses, including inflammatory responses, and contributes to ischemia–reperfusion injury [5–12]. In this study, we determined the effectiveness of serum sST2 in recognizing the onset of MIRI following PCI in patients with STEMI and investigated its prognostic implications.

Methods

Population and design of the study

We consecutively included STEMI patients who attended the Liaoning Provincial People's Hospital Heart Center for first-time diagnosis and emergency PCI from November 2020 to August 2022. The definition of STEMI was based on the following criteria: persistent symptoms of ischemia (within 12 h); an increase or decrease in cardiac biomarker levels; new ST-segment elevation occurring in ≥2 consecutive leads; or a left bundle branch block pattern [1]. The exclusion criteria were as follows: the onset of illness occurring ≥12 h, as well as acute or chronic infections; neoplastic conditions; rheumatic disorders; a history of myocardial infarction; structural heart abnormalities; a Killip classification of 3 or greater; hemodynamic instability that necessitated the implementation of an intra-aortic balloon pump (IABP) prior to revascularization. This research complied with the ethical guidelines set forth by the Declaration of Helsinki and received approval from the ethics committee of the hospital (2021 KS0008). Prior to engaging in the study, all participants gave their informed consent.

Laboratory tests

Before the coronary intervention, 2 mL of arterial blood was obtained following successful punctures of either the radial or the femoral artery. The serum was centrifuged and analyzed via a high-sensitivity second-generation enzyme-linked immunosorbent assay (ELISA) using a fully automated dry fluorescence immunoassay analyzer (A2000 model, Guangxi Ameyi Company, China) to determine the sST2 concentration, with a detection limit of 3.1 ng/mL, an intra-assay CV of 10% and inter-assay CV 15%. Serum sST2 levels were measured immediately after blood collection by trained personnel without freeze–thaw cycles or long-term storage, thereby precluding potential instability effects.

Interventional process

All patients received subcutaneous heparin (100 U/kg), aspirin (300 mg), and dual antiplatelet therapy (clopidogrel 300 mg or ticagrelor 180 mg) preoperatively. PCI was performed following standard procedures, achieving TIMI grade 3 distal blood flow and residual stenosis < 20%. A TIMI thrombus grade (TTG grade) ≥ 4 was considered to be a high thrombus load. No regurgitation (NR) was defined as a TIMI grade < 3 and a continuously corrected TIMI frame count (CTFC) > 40 or a TIMI 3 myocardial blush grade (MGB) of 0–1, excluding vasospasm, thrombus, residual stenosis, and entrapment. Lethal ventricular arrhythmias were characterized as sustained ventricular tachycardia and polymorphic ventricular fibrillation. Two experts, who had considerable experience and were blinded to this patient information, interpreted the angiograms. Data on the patient's postoperative electrocardiogram, intraoperative electrocardiogram and blood pressure, and surgical records were also included in the analysis.

Definitions, criteria and classifications of MIRI

MIRI refers to a sudden cardiac incident that occurs immediately after the reopening of an artery affected by an infarction, encompassing three principal manifestations: 1) hypotension (defined as post-reperfusion blood pressure below 90/60 mmHg or a ≥ 30% reduction in systolic and/or diastolic pressure from baseline), requiring pharmacological intervention or intra-aortic balloon pump (IABP) support; 2) reperfusion arrhythmias (specifically life-threatening ventricular arrhythmias) necessitating pharmacological treatment or device-assisted support (defibrillation, temporary pacemaker implantation); and 3) angiographically confirmed no-reflow phenomenon despite successful coronary recanalization [29, 34]. We classified the three types of MIRI phenomena into three categories: suppression type, irritation type, and no-reflow type. [13]. The duration between the start of chest pain symptoms and the reopening of the artery linked with the infarction was referred to as the symptom-to-balloon (STB) time.

Clinical outcomes

The main objective of this study was to assess all-cause mortality, whereas the secondary objective focused on major adverse cardiovascular and cerebrovascular incidents (MACCEs) (which included all-cause mortality, hospitalization due to heart failure, ischemic drive revascularization, malignant arrhythmia, and nonfatal stroke). In cases where a patient experienced two or more clinical events, the first event was regarded as the endpoint.

Analyses of statistics

For data conforming to a normal distribution, results were presented as mean ± standard deviation, followed by an independent t-test for analysis. When the data failed to satisfy normality assumptions, the median (*Q1, Q3*) was computed, and the Mann–Whitney *U*-test was applied. Categorical variables were displayed as frequencies or percentages, with comparisons carried out using either the Chi-square test or Fisher's exact test. The Kruskal–Wallis test was utilized for comparing multiple groups. Furthermore, a multifactorial logistic regression analysis was conducted to identify independent risk factors linked to MIRI following PCI in STEMI patients. Receiver operating characteristic (ROC) curves were generated to assess the predictive capability of serum sST2 levels in foreseeing MIRI. Spearman's method facilitated the execution of rank correlation analysis. Subgroup analysis was performed to assess the interaction between serum sST2 and MIRI. The Kaplan–Meier method was used to investigate clinical outcomes, while group comparisons were analyzed with the log-rank test. Cox proportional hazard regression models, both univariable and multivariable, were established to evaluate independent predictors of major adverse cardiovascular and cerebrovascular events (MACCEs). The C-indexand time-dependent receiver operating characteristic (t-ROC) curves were applied to assess the model's discriminative ability, while Bootstrap resampling was employed to validate the calibration accuracy of bar-line plots. DCA was utilized to evaluate clinical utility. All results were regarded as statistically significant at a threshold of $P < 0.05$. Data analysis was performed using SPSS version 27.0 and R version 4.2.2 (http://www.R-project.org, The R Foundation).

Results

Clinical characteristics

In this research, a total of 223 individuals identified with STEMI were examined. The average age of the cohort

was 60.77 ± 12.61 years, 175 patients (78.5%) were male, and the mean BMI was 24.95 ± 3.55 kg/m^2. In total, 86 patients (38.6%) experienced MIRI after PCI. Among them, 37 (16.6%) patients were classified into the suppression group, 15 (6.7%) patients were classified into the irritation group, and 33 (14.8%) patients were classified into the NR group. After admission, the MIRI group had a greater serum sST2 level (73.17 [51.56, 86.27] ng/mL *vs.* 41.08 [29.30, 53.72] ng/mL) and thrombotic load than the non-MIRI group (all $P < 0.001$). The MIRI group had higher Lp(a), peak NT-proBNP, peak CK-MB, and peak cTnI levels, higher rates of thrombus aspiration and adenosine administration (all $P < 0.05$). The MIRI group had a lower postoperative diastolic blood pressure (DBP), lower perioperative TIMI flow grades and differences between the two groups were also found in the location of the coronary artery lesions and infarct-related artery (IRA) (all $P < 0.05$). The other baseline characteristics showed no significant differences (all $P > 0.05$) (Table 1.).

Serum sST2 has good predictive value for MIRI

The examination of sST2 concentrations within the MIRI patient subgroup demonstrated that those in the irritation group exhibited elevated serum sST2 levels compared to the suppression and NR groups (101.43 [79.48, 122.10] vs. (73.22 [49.24, 90.54] and 71.25 [53.23, 87.34], respectively; all $P < 0.05$, Cohen's $f = 0.088$) (Fig. 1A). The results of ROC analysis revealed that the area under the curve (AUC) for serum sST2 in cases of MIRI was 0.762 (95% CI: 0.696–0.829, $P < 0.001$), demonstrating a sensitivity of 0.698 and a specificity of 0.825, resulting in a Youden's index of 0.523 and a cutoff value of 56.84 ng/mL. Serum sST2 levels also have a certain diagnostic value for different MIRI subgroups (AUC = 0.709, 0.882, and 0.748, respectively; all $P < 0.01$) (Fig. 1B). Compared to the peak values of NT-proBNP, CK-MB, and cTnI for predicting MIRI in STEMI patients (AUC = 0.649, 0.659, and 0.665, respectively, all $P < 0.05$), DeLong's test suggested that the serum sST2 test was more effective (Z/P = 4.375/0.000, 4.724/0.000, and 4.595/0.000, respectively)(Fig. 1C). The analysis using multivariable logistic regression indicated that significant independent risk factors for MIRI after PCI in individuals with STEMI consisted of a substantial thrombus burden, the presence of serum sST2, and IRA being the RCA [OR (95% CI) = 2.354(1.176–4.714), 1.037(1.024–1.051), and 2.888(1.491–5.594), respectively] (Table 2). Analysis using Spearman's correlation indicated a weak positive relationship between serum sST2 levels and NT-proBNP, while also showing a weak negative correlation with LVEF (r/P = 0.290/0.003 and −0.326/0.001, respectively), and no linear relationship was found for serum sST2 levels with age, CK-MB, cTnI, Lp(a), the neutrophil–lymphocyte ratio (NLR), Gensini, bracket length, or DBP (all $P > 0.05$).

Subgroup analyses and interaction tests

Subgroup analyses and interaction tests were conducted to evaluate the influence of demographic and health characteristics on the association between serum sST2 levels and MIRI after percutaneous coronary intervention (PCI) in STEMI patients *(Supplement)*. In terms of gender, the association between serum sST2 and MIRI was statistically significant in the male subgroup (*95% CI*: 1.032–1.068, $P < 0.001$) but not in the female subgroup ($P = 0.2002$). The interaction analysis showed no statistically significant difference in effect between the two groups (interaction $P = 0.3811$), suggesting insufficient evidence to support gender-specific associations. Age-related analyses revealed that serum sST2 was significantly associated with MIRI in participants aged 40–60 years (*95%CI*:1.0165–1.0631, $P < 0.001$) and those over 60 years (*95% CI*: 1.0266–1.0629, $P < 0.001$), but not in the under- 40 age group ($P = 0.1806$), with an interaction *P*-value of 0.3967 across age subgroups. The study demonstrated weak positive associations between serum sST2 and MIRI risk in both hypertensive and non-hypertensive populations, as well as in diabetic and non-diabetic populations (all $P < 0.05$). Interaction analyses indicated that neither hypertension nor diabetes significantly modified the association between sST2 and post-PCI MIRI (interaction $P > 0.05$).

Relationships between adverse outcomes and MIRI and serum sST2

During the follow-up period of 630 ± 433 days, 37 (17.0%) patients reached the primary or secondary clinical endpoints, including eight (3.6%) all-cause deaths, 15 (6.7%) heart failure readmissions, seven (3.1%) ischemia-driven revascularizations, four (1.8%) malignant arrhythmias or ICD implantations, and three (1. 3%) non-fatal strokes. The cumulative one-year all-cause mortality and MACCE rates in the MIRI group and the non-MIRI group were 16.3% vs. 4.3% and 5.8% vs. 2.2%, respectively (all $P < 0.01$). Higher serum sST2 levels were associated with poorer prognostic outcomes, with patients experiencing all-cause mortality and MACCE displaying elevated serum sST2 levels than those with negative outcomes (107.84 [74.80, 200], 70.92 [48.42, 103.9] vs. 47.15 [33.37, 65.50], respectively; all $P < 0.01$). Additionally, the distribution of serum sST2 across various clinical endpoints was found to be significantly different ($P < 0.05$, Cohen's $f = 0.321$) (Fig. 1D). The Kaplan–Meier analysis showed that both the cumulative survival rate and the cumulative non-MACCE survival rate for patients in the MIRI group

Table 1 Clinical characteristics of patients in the MIRI and non-MIRI groups

Variable	non-MIRI group (n=137)	MIRI group (n=86)	*P*
Baseline characteristics			
Male sex,n (%)	112 (81.8)	63 (73.3)	0.133
Age,y	60.28±12.28	61.56±13.15	0.461
Body mass index,(kg/m^2)	24.69±3.34	25.35±3.84	0.178
Hypertension ,n (%)	65 (47.40)	39 (45.43)	0.760
Diabetes mellitusn,n (%)	34 (24.8)	27 (31.4)	0.283
Smoking,n (%)	84 (61.3)	50 (58.1)	0.638
sST2 (ng/mL)	41.08 (29.30, 53.72)	73.17 (51.56, 86.27)	**<0.001**
Blood uric acid (μmol/L)	327 (268.5, 396.5)	326 (276.5, 417.5)	0.356
Fasting blood glucose (mmol/L)	6.10 (5.18, 8.36)	6.55 (5.64, 8.35)	0.230
Hemoglobin (g/L)	146 (138, 155)	144 (133, 154)	0.262
Platelet count (10^9 /L)	228 (191, 280)	233 (195, 273)	0.928
NLR	3.77 (2.39, 6.34)	5.05 (2.50, 9.09)	0.060
Total cholesterol (`x ±s, mmol/L)	4.93±1.25	4.75±1.08	0.293
LDL-c (`x ±s, mmol/L)	3.08 (2.59, 3.70)	2.99 (2.52, 3.44)	0.298
Lp(a) (g/L)	108.1 (63.5, 233.9)	157.9 (88.2, 260.9)	**0.042**
HDL-c (mmol/L)	1.02 (0.87, 1.20)	0.97 (0.85, 1.17)	0.290
Peak NT-proBNP (pg/mL)	977 (426, 2035)	1515 (728, 2972)	**0.003**
Peak CK-MB (U/L)	73.4 (35.75, 148.5)	122 (65.4, 201.7)	**0.007**
Peak cTnI (μg/L)	34.7 (14.1, 80.0)	59.5 (35.4, 80.0)	**0.001**
LEDV (mL)	97 (89, 110)	100 (89, 115)	0.362
LESV (mL)	55 (49, 62)	56 (52, 67)	0.196
LVEF	0.42 (0.40, 0.46)	0.41 (0.38, 0.45)	0.117
Symptom-to-balloon time (h)	5.42 (3.33, 9.09)	7.51 (3.00, 8.55)	0.426
Killip classification ≥ II,n (%)	16 (11.7%)	14 (16.3%)	0.327
Angiographic and procedural characteristics			
High thrombotic load ,n (%)	29 (21.2)	41 (47.7)	**<0.001**
Number of blood vessels ,n (%)			
Single vessel disease	35 (25.5)	24 (27.9)	0.697
Multivessel disease	41 (74.5)	60 (69.8)	
IRA,n (%)			
LM	11 (8.0)	6 (7.0)	**0.009**
LAD	68 (49.6)	30 (34.9)	
LCX	21 (15.3)	8 (9.3)	
RCA	48 (55.8)	49 (35.8)	
Site of lesion,n (%)			
Proximal	47 (34.3)	44 (51.2)	**0.030**
Middle	61 (44.5)	23 (26.7)	
Distal	36 (26.3)	19 (22.1)	
Immediate postoperative blood pressure (beats/min)			
Systolic blood pressure	130 (118, 151)	128 (116, 142)	0.165
Diastolic blood pressure	83 (75, 90)	78 (70, 87)	**0.024**
Total stent length (mm)	34 (24, 54)	36 (25, 58)	0.292
Lateral branch formation	13 (9.5)	12 (14.0)	0.304
Gensini	54 (39.5, 84.0)	57.5 (41.8, 84.0)	0.578
SYNTAX	17.6(12.2, 26.4)	20.05(14.1, 25.9)	0.295
TIMI pre-PCI≤1,n (%)	73 (53.3%)	61 (70.9%)	**0.009**
TIMI post-PCI≤2,n (%)	0 (0.00%)	16 (18.6%)	**<0.001**
Manual thrombus aspiration,n (%)	24 (17.5%)	29 (33.7%)	**0.006**

Table 1 (continued)

Variable	non-MIRI group (n=137)	MIRI group (n=86)	*P*
Medication			
Aspirin,n (%)	137 (100.0%)	83 (96.5%)	0.056
P2Y12 inhibitorn,n (%)	136 (99.3%)	85 (98.8%)	1.000
Clopidogre,n (%)	119 (86.9%)	76 (86.4%)	0.740
Ticagrelor,n (%)	17 (12.4%)	9 (10.5%)	0.660
Glycoprotein IIb/IIIa antagonists,n (%)	58 (42.3%)	35 (40.7%)	0.809
β-blockers,n (%)	86 (62.8%)	44 (51.2%)	0.087
RAAS blockers,n (%)	68 (49.6%)	33 (38.4%)	0.100
Adenosine,n (%)	1 (0.70%)	36 (41.9%)	**<0.001**

Values indicate the mean ± SD, n (%), or the mean (1 st and 3rd quartiles)

sST2 soluble ST2, *LDL-c* low-density lipoprotein cholesterol, *HDL-c* high-density lipoprotein cholesterol, *Lp(a)* lipoprotein a, *NLR* neutrophil–lymphocyte ratio, *CK-MB* creatine kinase isoenzyme, *cTnI* cardiac troponin I, *LEDV* left ventricular end-diastolic volume, *LESV* left ventricular end-systolic volume, *LVEF* left ventricular ejection fraction, *RAAS* renin–angiotensin–aldosterone system, *LM* left main stem, *LAD* anterior descending branch, *LCX* retrograde branch, *RCA* right coronary artery

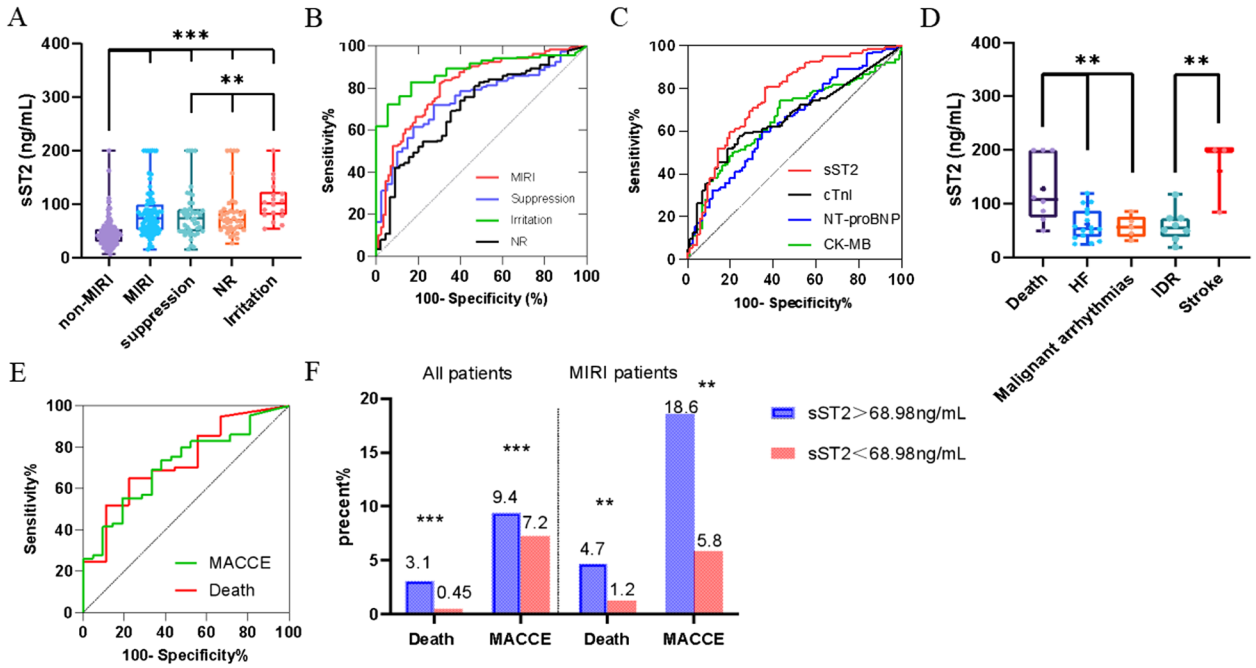


Fig. 1 Serum sST2 distribution (**A**) and ROC curve (**B**) for each subgroup of MIRI; ROC curve for predicting MIRI after PCI in STEMI patients using serum sST2, peak NT-proBNP, peak CK-MB, and peak cTnI (**C**);serum sST2 levels in patients with different outcomes (**D**); ROC curve for serum sST2 to predict all-cause mortality and MACCE in patients with MIRI (**E**); clinical outcomes and incidence of outcomes based on whether sST2 is greater than 68.98 ng/mL as the cutoff for clinical outcomes and the incidence of adverse events (**F**) (** $P < 0.05$ and *** $P < 0.01$)

were greater than those observed in the non-MIRI group (all log-rank P < 0.05). Within the MIRI subgroup, it was found that the cumulative survival rate for patients in the suppression subgroup was notably lower (log-rank $P < 0.05$), while the cumulative non-MACCE survival rates among all subgroups did not exhibit significant differences (log-rank P > 0.05) (Fig. 2).

MIRI prognostic clinical prediction model

Initially, the ROC curve was used to evaluate the ability of sST2 to predict clinical outcomes. The AUC of serum sST2 for predicting all-cause mortality was 0.732 (95% CI: 0.568–0.895, $P < 0.001$), and the optimal cut-off value was 82.82 ng/mL. The AUC for serum sST2 in predicting MACCEs following discharge in patients

Table 2 Multivariable logistic regression analysis of potential predictors of MIRI

Variant	Univariate Analysis		Multifactor analysis	
	P	*OR (95% CI)*	*P*	*OR (95% CI)*
sST2	< 0.001	1.038 (1.025–1.052)	**< 0.001**	1.037(1.024–1.051)
Age	0.460	1.008 (0.987–1.030)	-	-
Male gender	0.135	0.611 (0.321–1.165)	-	-
CK-MB	0.137	1.002(0.999,1.004)	-	-
cTnI	< 0.001	1.018(1.008,1.028)	0.784	0.997(0.979–1.016)
NT-proBNP	0.006	1.009(1.003,1.015)	0.166	1.005(0.998–1.013)
Lp(a)	0.133	1.001 (1.000–1.002)	-	-
High thrombotic load	< 0.001	3.393 (1.882–6.116)	**0.016**	2.354(1.176–4.714)
Site of lesion				
Proximal	0.011	-	0.148	0.605(0.305–1.197)
Middle	0.003	0.439 (0.257–0.750)	0.379	0.695(0.309–1.563)
Distal	0.053	0.561 (0.347–0.906)	-	-
IRA,n (%)				
LAD	< 0.001	-	0.369	1.588(0.579–4.353)
LCX	0.689	0.863 (0.421–1.711)	-	-
RCA	0.001	2.267 (1.392–3.692)	**0.002**	2.888(1.491–5.594)
DBP	0.035	0.979 (0.960–0.999)	0.515	0.993(0.968–1.017)

OR Odds Ratio, *CI* Confidence Interval

with STEMI was 0.714 (95% CI: 0.596–0.832, $P < 0.05$), with an optimal cutoff threshold established at 68.98 ng/mL (Fig. 1E). The clinical outcomes and event rates of patients with sST2 levels greater than 68.98 ng/mL are shown in (Fig. 1F). Variables related to MACCEs were screened (with $P < 0.05$ were included), and their ability to predict MACCEs was assessed using ROC curves. The cutoff value was included in univariable and multivariable Cox regression analyses along with sST2 > 68.98 ng/mL. The results are shown in Table 3. Multivariable analysis revealed that sST2 > 68.98 ng/mL, STB > 7.24 h, NT-proBNP > 1260 pg/mL, NLR > 4.08, and bracket length > 31 mm were independent risk factors for MACCEs. There was no significant interaction between variables ($P > 0.05$).The time-dependent AUC curves demonstrated the prognostic signature's sensitivity and specificity. The AUC values for 1-year, 2-year, and 3-year MACCE were 0.748, 0.792, and 0.865, respectively (Fig. 3A). Furthermore, the DCA curves indicated more pronounced clinical benefits in medium- to long-term follow-up (Fig. 3B). The calibration curves (Fig. 3C) revealed alignment with the ideal 45° line for 1, 2, and 3-year predictions, with the best-fit line showing a slope of 0.988 and intercept of 0.059, suggesting satisfactory calibration performance. However, further optimization through expanded sample sizes or dynamic calibration methods may enhance future model robustness.

Discussion

In earlier investigations of MIRI, markers indicating myocardial injury were frequently used to assess myocardial necrosis and predict unfavorable outcomes. Studies have shown that troponin I is more sensitive than CK-MB [22]. Mohammad et al. [23] reported that myocardial injury was evaluated by measuring late gadolinium Enhancemen (LGE), leading to the conclusion that peak NT-proBNP levels can predict the degree of myocardial injury and clinical results. In our study, the serum sST2 level, along with the peak levels of CK—MB, cTnI, and NT—proBNP, showed certain predictive ability for the occurrence of MIRI after surgery in STEMI patients. Among them, the serum sST2 level had a relatively better predictive ability. In previous studies, not much attention has been paid to the prognostic risk factors for patients with MIRI. In this study, the peak NT—proBNP levels andserum sST2 level were related to adverse outcomes in MIRI patients to some extent. Additionally, premenopausal female sex thought to have some possible protective effect against MIRI [24]. In this study, most patients were male [25], thus both age and sex factors were corrected for when the predictors of MIRI and factors affecting prognosis were analyzed. Although statistically significant results were observed in the male and age ≥ 40 subgroups, the effect sizes were small, and current evidence remains insufficient to support sex-specific associations. Further studies are warranted to validate potential sex-based

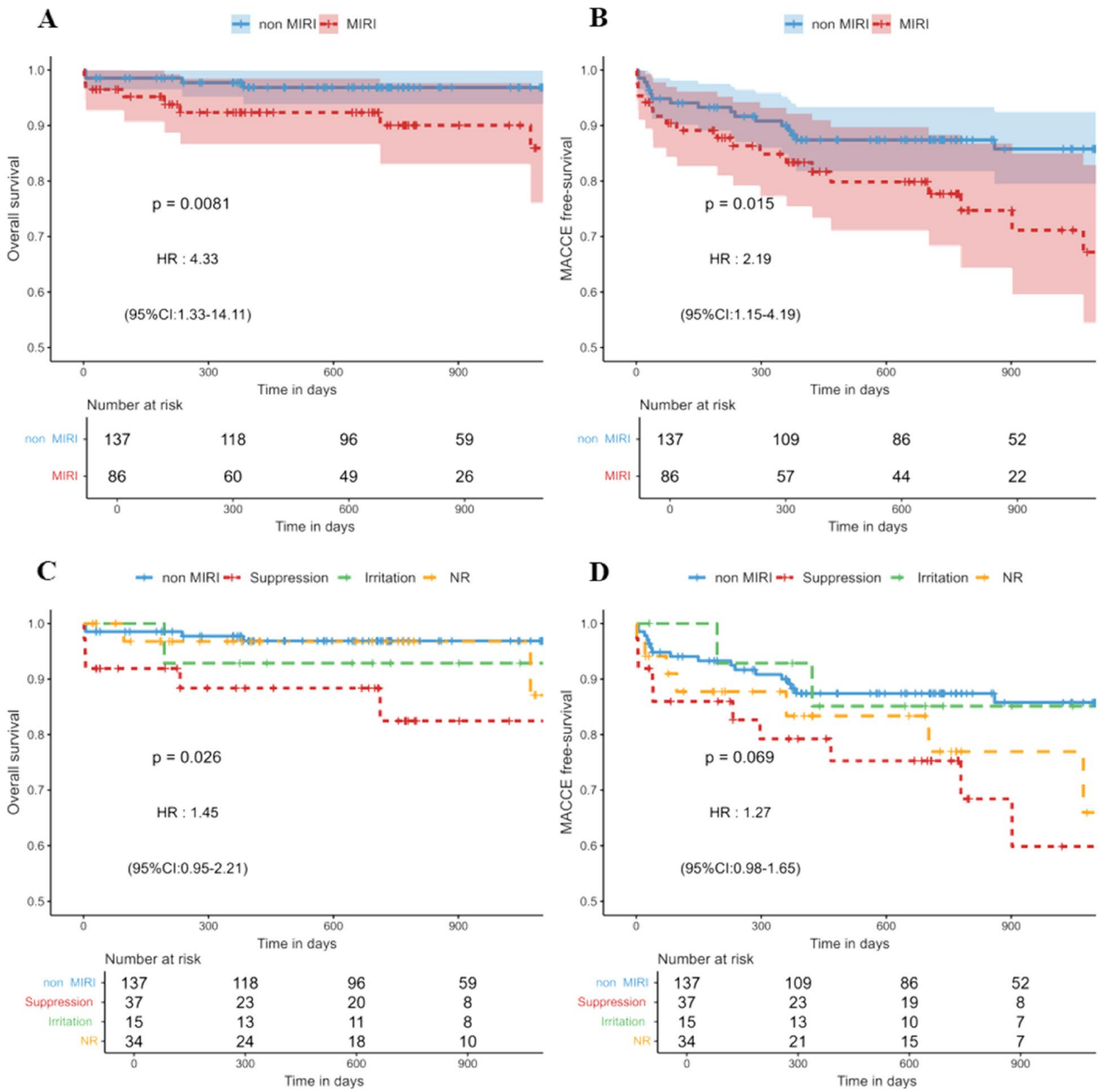


Fig. 2 **A** Comparison of cumulative all-cause survival rates between the MIRI group and the non-MIRI group. **B** Comparison of the cumulative MACCE-free survival rates between the MIRI and non-MIRI groups. **C** An examination of the cumulative all-cause survival rates in each MIRI subgroup. **D** Evaluation of cumulative MACCE-free survival rates across different MIRI subgroups

differences in ST2's role in myocardial infarction through larger cohorts or mechanistic experiments.

There are four different types of MIRIs: cardiac depression, arrhythmia, nonreflux, and lethal reperfusion injury. Ventricular arrhythmias are associated with larger myocardial infarction sizes [16]. Consequently, in the irritation subgroup primarily manifesting reperfusion arrhythmias, serum sST2 levels were significantly elevated on admission. Among these, the most severe outcome of MIRI is lethal reperfusion injury, which is a major hindrance to the healing of myocardial tissue [14, 15]. The prognosis of MIRI patients in this study was worse than that of non-MIRI patients, and the prognosis of the suppression subgroup was worse than that of the other two subgroups and the non-MIRI subgroup.

Recent studies have proposed that fatal reperfusion injury essentially represents the terminal stage of three other injury types [35]. In this study, the stimulated

Table 3 Univariable and multivariable analyses for predicting MACCEs in MIRI patients

Variant	Univariable Analysis		Multivariable analysis		*P* for interaction
	P	*HR (95% CI)*	*P*	*HR (95% CI)*	
sST2 > 68.98 ng/mL	0.014	6.404 (1.463–28.036)	**< 0.001**	4.038(2.077–7.852)	
Age > 65 year	0.761	0.856 (0.315–2.328)	-	-	0.524
Male gender	0.439	0.661 (0.232–1.886)	-	-	0.802
STB > 7.24 h	0.088	5.802 (0.768–43.806)	**< 0.001**	9.383(6.344–13.876)	0.469
NT-proBNP > 1260 pg/mL	0.024	5.501 (1.255–24.112)	**< 0.001**	4.038(2.077–7.852)	0.822
Gensini > 52.5	0.053	3.446 (0.986–12.042)	0.860	0.880(0.212–3.656)	0.684
High thrombotic load	0.044	0.316 (0.103–0.970)	0.384	1.169(0.822–1.664)	0.966
NLR > 4.08	0.025	3.301 (1.161–9.389)	**< 0.001**	3.633(2.022–6.527)	0.354
Bracket length > 31 mm	0.019	5.884 (1.341–25.805)	**< 0.001**	2.146(1.432–3.214)	0.554
Hypertension	0.132	2.155 (0.793–5.853)	-	-	0.131
LVEF < 0.41	0.015	6.238 (1.425–27.315)	0.133	4.067(0.651–25.408)	0.874
SYNTAX > 14.9	0.090	5.750 (0.761–43.441)	0.088	1.921(0.907–4.072)	0.639

HR Hazard Ratio

group demonstrated higher all-cause survival rates than the other two groups. Previous research indicates that reperfusion-associated ventricular arrhythmias (VAs) in STEMI patients correlate with larger infarct size, reduced left ventricular function, and adverse clinical outcomes. However, their long-term prognostic impact appears limited [36, 37], with low incidence of late sudden cardiac death (SCD) observed over 5-year follow-up in related cohort studies. Notably, the prognostic significance may vary depending on the initial arrhythmia subtype [17, 38].For the no-reflow group, although epicardial coronary patency was restored, severe myocardial perfusion defects persisted [39, 40]. The no-reflow phenomenon reflects significant microvascular damage in patients with successful primary percutaneous coronary intervention (pPCI) and is established as being associated with impaired left ventricular function and poor prognosis [41, 42]. Furthermore, the extent of preserved microvasculature during the acute phase serves as one of the principal determinants of long-term myocardial functional and structural recovery [43].The inhibition group exhibited the worst all-cause survival rate in this study, potentially explained by several factors: First, while animal studies of myocardial ischemia–reperfusion injury generally consider myocardial stunning and hibernation as potentially reversible [44, 45], clinical patients may suffer from extensive myocardial stunning or microcirculatory failure, with hemodynamic instability creating pathophysiological complexities beyond those observed in isolated experimental models. Additionally, recent research on intraoperative hypotension suggests that even brief periods of mild hypotension are strongly associated with myocardial injury, renal injury, and mortality [46, 47]. Notably, the mean arterial pressure (MAP) threshold linked to myocardial injury is approximately 65 mmHg, whereas the threshold for renal injury appears higher, possibly around 75 mmHg [48, 49].The lack of statistically significant differences in MACCE-free survival among subgroups implies that mortality causes may not fully overlap with MACCE definitions. Patients in the inhibition group might experience increased non-cardiac mortality risks due to multiorgan dysfunction, such as renal failure and cerebral hypoperfusion. However, the absence of statistical significance could also stem from insufficient sample size, inadequate follow-up duration, or the lack of advanced assessments, particularly cardiac MRI, in the inhibition group. These limitations highlight the need for further research to validate the conclusions.

MIRI involves the interaction of various signaling molecules and cell types, and the inflammatory response plays a key role in the development of MIRI, including the release of various cytokines, such as tumor necrosis factor-alpha (TNF-α) and high mobility group protein B1 (HMGB1), as well as neutrophil activation and vascular endothelial damage [4, 14]. ST2 is an biomarker that shows higher expression levels during myocardial stress or injury and is directly or indirectly involved in MIRI through the above processes of the inflammatory response and apoptosis [17–20]. Besides this study, there are no clinical reports yet on the predictive and prognostic relationships between serum sST2 levels and MIRI. Patients with AMI and high serum sST2 levels are more likely to suffer heart failure or die because of cardiac problems. Emerging evidence indicates that sST2 serves as an independent prognostic predictor in patients with

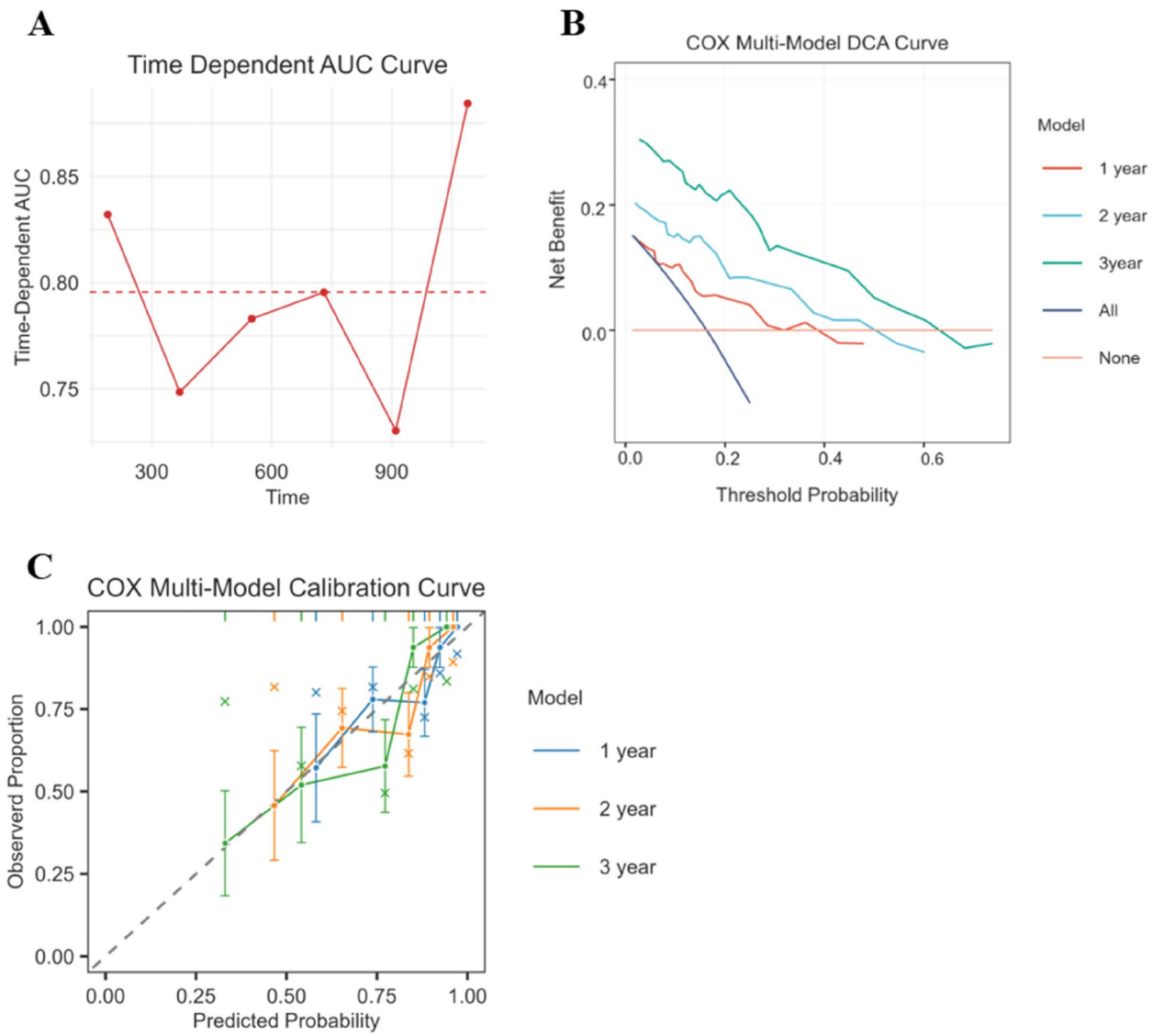


Fig. 3 **A**, **B** and **C** correspond to the time-dependent AUC curves, DCA curve and regression calibration curve for the multifactorial Cox regression model

elevated left ventricular filling pressure [32] and heart failure, underscoring its potential as a trans-disease biomarker. Serum sST2 provides prognostic information independent of traditional risk factors and complements NT-proBNP [18]. In this study, the proportion of patients with higher serum sST2 levels was greater for all-cause cardiac death or MACCE outcomes, and this proportion was unchanged in the overall cohort or in MIRI patients. Aleksova et al. [21] reported that in patients with AMI, serum sST2 concentrations exceeding 70 ng/mL were linked to the activation of fibrotic and neurohormonal pathways, as well as an elevated risk of unfavorable left ventricular remodeling, which was similar to the level of serum sST2 >68.98 ng/mL in our study predicting adverse event outcomes in patients.

In STEMI patients undergoing mechanical reperfusion, a long STB, high NLR, and longer stent length are associated with microcirculatory damage and poor prognosis, which is consistent with the findings of previous studies [26–28]. Patients with IRA due to RCA often have higher-grade MIRI due to the presence of the unique Bezold-Jarisch reflex [29]. In individuals exhibiting a significant thrombus load, the perfusion of the myocardium is decreased, which leads to a greater occurrence of slow flow following PCI [30]. Therefore, along with the timely

opening of the infarct artery to achieve early reperfusion, measures to reduce reperfusion injury, such as left ventricular unloading, whole-body and intracoronary hypothermia, and remote ischemic conditioning (RIC) [31], should also be considered for patients at high risk of MIRI to reduce MIRI and improve prognosis. Our findings indicate that sST2 holds potential for guiding personalized therapy in high-risk patients. It is important to note, however, that intensified antithrombotic regimens (such as GP IIb/IIIa inhibitor combination therapy) failed to significantly enhance long-term prognosis in STEMI patients [33]. Consequently, future studies should aim to combine biomarker insights with therapeutic optimization to prevent overintervention.

Limitation

This study faces the following limitations. This study represents a small-sample, single-site investigation with a brief follow-up duration; thus, its conclusions require verification through a prospective cohort study. In this study, the cohort was initially divided by qualitative means. In the future, the accuracy of the conclusions need to be improved by further dividing the subgroups using quantitative methods to evaluate myocardial injury, such as MRI. Furthermore, this research solely gathered serum sST2 levels in STEMI patients prior to emergency PCI and did not include dynamic assessments of serum sST2 throughout hospitalization, and did not include data on patients undergoing elective PCI. This aspect requires enhancement in upcoming prospective studies and should be integrated with quantitative MIRI testing to improve the reliability and comprehensiveness of the findings.

Conclusion

In patients with STEMI undergoing PCI, increased serum sST2 levels may serve as a predictor for the development of MIRI. A serum sST2 concentration greater than 68.98 ng/mL was identified as an independent risk factor for all-cause mortality and MACCE in individuals affected by MIRI.

Supplementary Information

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Supplementary Material 1

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Clinical trial number
Not applicable.

Authors'contributions
Che. and J. contributed to the statistical analysis, interpretation of the findings, and manuscript preparation. In addition, Cha. was instrumental in the conception and design of the study. W.& S. and H. were involved in the design, the drafting revisions, and oversight of the project. The final manuscript was reviewed and approved by all authors.

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Data availability
Due to the confidentiality of the individuals involved in the study, the data underlying this article cannot be made available to the public. Nevertheless, the data can be shared upon a reasonable request directed to the corresponding author.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of The People's Hospital of Liaoning Province. The approval number was 2021 KS0008.

Consent for publication
Written informed consent was obtained from all participants.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Cardiology, The People'S Hospital of China Medical University, the People'S Hospital of Liaoning Province, Shenhe, Shenyang, Liaoning Province 110016, China.

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