

The Elevated Soluble ST2 Predicts No-Reflow Phenomenon in ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Aim: The primary percutaneous procedure resulted in a significant improvement in the prognosis of myocardial infarction. However, no-reflow phenomenon restrains this benefit of the process. There are studies suggesting that soluble suppression of tumorigenicity (sST2) can be valuable in the diagnosis and progression of heart failure and myocardial infarction. In this study, we aimed to investigate the effect of sST2 on no-reflow phenomenon in ST-elevated myocardial infarction (STEMI).

Method: This study included 379 patients (258 men; mean age, 60 ± 11 years) who underwent primary percutaneous treatment for STEMI. sST2 levels were measured from blood samples taken at admission. Patients were divided into two groups according to Thrombolysis in Myocardial Infarction (TIMI) flow grade: group 1 consists of TIMI 0,1,2, accepted as no-reflow, and group 2 consists of TIMI 3, accepted as reflow.

Results: No-reflow phenomenon occurred in 60 patients (15.8%). The sST2 level was higher in the no-reflow group (14.2 ± 4.6 vs. 11.3 ± 5.0, $p=0.003$). Moreover, regression analysis indicated that diabetes mellitus, lower systolic blood pressure, multivessel vascular disease, high plaque burden, and grade 0 initial TIMI flow rate were other independent predictors of the no-reflow phenomenon in our study. Besides, when the patients were divided into high and low sST2 groups according to the cut-off value from the Receiver operating characteristics analysis, being in the high sST2 group was associated with 2.7 times increased odds for no-reflow than being in the low sST2 group.

Conclusion: sST2 is one of the independent predictors of the no-reflow phenomenon in STEMI patients undergoing primary percutaneous coronary intervention.

Key words: Myocardial infarction, soluble ST2, No-reflow-phenomenon, Inflammation, In-hospital mortality

Introduction

Acute coronary syndrome (ACS) is considered to be the most important cause of death throughout the world, especially in western countries, despite technological improvements, new drugs, and an increasing level of awareness¹. Percutaneous coronary interven-

tion (PCI) provides normal blood flow in the responsible artery in patients with myocardial infarction, contributing significantly to the regression of symptoms and better prognosis^{2,3}. But no-reflow phenomenon reduces the positive effects of PCI.

No-reflow phenomenon is defined as the insufficiency of myocardial perfusion despite the mechani-

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Received: December 10, 2018 Accepted for publication: January 21, 2019

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cally responsible lesion being opened. The rate of no-reflow can reach 50% depending upon assessing methods especially in patients with ACS⁴). This phenomenon has been shown to be associated with poor prognoses, such as in-hospital and long-term mortality and advanced heart failure^{5, 6}). The methods used in the treatment of no-reflow provide very limited benefits. Therefore, no-reflow is becoming more important to prevent it from occurring. For this reason, our priority should be to find out the causes of this phenomenon and the markers or clinical conditions that can predict no-reflow. Although some independent risk factors of the no-reflow phenomenon have been shown, new biomarkers are needed for the predictability of this complication.

The soluble suppression of tumorigenicity 2 (sST2), a member of the interleukin (IL)-1 family, is thought to play a role in cardiac remodeling and the inflammatory process⁷). sST2 levels are considered to increase with cardiovascular stress and cardiac fibrosis that ultimately creates a substrate for fatal arrhythmia^{8, 9}). On a cellular basis, this molecule binds IL-33 to reduce its bioavailability. Thus, circulating sST2 eliminates the positive effects of IL-33 on myocardial fibrosis, hypertrophy, apoptosis, and myocardial function (MI)¹⁰). There are studies suggesting that sST2 is a predictor of mortality in patients with ACS. In these studies, independent of MI type, sST2 has been shown to be an independent predictor in both short-term and long-term follow-up^{11, 12}). Furthermore, as stated in the guidelines, sST2 can be used in the diagnosis and follow-up of heart failure in addition to N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP)¹³).

The relationship between high sST2 levels and major cardiovascular events are well-established in patients with MI¹⁴); however, as far as we know, the predictive value of sST2 on the no-reflow prediction in ST-elevation myocardial infarction (STEMI) patients has not been described to date. In this study, we aimed to investigate the no-reflow rate in our study population and the relationship of the no-reflow phenomenon with sST2 levels in patients undergoing primary PCI due to STEMI.

Methods

Study Population

In this single-center study, we included 379 patients who were admitted to a large-volume center between May 2017 and April 2018 with a diagnosis of STEMI and underwent primary PCI. We excluded patients who have missing or unavailable data or malignant and infectious diseases or other systemic

inflammatory conditions or no indication of PCI. STEMI patients were defined as patients with typical chest discomfort or other ischemic symptoms, who develop new ST-segment elevations in two or more contiguous leads or new bundle branch blocks with ischemic repolarization patterns on the standard 12-lead electrocardiogram. All PCI procedures were performed by operators who execute more than 100 PCIs/year at a single center (>1000 PCIs/year). Informed consent was taken from all patients, along with approval from the local ethical committee. The study follows the guidelines of the Helsinki Declaration.

Analysis of Patient Data

Patient demographics, medical charts, and laboratory parameters were recorded. Patients who had smoked within the previous month were regarded as smokers. Hypercholesterolemia was defined as having a low-density lipoprotein (LDL) level above 130 mg/dL or using antihyperlipidemic drugs. Diabetes mellitus (DM) was defined as having a fasting glucose level above 125 mg/dL or using antidiabetic drugs. Hypertension was defined as systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg or having used antihypertensive drugs for longer than two weeks.

Five milliliters of peripheral venous blood was taken from all patients and placed in EDTA-coated vacutainer tubes at the time of hospital admission. Immediately after that, the blood samples were separated by centrifugation and eventually stored at -70°C . We reached sST2 levels by measuring with sandwich enzyme immunoassay using ELISA kits (Shanghai YL Biotech, Shanghai, China) by following the manufacturer's protocol. The coefficients of intra-assay and inter-assay variation of sST2 were 8%–10%. The sensitivity of both sST2 assays, intra- and inter-assay for plasma samples is 0.13 ng/L. Patients were divided into two groups according to Thrombolysis in Myocardial Infarction (TIMI) flow grade:¹⁵) group 1 ($n=60$, mean age: 59.5 ± 11.8 years) consists TIMI 0,1,2, accepted as no-reflow, and group 2 ($n=319$, mean age: 64.0 ± 11.6 years) consists of TIMI 3 as accepted reflow.

Coronary Intervention Procedure

All participants received a chewable acetylsalicylic acid (loading dosage 300 mg) and clopidogrel (600 mg loading dosage) or ticagrelor (180 mg loading dosage) before coronary angiography. In our study, the first choice for second antiplatelet therapy was ticagrelor. Clopidogrel was preferred as the second antiplatelet agent in patients with contraindicated

ticagrelor use. When we looked at the second antiplatelet agent ratio, 83.3% of the patients had ticagrelor use, and 16.6% of the patients had clopidogrel. There was also no difference between the two groups in terms of ticagrelor use (reflow 82.9% vs. no-reflow 85.0%, $p=0.919$). Heparin (100 IU/kg) was administered after the decision to perform a coronary intervention. After angioplasty, all patients were admitted to the coronary care unit where routine antithrombotic therapy was given as a daily dose of 100 mg of aspirin, 75 mg of clopidogrel or 90 mg ticagrelor, and subcutaneous administration of enoxaparin. Patients' angiographic data were reached by assessing catheter laboratory records. The artery that was assumed to be a non-infarct-related artery (IRA) was injected first. Blood flow in the IRA was calculated by using TIMI classification. Primary angioplasty was performed only for IRA occlusion (either total or partial). Multivessel disease was defined as more than 50% stenosis in one or more major epicardial vessels, or in major branches except for IRA. TIMI thrombus scale was used to determine the thrombus burden¹⁶. According to this scale, Grade 4 is definite thrombus with the largest dimension >2 vessel diameters and grade 5 was total occlusion. Those which did not provide these features angiographically were defined as grade 0, 1, 2, 3. Finally, we classified patients as a high thrombus burden (grade 4 and 5) and low thrombus burden (grade 0, 1, 2, 3) in our study¹⁷.

Statistical Analysis

Statistical analysis was performed using the SPSS software version 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Whether the values are normally distributed or not were determined by using visual and analytical methods. Descriptive analyses are presented as means and standard deviations for variables with normal distribution, as the median and interquartile range for non-normal distribution. The categorical variables are expressed as numbers and percentages. Study groups were compared using the unpaired Student's *t*-test for continuous variables that presented normal distribution and using the Mann-Whitney *U* test for continuous variables that did not present normal distribution. Categorical data were compared with a chi-square test. Receiver operating characteristics (ROC) curves were drawn to distinguish the no-reflow phenomenon. Youden's index was used to derive the best cut-offs of plasma concentrations of sST2 value. With the obtained value, patients were divided into two groups as high- and low-sST2 groups. Multivariate logistic regression backward stepwise that included variables with $P<0.1$ on univariate analysis was carried out to identify independent predictors of the no-

reflow phenomenon. A *P* value less than 0.05 was considered statistically significant.

Results

After excluding patients with exclusion criteria, a total of 379 patients were included. The prevalence of the no-reflow phenomenon was 16.5%. There was no statistical difference in terms of traditional risk factors except age and DM. Patients with no-reflow were older (64.0 ± 10.6 vs. 59.5 ± 11.8) and more had DM (40.0% vs 24.8%) compared with TIMI 3 patients ($p=0.006$, $p=0.015$, respectively). Medical treatment was compared before the occurrence of MI, and a lower rate of statin treatment was detected in the no-reflow group (25.0% vs. 38.6%, $p=0.046$). In addition, patients with no-reflow had lower systolic blood pressure upon admission (128.8 ± 24.4 vs. 118.0 ± 22.5 , $p=0.002$). When two groups were compared in terms of laboratory values, there was only a difference in sST2 levels between the groups (no-reflow group = 14.2 ± 4.6 vs. reflow group = 11.3 ± 5.0 , $p=0.003$) (Table 1).

These two groups were compared according to the process characteristics (Table 2). There were no differences in terms of IRA, stent type, stent length, and diameter in the two groups. No-reflow was more common in patients with grade 0 initial TIMI flow rate (82.8% vs. 50.0%, $p<0.001$). The high thrombus burden was more frequent in the no-reflow group (61.7% vs. 38.6%, $p=0.002$). The presence of a multivessel lesion, Syntax, and Gensini score, which are the indicators of severity of coronary artery disease, was found to be statistically significant in the no-reflow group. Furthermore, an sST2 cut-off of 11.6 ng/ml had an AUC of 0.699 for distinguishing no-reflow with an 82.7% sensitivity, and 64.0% specificity showed in the ROC analysis (Fig. 1).

A total of 17 deaths (4.4%) occurred in-hospital follow-up. We found that 7 deaths occurred in the no-reflow group (11.7%) and 10 deaths occurred in the reflow group (3.1%) after examining the groups separately. The mortality rate was significantly higher in the no-reflow group as expected ($P=0.003$) (Table 2). Furthermore, more in-hospital mortality occurred in the high-sST2 group than low-sST2 group (9.1% vs. 2.0%, $p=0.002$).

In the logistic regression analysis; DM, high thrombus burden, grade 0 initial TIMI flow rate, the presence of multivessel disease, lower systolic blood pressure were independent risk factors of the no-reflow phenomenon. Besides, being in the high-sST2 group had 2.7 times increased odds for the no-reflow compared to the low-sST2 group independent of

Table 1. Baseline Characteristics of Study Population, mean \pm SD or *n* (%)

Variable	Reflow (<i>n</i> =319)	No-reflow (<i>n</i> =60)	<i>P</i>
Age, years	59.5 \pm 11.8	64.0 \pm 10.6	0.006
Male, <i>n</i> (%)	258 (80.9%)	50 (83.3%)	0.655
BMI(kg/m ²)	26.2 \pm 2.4	25.8 \pm 3.0	0.396
Smoking, <i>n</i> (%)	160 (50.2%)	25 (41.7%)	0.227
DM, <i>n</i> (%)	79 (24.8%)	24 (40.0%)	0.015
HT, <i>n</i> (%)	108 (33.9%)	23 (38.3%)	0.503
HL, <i>n</i> (%)	90 (28.2%)	22 (36.7%)	0.188
Family History, <i>n</i> (%)	34 (10.7%)	5 (8.3%)	0.587
Stroke, <i>n</i> (%)	1 (0.3%)	1 (1.7%)	0.184
MI history, %	48 (15.0%)	11 (18.3%)	0.519
eGFR	91.6 \pm 23.7	85.8 \pm 24.4	0.205
Total cholesterol (mg/dL)	200.2 \pm 93.3	173.6 \pm 48.4	0.104
LDL(mg/dL)	124.8 \pm 39.1	116.5 \pm 39.8	0.272
HDL (mg/dL)	40.7 \pm 14.1	40.6 \pm 7.8	0.966
Peak troponin (mg/dL)	4.0 \pm 3.4	4.9 \pm 3.4	0.181
Peak CK-MB (mg/dL)	130.1 \pm 114.2	147.7 \pm 101.7	0.423
WBC count (10 ³ /L)	12.7 \pm 8.5	13.3 \pm 4.1	0.707
Platelet (10 ³ /L)	244.8 \pm 71.4	245.5 \pm 72.7	0.964
Hemoglobin (g/dL)	13.9 \pm 5.2	12.8 \pm 2.1	0.279
SBP, mmHg	128.8 \pm 24.4	118.0 \pm 22.5	0.002
DBP, mmHg	73.1 \pm 13.3	69.8 \pm 12.5	0.080
Periprocedural Medications			
Aspirin, <i>n</i> (%)	79 (24.8%)	18 (30.0%)	0.394
Beta Bloker, <i>n</i> (%)	52 (16.3%)	11 (18.3%)	0.698
RAS bloker, <i>n</i> (%)	79 (24.8%)	19 (31.7%)	0.263
Ca channel bloker, <i>n</i> (%)	66 (20.7%)	13 (21.7%)	0.864
Oral antidiabetic, <i>n</i> (%)	75 (23.5%)	17 (28.3%)	0.424
Insulin, <i>n</i> (%)	40 (12.5%)	10 (16.7%)	0.386
Statin, <i>n</i> (%)	123 (38.6%)	15 (25.0%)	0.046
sST2 (ng/ml)	11.3 \pm 5.0	14.2 \pm 4.6	0.003

Abbreviations; sST2, soluble ST2; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; PCI, percutaneous coronary intervention; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; WBC; white blood cell; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; CK, creatine kinase; RAS, Renin angiotensin system; SD, standard deviation

Remark: eGFR was not mentioned in the main text. Therefore, including this in the table is not clear. Please check this for all such parameters, if applicable and revise as necessary.

other risk factors (Table 3).

Discussion

We can summarize the findings of our study as follows: (a) among STEMI patients who underwent primary PCI, 16.5% had no-reflow complications, (b) higher levels of sST2 patients had a significantly higher level of no-reflow compared with lower levels of sST2, (c) after adjustment for potential confounders, it was found that being in a high-sST2 group was one of the independent predictors of no-reflow (OR:

2.741 CI 95% 1.433–5.244, *p*=0.002). Moreover, DM, grade 0 initial TIMI flow rate, the presence of multivessel disease, lower systolic blood pressure, and high thrombus burden were the other independent predictors of no-reflow.

Early mortality risk may vary considerably in STEMI patients undergoing PCI. One of the most important parameters used in risk classification is the success of the primary percutaneous procedure. Rapid restoration of the arterial flow in total lesions provides serious benefits for STEMI patients in the short- and long-term¹⁸). However, the inability to provide coro-

Table 2. Angiographic procedural characteristics and drug use of the study population mean \pm SD or *n* (%)

Variable	Reflow (<i>n</i> =319)	No-reflow (<i>n</i> =60)	<i>P</i>
IRA, <i>n</i> (%)			0.824
LAD	133 (41.7)	27 (45.0)	
CX	65 (17.2)	9 (15.0)	
RCA	112 (35.1)	19 (31.7)	
Others	19 (6.0)	5 (8.3)	
Grade 0 initial TIMI flow rate, <i>n</i> (%)	153 (50.0)	24 (82.8)	<0.001
PreTIMI, <i>n</i> (%)			0.001
0	155 (48.6)	44 (73.3)	
1	4 (1.3)	3 (5.0)	
2	29 (9.1)	2 (3.3)	
3	131 (41.1)	11 (18.3)	
TIMI thrombus grade, <i>n</i> (%)			0.002
High thrombus burden	123 (38.6%)	37 (61.7%)	
Low thrombus burden	196 (61.4%)	23 (38.3%)	
Gensini Score	42.8 \pm 21.1	51.6 \pm 24.6	0.033
Syntax score	9.3 \pm 5.5	12.9 \pm 6.6	0.009
Multi vessel, <i>n</i> (%)	66 (20.7%)	25 (41.7%)	0.002
PCI procedure, <i>n</i> (%)			0.027
Balloon and stenting	191 (59.9%)	45 (75.0%)	
Direct stenting	128 (40.1%)	15 (25.0%)	
Stent type, <i>n</i> (%)			0.376
BMS	174 (54.5%)	29 (48.3%)	
DES	145 (45.5%)	31 (51.7%)	
Stent Length, mm	19.2 \pm 5.5	19.1 \pm 6.2	0.844
Stent Diameter, mm	2.95 \pm 0.31	3.01 \pm 0.34	0.148
>1 Stent used, <i>n</i> (%)	81 (25.4%)	20 (33.3%)	0.202
In-hospital mortality	10 (3.1%)	7 (11.7%)	0.003

Abbreviations: LAD, left anterior descending; CX, circumflex; RCA, right coronary artery; PCI, percutaneous coronary intervention; DES, drug eluting stent; SD, standard deviation

nary flow prevents us from benefiting from the process¹⁹.

Since it is clearly demonstrated that the inflammatory conditions have a role in both onset and progression of atherosclerosis, studies were conducted to investigate the relationship between the inflammatory status and adverse events in patients with ACS in the next step. No-reflow phenomenon, which is one of the determinants of early mortality, especially, can be defined as incomplete reperfusion at the microvascular level despite the reopening of the IRA. This may be caused by tissue edema, the presence of microthrombi, neutrophil accumulation, and free radical formation, which are thought to be associated with inflammation following coronary perfusion²⁰. The possible risk factors of no-reflow are considered to be associated with inflammatory activity after MI. Moreover, the complexity of the no-reflow mechanism, as mentioned before, makes the predictability of this phenomenon

difficult.

Since the contractility and relaxation capacities of both the necrotic and penumbra parts of the left ventricle decrease after acute MI, the interventricular pressure causes extra wall tension in the healthy myocardium. Depending on this wall tension, cardiomyocytes release a number of molecules to increase MI. sST2 is one of these molecules²¹. Recently, especially after entering guidelines in heart failure, this cardiac biomarker has been used in clinical practice, but its clinical and pathophysiological features have not been clearly determined. A lot of studies have been carried out on the relationship of sST2 with both diagnosis and prognosis in heart failure. However, there is little and contradictory information about the role of sST2 in STEMI patients^{22, 23}. In addition, a study examining the relationship between no-reflow and sST2 is not present in the literature.

Studies showed that sST2 levels were found to be

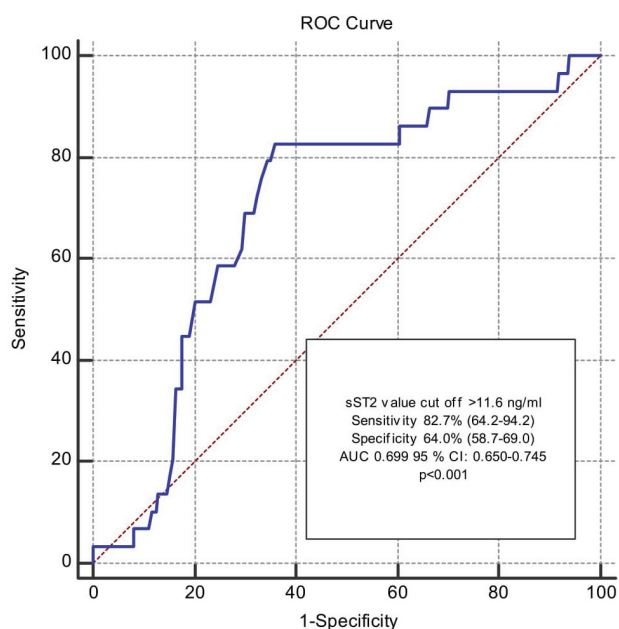


Fig. 1. ROC curve showing the distinguishing ability of soluble ST2 level for the no-reflow phenomenon

AUC, area under the ROC curve; CI, confidence interval; ROC, receiver operating characteristics.

significantly increased as a result of neutrophil infiltration during the exacerbation of diseases such as chronic obstructive pulmonary disease (COPD) and pneumonia^{24, 25}). Since sST2 has been shown to play a role in the release of proinflammatory cytokines from macrophages, it is thought that these cytokines may cause inflammation and free radicals in the acute phase and cause no-reflow in STEMI patients. Given the correlation of no-reflow frequency with inflammatory activity, this assumption supports our hypothesis that no-reflow may be more common in individuals with high sST2 levels. Furthermore, studies have found a poor association with sST2 and other clinical features of MI which indicate that sST2 elevation reflects a separate mechanical pathway from other known biomarkers²⁶). So, sST2 can provide us with new information about the course of MI.

The IL-33/sST2 pathway also plays a role in the induction of allergic inflammation. In particular, this pathway is thought to be one of the primary pathways responsible for allergic diseases such as asthma, atopic dermatitis, and autoimmune diseases such as rheumatoid arthritis²⁷). In a study on smoke-induced COPD mice, the IL-33/sST2 pathway has been shown to

Table 3. Multivariate Logistic Regression Analysis for Potential Predictors of No-Reflow Phenomenon

	Univariate analysis		Multivariate analysis [‡]	
	OR (CI 95%)	<i>p</i> value	OR (CI 95%)	<i>p</i> value
Demographic variables				
Age, years	1.034 (1.010–1.060)	0.006	1.016 (0.989–1.045)	0.253
Male, yes	1.144 (0.448–2.922)	0.779	----	----
DM, yes	2.025 (1.139–3.602)	0.016	2.126 (1.096–4.125)	0.026
Statin use, yes	0.531 (0.284–0.994)	0.048	0.554 (0.276–1.111)	0.096
SBP, mmHg	0.974 (0.958–0.990)	0.002	0.982 (0.969–0.995)	0.007
Killip Class > 1	1.708 (0.725–4.343)	0.208	----	----
Laboratory data				
eGFR, (mL/min/1.73m ²)	0.990 (0.975–1.005)	0.206	----	----
WBC, count (10 ³ /L)	1.007 (0.972–1.043)	0.710	----	----
Peak troponin, mg/dl	1.053 (0.972–1.140)	0.206	----	----
Procedural features				
IRA*	1.505 (0.709–3.235)	0.283	----	----
Total lesion, yes	3.565 (1.885–6.743)	<0.001	2.505 (1.249–5.023)	0.010
Multivessel disease, yes	2.738 (1.533–4.892)	0.001	2.288 (1.174–4.456)	0.015
High thrombus burden, yes	2.563 (1.464–4.520)	0.002	2.737 (1.464–5.118)	0.002
Predilatation, yes	2.010 (1.075–3.759)	0.029	1.287 (0.606–2.735)	0.511
Syntax score	1.081 (1.033–1.131)	0.001	0.979 (0.919–1.041)	0.489
High sST2 [‡]	3.432 (1.925–6.119)	<0.001	2.741 (1.433–5.244)	0.002

*IRA was divided into two groups as LAD and non LAD lesions.

[‡]High sST2 was formed according to the cut-off value 11.6 ng/ml which is derived from ROC analysis

[‡]Nagelkerke R square of the full model was 29.8%.

Abbreviations: CI, confidence interval; DM, Diabetes mellitus; OR, odds ratio; SBP, systolic blood pressure; WBC, white blood cell; eGFR, estimated glomerular filtration rate; sST2, soluble ST2; IRA, infarct-related artery

induce IL-6 and IL-8 and cause systemic inflammation²⁸). In addition, in another study, the increase in IL 6 via ST2 receptor in human arterial endothelial cells may have a role in the pathophysiology of idiopathic pulmonary arterial hypertension²⁹). Moreover, the study³⁰) that shows a relationship with IL-6 and a slow coronary flow phenomenon may explain the high ST2 levels leading to an increase in the no-reflow phenomenon. The reflection of the above-mentioned pathophysiological mechanisms to the clinical status has been shown in our study; that being in the high-sST2 group had 2.7 times increased odds for the no-reflow compared to the low-sST2 group independent of known risk factors such as age, DM, thrombus burden, and the presence of a total lesion before the intervention.

The findings of our study confirm the data in the studies investigating the role of sST2 in predicting the adverse outcome after STEMI. Shimpo *et al.* showed that high-sST2 levels were associated with increased major cardiovascular adverse events in the short-term follow-up after STEMI³¹). This study has also shown that sST2 is the predictor of mortality independent of parameters such as age, heart rate, blood pressure, and Killip class during the 30-day period after PCI. In parallel to this study, Sabatine and his colleagues found that sST2 levels above the median value predicted in-hospital mortality³²). No-reflow rate in PCI-treated STEMI patients was 15.4% in our study. In addition, in-hospital mortality was higher in the high-sST2 group compared to the low-sST2 group similar to the above-mentioned studies (9.1% vs. 2.0%, $p=0.002$).

In addition to sST2, other parameters that may affect no-reflow were also investigated. More no-reflow was observed in elderly individuals in parallel with other studies³³). DM was found to be an independent predictor of no-reflow as shown in most of the studies (OR: 2.12, 95% CI 1.09–4.12, $p=0.026$)^{34, 35}). The burden of thrombus in the occluded vessel is generally high, which may increase the risk of no-reflow³⁶). Particularly, as a possible mechanism, the removal of atherothrombus plates after stent placement and embolism of the thrombus fragments to the distal region leads to no-reflow, and consequently, the poor prognosis will become inevitable with decreasing myocardial perfusion and increasing infarct area³⁷). In our study, the high thrombus burden was one of the independent predictors of no-reflow (OR: 2.73, 95% CI 1.46–5.11, $p=0.002$).

There are some limitations in our study. First, this was a single-center study which may result in selection bias. Second, it seems difficult to compare our results with other studies on this subject due to

differences in pre-analytical medical therapy, storage techniques, and ELISA kits. Besides, repeated measurements of sST2 were not calculated, so, changes which may affect the result could not be derived. We investigated the predictive value of the sST2 using the 11.6 ng/ml value acquired from the ROC analysis. Therefore, our results can be evaluated only for our cohort and needs validation in other large populations. But, this limitation is present in all studies with the particular population on the use of biomarkers. Finally, there were no data about the admission time of the patients in our study. Patient or system-induced delays in STEMI patients may also affect the no-reflow phenomenon³⁸). In particular, the delayed presentation has been shown to be associated with edema in the capillary bed, swelling of the myocardial cells, and neutrophil accumulation³⁹). Since the pathophysiological mechanisms in no-reflow in delayed patients may be triggered by sST2, it can be speculated that delayed patients may have high levels of sST2, although the admission time was not included in our study.

Conclusion

In summary, sST2 can help physicians predict the no-reflow phenomenon after primary PCI in STEMI patients. Moreover, patients with DM, more severe coronary artery disease, grade 0 initial TIMI flow rate, and lower systolic blood pressure constitute the risk for the no-reflow group. Our choice of treatment is very limited after the occurrence of this complication, so it is important to recognize patients who may develop no-reflow after PCI. As STEMI patients with high levels of sST2 have lower successful procedure rates and consequently have adverse events in the hospital more frequently, it may be considered to use methods such as more intensive antithrombotic use or stent implantation without predilatation to reduce no-reflow in this group of patients. Further studies are needed to understand the effect of sST2 on the no-reflow pathogenesis and to identify protective strategies in high-risk patients.

Conflicts of Interest

The authors declare that there was no conflict of interest.

Funding

No funding was received for this research.

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