

Soluble ST2 in Predicting Adverse Outcome after Revascularization with Percutaneous Coronary Intervention in Patients with ST-Elevation Myocardial Infarction

ST-Yükselmeli Miyokard Enfarktüsülü Hastalarda Perkütan Koroner Girişim ile Revaskülarizasyon Sonrası Advers Sonucu Öngörmede Çözünür ST2

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ABSTRACT

Aim: The aim of the study was to investigate the relationship between the soluble suppression of tumorigenicity 2 (sST2) level and the degree of epicardial blood flow recovery in patients with myocardial infarction with ST-segment elevation (STEMI) after percutaneous coronary intervention.

Material and Methods: The study involved 61 patients (83.6% males), with a mean age of 59.85±10.01 years. sST2 level was measured by enzyme immunoassay. Patients were divided into two groups. The first group (n=12) included patients with thrombolysis in myocardial infarction (TIMI) ≤II flow grade, the second group (n=49) with TIMI III flow grade.

Results: The sST2 level was significantly higher in the first hours of the disease in the group with decreased epicardial blood flow (TIMI ≤II) after percutaneous coronary intervention (p=0.003). Receiver operating characteristics curve analysis showed that sST2 levels over 34.2 ng/ml, detected on admission, was an independent predictor of adverse revascularization (TIMI ≤II) in patients with STEMI with a sensitivity of 92.3% and a specificity of 62.5%; the area under curve was 0.811 (95% CI: 0.651 - 0.873; p=0.001). Both the univariate (OR: 1.020, 95% CI: 1.001-1.041, p=0.028) and multivariate (OR: 1.030; 95% CI: 1.002-1.057; p=0.033) analyzes showed that sST2 was a significant predictor of the unfavorable outcome of epicardial vascular revascularization (TIMI ≤II).

Conclusion: sST2 is highly associated with the degree of blood flow recovery after percutaneous coronary intervention in patients with STEMI and is of great clinical importance as a prognostic marker.

Keywords: Acute myocardial infarction; sST2; no-reflow phenomenon; percutaneous coronary intervention.

ÖZ

Amaç: Bu çalışmanın amacı, ST-segment yükselmesi (STEMI) olan miyokard enfarktüsülü hastalarda perkütan koroner girişim sonrası tümörjenisitenin çözünür baskılanması 2 (soluble suppression of tumorigenicity 2, sST2) seviyesi ile epikardiyal kan akımının düzelleme derecesi arasındaki ilişkinin araştırılmasıdır.

Gereç ve Yöntemler: Çalışmaya ortalama yaşı 59.85±10.01 yıl olan 61 hasta (%83,6 erkek) dahil edildi. sST2 seviyesi enzim immunoassay ile ölçüldü. Hastalar iki gruba ayrıldı. Birinci grup (n=12) miyokard enfarktüsünde tromboliz (thrombolysis in myocardial infarction, TIMI) ≤II akım dereceli hastaları, ikinci grup (n=49) ise TIMI III akım dereceli hastaları içeriyordu.

Bulgular: Epikardiyal kan akımı azalmış (TIMI≤II) olan grupta perkütan koroner girişim sonrası hastalığın ilk saatlerinde sST2 düzeyi anlamlı olarak daha yüksekti (p=0.003). Alıcı işlem karakteristiği eğrisi analizi, başvuru sırasında saptanan 34,2 ng/ml'nin üzerindeki sST2 düzeylerinin, STEMI hastalarında %92,3 duyarlılık ve %62,5 özgüllük ile advers revaskülarizasyonun (TIMI ≤II) bağımsız bir ön gördürücüsü olduğunu göstermiştir; eğri altında kalan alan 0,811 (%95 GA: 0,651 - 0,873; p=0,001) idi. Hem tek değişkenli (OR: 1,020; %95 GA: 1,001-1,041; p=0,028) ve hem de çok değişkenli (OR: 1,030; %95 GA: 1,002-1,057; p=0,033) analizler sST2'nin epikardiyal vasküler revaskülarizasyonun olumsuz sonucunun (TIMI≤II) anlamlı bir ön gördürücüsü olduğunu gösterdi.

Sonuç: sST2, STEMI olan hastalarda perkütan koroner girişim sonrası kan akımındaki iyileşme derecesi ile yüksek oranda ilişkilidir ve prognostik bir belirteç olarak büyük klinik öneme sahiptir.

Anahtar kelimeler: Akut miyokard enfarktüsü; sST2; no-reflow fenomeni; perkütan koroner girişim.

INTRODUCTION

Acute coronary syndrome (ACS) continues to be among the most significant causes of death worldwide, which is clearly seen in developed countries. Despite the introduction of high-tech interventions, the use of new highly effective drugs and an increase in public awareness of the need to seek early medical care, mortality remains high. Percutaneous coronary intervention (PCI) restores blood flow in infarction-dependent artery in patients with acute myocardial infarction (AMI), making a significant contribution to the regression of disease symptoms and improving a prognosis. However, the effectiveness of stenting of subepicardial arteries is not 100% always. It is considered that the no-reflow phenomenon is among the reasons for this, which reduces the beneficial effects of PCI. The no-reflow phenomenon is defined as insufficient myocardial perfusion that persists despite a mechanically open infarction-dependent artery. The frequency of the no-reflow phenomenon varies and reaches 50%, depending on the assessment methods, especially in patients with ACS (1). There are studies that show that this phenomenon is associated with a poor prognosis, such as increased hospital and long-term mortality, and progression of heart failure (HF) (2,3) The thrombolysis in myocardial infarction (TIMI) scale is used to assess the degree of blood flow restoration in the infarction-related artery. It is of great importance to identify new sustainable markers that can predict the unfavorable course of revascularization.

Soluble suppression of tumorigenicity 2 (sST2) can be considered as the newest marker, and it is a member of the IL-1 family. It plays an important role in myocardial remodeling and inflammation processes (4). It has been shown that sST2 levels are increased in cardiovascular stress and myocardial fibrosis (5,6). sST2 competitively binds to IL-33 and blocks its positive effect on the myocardium, causing fibrosis and myocardial hypertrophy (7). There are some studies that show sST2 as an independent predictor of mortality in patients with ACS, both in the short and in the long term (8,9). The relationship between high sST2 levels and adverse cardiovascular events in patients with AMI has been established (10). Recent data suggest sST2 as a promising prognostic marker in heart failure (11). There are findings showing that sST2 in contrast to the rest of heart biomarkers is linked to cardiac remodeling irrespective of renal function (12).

Herewith, the prognostic value of sST2 in the prognosis of an unfavorable course of revascularization in patients with AMI with ST-segment elevation has not yet been sufficiently studied. In our study the relationship between sST2 levels and unfavorable outcomes of revascularization in patients with ST-elevation myocardial infarction (STEMI) after PCI was analyzed.

The purpose of the study was to find out the relationship between the level of sST2 and the degree of epicardial blood flow restoration in patients with ST-elevation myocardial infarction after PCI.

MATERIAL AND METHODS

The study involved 61 patients with AMI with ST segment elevation, among them 51 (83.6%) male and 10 (16.4%) female, with a mean age of 59.85 ± 10.01 years. The patients were hospitalized and examined during the first

hours of the disease. The adverse event was considered as coronary flow $TIMI \leq II$ after PCI.

The study was conducted at the Department of Prevention and Treatment of Emergency Conditions in Government Institution "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine", Kharkiv, between 2016 and 2017.

The diagnosis of AMI was established on the basis of data from clinical, electrocardiographic and biochemical studies in accordance with the European guidelines for the diagnosis and treatment of AMI with ST segment elevation, 2017 (13).

The studies were carried out in accordance with the provisions of the Declaration of Helsinki. The study protocol was approved by the Ethics and Deontology Commission (№ 12 from 21.10.2015). Each patient signed an informed consent to participate in the study.

Clinical and biochemical parameters were determined in all patients on the first day of the disease. Additionally, the level of sST2 was determined by the enzyme immunoassay using the Presage ST2 Assay reagent kit, Critical Diagnostics (USA) and NT-proBNP using the NTproBNP-ELISA-BEST kit (Russia). Immunoassay studies (sST2, NT-proBNP, troponin I) were carried out on an Immunochem-2100 enzyme immunoassay analyzer (USA), head. No. 501322057FSE. Echocardiographic examination was carried out using the Medison SonoAceX6 apparatus (Korea), end-systolic volume (ESV), end-diastolic volume (EDV) of the left ventricle (LV), LV diastolic dysfunction were assessed - the maximum early diastolic filling velocity E (m/s), maximum speed of atrial diastolic filling A (m/s), their ratio E/A and LV ejection fraction (EF) according to Simpson method.

Patients received therapy in accordance with the current recommendations of the European Society of Cardiology during the entire period of treatment (13).

Inclusion criteria in the study were: patients with AMI with ST-segment elevation, hospitalization within 24 hours after the onset of the disease, age $\geq 50 \leq 75$ years, signed informed consent to participate in the study.

Exclusion criteria were refused informed consent, infectious and inflammatory diseases in the acute stage, glomerular filtration rate (GFR) < 60 ml/min/1.73m², acute liver failure, type 1 diabetes mellitus, hypertrophic cardiomyopathy, life-threatening arrhythmias, thyroid disease, severe obesity (body mass index, BMI > 35 kg/m²), arrhythmias, inability to follow the study protocol, and patient's discontinuation at any stage of the study.

Sample size were calculated with help of online sample calculator <http://www.raosoft.com/samplesize.html>, with margin of error accepted 10%, confidence level of 95%, the size of all performed PCI in the center of 200, the recommended sample size was 66 patients.

Statistical Analysis

Statistical processing of the obtained data was carried out using the statistical software Statistica 10.0 (StatSoft Inc, USA), Microsoft Office Excel 2013. Shapiro-Wilk test was used to test normality of distribution. Indicators were presented as median (interquartile range, IQR) [min-max] in descriptive statistics, taking into account the different from the normal distribution of variables. Categorical

variables were given as percentages. Intergroup differences in qualitative characteristics were assessed using a non-parametric test, Mann-Whitney U test. The Kruskal-Wallis test was used to compare more than two independent groups. Two-sided p-value of Fisher's exact test was used for categorical variables comparison. The determination of optimal cut-off value of sST2 to distinguish the degree of blood flow restoration in the infarction-related artery was performed by the receiver operating characteristics (ROC) curve analysis. In order to find independent predictors of degree of blood flow restoration in the infarction-related artery (TIMI score) logistic regression analysis was used. Possible confounding factors were analyzed in univariate regression analysis and confounders with a p value of <0.1 were tested in multivariate logistic regression analysis. A p value of <0.05 was accepted as statistically significant.

RESULTS

The patients were divided into two groups depending on the degree of blood flow restoration in the infarction-dependent artery (TIMI): the first group (n=12) included patients with TIMI 0, I, II, the second group (n=49) with TIMI III. Table 1 presents the baseline clinical characteristics of patients with STEMI who participated in the study. As it comes from Table 1, the both groups divided by blood flow recovering were matched by all baseline parameters; sex, age, presence of arterial hypertension, diabetes mellitus type 2 and hypercholesterolemia, smoking state, BMI, kidney

function and STEMI localization. Examined initial levels of biomarkers troponin I peak and NT-pro BNP were also statistically similar in the groups, in contrast to this the sST2 values differed significantly (81.39; 95% CI: 38.53-136.19 ng/mL vs 29.26; 95% CI: 22.77-52.78 ng/mL; p=0.003). Herewith, there were significant differences in percentage of patients with infarction-dependent artery: patients with TIMI III were prevalent with left main coronary artery (0% vs 49%, p=0.002), but those with TIMI ≤2 with left anterior descending artery (47.1% vs 6.1%, p=0.001). Right main coronary artery and first diagonal (D1) artery of the left anterior descending artery were involved without statistical differences in proportions, p=1.000 and p=0.357, respectively.

The data presented in Table 2 evidence statistically similar of majority hemodynamic and ultrasound values in both groups. It should be marked that there was a significant difference between TIMI groups just in systolic blood pressure (SBP, p=0.029) and LVEF (p=0.041). Aside from that, the rest investigated parameters: heart rate, diastolic blood pressure (DBP), left atrium (LA), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), the ratio (E/A) of mitral peak velocity of early filling (the E wave) to mitral peak velocity of late filling (the A wave), left ventricle mass (LVM) did not demonstrated significant differences.

There were also analyzed the differences in sST2 and NT-pro BNP levels in dependence of occlusion localizations with the aim to find out the possible association between biomarker values and occlusion localizations - right main

Table 1. Baseline characteristics of patients with STEMI

	Patients with TIMI 0-II (n=12)	Patients with TIMI III (n=49)	p
Demographic parameters and risk factors			
Age (years)	62.7 (17.5) [52 - 74]	57.2 (14.0) [50 - 75]	0.104
Males, n (%)	10 (83.3%)	41 (83.7%)	1.000
Arterial hypertension, n (%)	11 (91.7%)	34 (69.4%)	0.156
Diabetes mellitus type 2, n (%)	1 (8.3%)	12 (24.5%)	0.432
Smoking, n (%)	8 (66.7%)	19 (38.8%)	0.109
Hypercholesterolemia, n (%)	8 (66.7%)	34 (69.4%)	1.000
Body mass index (kg/m ²)	29.57 (4.45) [26.30 - 34.51]	30.07 (5.91) [21.97 - 35.00]	0.863
GFR CKD-EPI (ml/min/1.73m ²)	79.13 (23.07) [61.45 - 119.82]	78.03 (31.26) [60.06 - 135.42]	0.498
STEMI localization, n (%)			
Anterior MI	7 (58.3%)	23 (46.9%)	0.534
Posterior MI	5 (41.7%)	22 (44.9%)	1.000
Other	0 (0.0%)	3 (6.1%)	1.000
Number of affected vessels, n (%)			
1 vessel	2 (16.7%)	10 (20.4%)	1.000
2 vessels	4 (33.3%)	11 (22.4%)	0.467
3 vessels	0 (0.0%)	16 (32.7%)	0.028
Infarction-dependent artery, n (%)			
Left main coronary artery	0 (0.0%)	24 (49.0%)	0.002
Left anterior descending artery	6 (50.0%)	3 (6.1%)	0.001
Right main coronary artery	5 (41.7%)	21 (42.9%)	1.000
D1 Left anterior descending artery	1 (8.3%)	1 (2.0%)	0.357
Biomarkers' level			
Troponin I peak (ng/ml)	32.4 (32.6) [8.8 - 51.0]	22.4 (17.8) [9.2 - 49.8]	0.446
sST2 (ng/ml)	81.39 (98.19) [20.94 - 319.12]	29.26 (30.01) [13.05 - 155.70]	0.003
NT-proBNP (pg/ml)	232.87 (275.51) [62.67 - 415.83]	247.54 (268.86) [55.99 - 431.67]	0.668

STEMI: ST-elevation myocardial infarction, TIMI: thrombolysis in myocardial infarction, GFR: glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, MI: myocardial infarction, sST2: soluble suppression of tumorigenicity 2, descriptive statistics were presented as median (interquartile range) [min-max].

Table 2. Hemodynamic and ultrasound parameters in patients with STEMI

Indices	Patients with TIMI 0-II (n=12)	Patients with TIMI III (n=49)	p
Heart rate (per min)	70 (27.5) [38 - 100]	76 (20.0) [44 - 115]	0.617
SBP (mm Hg)	145.5 (30.5) [110.0 - 175.0]	130.0 (17.5) [100.5 - 155.0]	0.029
DBP (mm Hg)	85.0 (15.2) [55.0 - 100.5]	83.5 (22.5) [60.0 - 110.0]	0.325
LA (cm)	4.2 (0.8) [3.0 - 5.5]	3.9 (0.8) [3.1 - 5.3]	0.322
LVEDV (ml)	136.5 (62.5) [89.0 - 196.0]	126.0 (39.0) [90.5 - 180.0]	0.480
LVESV (ml)	69.8 (35.2) [40.0 - 102.5]	65.1 (29.5) [35.0 - 104.5]	0.328
LVEF (%)	48.7 (12.0) [45.0 - 59.0]	53.5 (11.7) [45.0 - 73.5]	0.041
E/A	1.08 (0.70) [0.59 - 1.75]	1.22 (0.39) [0.67 - 2.39]	0.163
LVM (gr)	263 (64) [150 - 354]	239 (79) [105 - 390]	0.414

STEMI: ST-elevation myocardial infarction, TIMI: thrombolysis in myocardial infarction, SBP: systolic blood pressure, DBP: diastolic blood pressure, LA: left atrium, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricle ejection fraction, E/A: the ratio of mitral peak velocity of early filling (the E wave) to mitral peak velocity of late filling (the A wave), LVM: left ventricle mass, descriptive statistics were presented as median (interquartile range) [min-max].

coronary artery, left anterior descending artery, D1 artery of the left anterior descending artery, left main coronary artery. The Kruskal-Wallis test indicated no significant difference in the levels of the both studied biomarkers sST2 and NT-proBNP in dependence of the infarct-dependent coronary artery ($p=0.687$). When analyzing the level of sST2 in the studied patients, it was found that its level was significantly higher in the first hours of the disease in the group with unrecovered or decreased epicardial blood flow ($TIMI \leq II$) after PCI ($p=0.003$).

The receiver operating characteristics (ROC) curve analysis was used for determination of optimal cut-off value of sST2 for the prediction revascularization degree (TIMI 0-II). During the ROC analysis, it was found that the sST2 level above 34.20 ng/ml, determined in the first hours of the disease, is suggested to be a possible biomarker for distinguishing TIMI $\leq II$ from TIMI $> II$ in patients with STEMI with a sensitivity of 92.3% and a specificity of 62.5%; the area under the AUC curve was 0.811 (95% CI: 0.651 - 0.873; $p=0.001$).

Univariate and multivariate logistic regression analyses were performed to study independent predictors of the adverse outcome of revascularization indicated as TIMI level degree. When conducting univariate regression analysis it was found that sST2 level (OR: 1.020, 95% CI: 1.001 - 1.041, $p=0.028$); SBP (OR: 1.083, 95% CI: 1.036 - 1.151, $p=0.011$); LVEDV (OR: 0.776, 95% CI: 0.511 - 0.983, $p=0.039$); LVESV (OR: 0.675, 95% CI: 0.351 - 0.997, $p=0.042$); and EF (OR: 1.011, 95% CI: 1.003 - 1.263, $p=0.017$) were independent confounding factors for unfavorable outcome of epicardial revascularization (TIMI 0-II). The multivariate logistic regression analysis which included confounders with a p value of <0.1 obtained from univariate logistic regression analysis indicated that sST2 remained as significant predictor of TIMI 0-II by PCI in patients with STEMI (OR: 1.030; 95% CI: 1.002 - 1.057; $p=0.033$) as is shown in Table 3.

DISCUSSION

It can be highlighted three main findings of our study. First, the values of sST2 in STEMI patients with TIMI $\leq II$ were significantly higher than that of TIMI $> II$ patients. Second, sST2 is independent predictor for the development of adverse revascularization in patients with STEMI after PCI treatment. At last, high sST2 levels on admission evidence on increased risk for no-reflow

Table 3. Univariate and multivariate logistic regression analysis of the influence of the studied factors on the TIMI score ($\leq II$) in patients with STEMI after PCI

Indices	OR (95% CI)	p
Univariate logistic regression		
sST2, ng/ml	1.020 (1.001 - 1.041)	0.028
SBP (mm Hg)	1.083 (1.036 - 1.151)	0.011
DBP (mm Hg)	1.029 (0.889 - 1.076)	0.343
Gender (M/F)	2.155 (0.755 - 1.939)	0.477
Age (years)	0.989 (0.961 - 1.023)	0.949
BMI (kg/m ²)	1.058 (0.919 - 1.139)	0.280
Smoking	3.659 (0.541 - 29.187)	0.653
TC (mmol/L)	0.861 (0.519 - 1.314)	0.119
LVEDV (ml)	0.776 (0.511 - 0.983)	0.039
LVESV (ml)	0.675 (0.351 - 0.997)	0.042
LVEF (%)	1.011 (1.003 - 1.263)	0.017
Multivariate logistic regression		
sST2, ng/ml	1.030 (1.002 - 1.057)	0.033
SBP (mm Hg)	1.097 (0.991 - 1.189)	0.057
LVEDV (ml)	0.990 (0.931 - 1.062)	0.871
LVESV (ml)	0.903 (0.802 - 1.199)	0.576
LVEF (%)	1.845 (0.948 - 1.291)	0.633

STEMI: ST-elevation myocardial infarction, TIMI: thrombolysis in myocardial infarction, PCI: percutaneous coronary intervention, OR: odds ratio, CI: confidence interval, sST2: soluble suppression of tumorigenicity 2, SBP: systolic blood pressure, DBP: diastolic blood pressure, M: male, F: female, BMI: body mass index, TC: total cholesterol, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricle ejection fraction.

development compared with initial low sST2 levels. Our study is the first attempt to identify association between sST2 and no-reflow phenomenon in PCI-administered STEMI patients. The presented results prove that sST2 level on admission is significantly associated with no-reflow phenomenon and can be used to predict it development.

Our study possibly gave additional proof that the essential chain in the process of no-reflow is inflammation. The phenomenon of no-reflow, which is defined as incomplete reperfusion at the microvascular level, despite the complete opening of the infarction-dependent artery, which may be due to tissue edema, the presence of microthrombi, accumulation of neutrophils and the formation of free radicals, which are believed to be associated with

inflammation after coronary perfusion (14). Potential risk factors for no-reflow are thought to be associated with inflammatory activity after AMI. Most likely, the no-reflow phenomenon prediction becoming rather difficult due to the complexity of its occurrence mechanism.

sST2 is one of the molecules that cardiomyocytes release when the myocardium is damaged. Recently, this biomarker has been included in the clinical guidelines for HF and is widely used and studied in patients with HF (15-17). The search for an association of sST2 with genetic polymorphisms in HF continues (18). Herewith its pathophysiological features in AMI have not been adequately studied, especially in terms of the no-reflow phenomenon. The existing data on the role of sST2 in AMI are contradictory (19,20). In the study on mice, it was shown that the IL-33/sST2 pathway induces IL-6 and IL-8 and causes systemic inflammation (21).

In his study Tuegel et al. (22) found that in patients with renal disease with higher circulating sST2 levels have increased mortality, possibly through inflammatory, fibrotic changes and heart remodelling. Thus, this result indirectly is aligned with our preposition that higher sST2 levels give negative prognosis in patients. On the other hand, Tuegel et al. (22) did not find sST2 interconnection with heart failure or atherosclerotic CVD in multivariable models.

As we found a prognostic role of admission sST2 level in low TIMI score after PCI in STEMI patients, another investigation proved this biomarker is a possible predictor of contrast-induced nephropathy (CIN) in STEMI patients (23). Now, it can be seen that sST2 became great clinical prognostic parameter for several end-points.

Findings from European multicenter randomized placebo-controlled study (PROTECT) investigating 44 novel heart biomarkers in heart failure. It verified sST2 as a strong independent predictor all-cause mortality and cardiovascular or kidney rehospitalization (24). Therefore, we consider that our results are in correspondence with these conclusions from mentioned European study, because no-reflow can be essential reason for poor prognosis (25).

The results from our study are important due to appearance of a new predictor of no-reflow phenomenon in addition to previously described ones in Fajar et al. (26) review.

Balta et al. (27) devoted their investigation to find another new predictor of no-reflow in STEMI patients, and proved that monocyte to high density lipoprotein ratio (MHR) is an independent predictor of no reflow after pPCI. The ROC analysis from that study showed that the MHR level cut-off point was 22.5 ng/ml, with a sensitivity and specificity of 70.2% and 73.3%, respectively (AUC=0.768, 95% CI: 0.725-0.811), but we showed, that sST2 with a higher sensitivity level and 11% less specificity and the closely equal AUC. Our consideration is that the both parameters can be used for no-reflow predicting, and further researches obligatory to find optimal marker or to use them simultaneously.

The purpose of our study was close to Zhao et al. (28) study. In that study they evaluated if admission fibrinogen-to-albumin ratio (FAR) values is associated with no-reflow in 510 STEMI patients. It was similar to our study, because it also specifying TIMI \leq II flow grade influence on "no-reflow". Zhao et al. (28) showed that

admission FAR can be considered as an independent predictor of no-reflow. ROC analysis elucidated the FAR cut-off value can predict no-reflow with a sensitivity of 79.59% and a specificity of 69.42%, that was shade less than our ROC results. Zhao et al. (28) showed admission FAR value is positively associated with all-cause mortality, as well as sST2 (22,24).

sST2 plays a role in the release of proinflammatory cytokines from macrophages and induces inflammation and free radical release in the acute phase of myocardial infarction and, it seems that it may be the cause of the no-reflow phenomenon in AMI patients. This is consistent from our data according to which the level of sST2 in patients with blood flow according to the TIMI \leq II scale is significantly higher than in patients with TIMI III blood flow. There is a study showing the relationship of IL-6 with the phenomenon of slow coronary flow. Thus that results also impliedly accord idea that the high levels of sST2 might lead to an increase in the frequency of the phenomenon of no-reflow (29).

The study by Sabatine et al. (30) determined sST2 in patients with STEMI who underwent coronary angiography. The follow-up period was 30 days. The sST2 value was associated with a significantly greater risk of cardiovascular death or heart failure. In our study, when conducting a logistic regression analysis, sST2 turned out to be a significant predictor of an unfavorable outcome of revascularization in patients with AMI with ST segment elevation.

The obtained results confirm the data of studies in which the role of sST2 in predicting the unfavorable course of AMI was studied. Shimpo et al. (31), investigated sST2 in patients with STEMI in the TIMI 14 and TIMI 23 studies. The baseline sST2 level was significantly higher in deceased patients and in patients with heart failure developed by 30 follow-up days. When analyzing adverse events by day 30 of follow-up, both death and the combined death/HF endpoint showed a significant association with sST2 levels. Also, in-hospital mortality and death/HF were associated with higher sST2 levels. The data we obtained correspond to the available literature data - determination of sST2 over 34.2 ng/ml makes it possible to predict an unfavorable outcome of revascularization in patients with AMI with TIMI score \leq II.

This study presents several limitations. First, the limitation of our study was the small sample size to achieve definitive conclusions. Another was that only one clinical center was involved. Also, it should be indicated that males were predominantly presented in the study. Additionally, it was a prevalence of the patients with TIMI III compared to those ones with TIMI \leq II, hence it could intend to some statistical discordances, on the other hand, we used appropriate (non-parametric) statistical methods doing our best to avoid this. We also measured just TIMI score as outcome, without considering other possible endpoints.

Further studies are required on the role of sST2 in the pathogenesis of the no-reflow phenomenon, and the search for effective methods to prevent it. The promising for further study is the investigation of the no-reflow phenomenon with the assessment of the possible relationship of myocardial perfusion on the myocardial blush grade (MBG) scale with the studied marker.

CONCLUSION

No-reflow is incomplete reperfusion after percutaneous intervention in STEMI patients resulting in adverse endpoints. We demonstrated that the sST2 level at admission is independently associated with the no-reflow phenomenon in STEMI patients after PCI. The sST2 level estimation is suggested to be important to prevent the no-reflow phenomenon development in STEMI patients. Further research is needed to understand the sST2 influence on decreased blood flow development and to prognosticate patients at high risk for poor outcomes.

Ethics Committee Approval: The study was approved by the Ethics Committee of Government Institution “L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine” (21.10.2015, 12).

Conflict of Interest: This manuscript was produced based on the PhD thesis of Yaroslava Hilova, and all authors declare that there is no conflict of interest.

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