The Predictive Value of the Combination of Soluble ST2 and N Terminal-Pro Brain Natriuretic Peptide for Short-Term Mortality in ST-Elevation Myocardial Infarction Patients with Poor Post-Procedural TIMI Flow

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ABSTRACT

Introduction: The increase in soluble ST2 (sST2) and N Terminal-Pro Brain Natriuretic Peptide (NT-proBNP) in ST-elevation myocardial infarction (STEMI) is well established, however, the existing data regarding the combination of sST2 and NT-proBNP values as prognostic markers after STEMI are limited, particularly in the case of those with failed percutaneous coronary intervention (PCI). This study aimed to assess the clinical significance of the sST2 and NT-proBNP combination in predicting short-term mortality in STEMI patients with post-procedural poor thrombolysis in myocardial infarction (TIMI) flow.

Patients and Methods: A total of 104 patients with post-procedural poor TIMI flow were included in the study. Failure to provide a 3 flow grade was accepted as post-procedural poor TIMI flow. The study population was grouped according to the sST2 and NT-proBNP levels. Independent predictors of short-term mortality were investigated.

Results: A 30 day mortality was observed in 15 (14.4%) patients. sST2 (46.9 ± 23.8 ng/mL vs. 32.5 ± 12.0 ng/mL, p= 0.001) and NT-proBNP (2387.2 ± 2255.5 pg/mL vs. 1217.1 ± 1588.8 pg/mL, p= 0.015) levels were higher in patients with mortality. Multivariate regression analysis concluded that high serum sST2 (OR: 5.024, 95% CI 1.132-22.308, p= 0.034) independently predicted short-term mortality, while NT-proBNP did not (OR: 4.059, 95% CI 0.894-18.427, p= 0.070). Furthermore, when a high sST2 level was combined with a high NT-proBNP level, the odds ratio of the 30-day mortality was found to be the highest (13.02, 95% CI 5.41-31.23, p< 0.001).

Conclusion: These results suggest that the combined sST2 and NT-proBNP level are essential predictors of short-term mortality in STEMI patients with post-procedural poor TIMI flow.

Key Words: Brain natriuretic peptide; no-reflow phenomenon; mortality; percutaneous coronary intervention

Perkütan Koroner İşlem Sonrası Zayıf TIMI Akımı Olan ST Elevasyonlu Miyokart İnfarktüsü Hastalarında Soluble ST2 ve N Terminal-Pro Brain Natriüretik Peptid Kombinasyonunun Kısa Dönem Mortaliteyi Öngördürebilirlik Değeri

ÖZET

Giriş: ST elevasyonlu miyokart infarktüsü (STEMİ)'nde, soluble ST2 (sST2) ve N Terminal-Pro Brain Natriüretik Peptid (NT-proBNP) seviyelerindeki yükselme net olarak ortaya konmakla birlikte, STEMİ hastalarında, özellikle de başarısız perkütan koroner işlem (PKİ) uygulananlarda, sST2 ve NT-proBNP'nin kombinasyonunun prognostik değerine ait veriler kısıtlıdır. Bu çalışmada, işlem sonrası TIMI akımı düşük olan STEMİ hastalarında sST2 ve NT-proBNP kombinasyonunun kısa dönem mortaliteyi öngördürmesi açısından klinik önemini değerlendirmeyi amaçladık.

Hastalar ve Yöntem: İşlem sonrası düşük TIMI akımı olan 104 hasta çalışmaya dahil edildi. TIMI 3 akım sağlanamaması, işlem sonrası düşük TIMI akım olarak kabul edildi. Çalışma popülasyonu sST2 ve NT-proBNP seviyelerine göre gruplara ayrıldı. Kısa dönem mortalitenin bağımsız prediktörleri araştırıldı.

Bulgular: Otuz günlük mortalite 15 (%14.4) hastada gerçekleşti. Mortalite gerçekleşen hastalarda sST2 (46.9 ± 23.8 ng/mL vs. 32.5 ± 12.0 ng/mL, p= 0.001) ve NT-proBNP (2387.2 ± 2255.5 pg/mL vs. 1217.1 ± 1588.8 pg/mL, p= 0.015) seviyeleri daha yüksekti. Multivaryant regresyon analizi, yüksek serum sST2'nin (odds oranı 5,024, %95 CI 1.132-22.308, p= 0.034) kısa dönem mortaliteyi bağımsız olarak predikte edebildiğini, fakat aynı durumun NT-proBNP için geçerli olmadığını gösterdi (odds oranı 4.059, %95 CI 0.894-18.427, p= 0.070). Buna ek olarak, yüksek sST2 seviyeleri, yüksek NT-proBNP ile kombine edildiğinde 30 günlük mortalite için en yüksek odds oranına ulaşıldı (13.02, %95 CI 5.41-31.23, p< 0.001).

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Sonuç: Bu sonuçlar, sST2 ve NT-proBNP kombinasyonunun, işlem sonrası düşük TIMI akım olan STEMİ hastalarında kısa dönem mortalitenin önemli bir prediktörü olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Beyin natriüretik peptid; no-reflov fenomeni; mortalite; perkütan koroner girişim

INTRODUCTION

Acute coronary syndrome (ACS) remains one of the most important causes of mortality, despite advances in diagnosis and treatment[1]. Rapid restoration of the arterial flow in total lesions provides serious benefits for ST-elevation myocardial infarction (STEMI) patients in the short- and long-term[2]. However, the inability to provide reflow prevents the patient from experiencing any benefit from the process[3]. Since adverse events occur more frequently in patients who do not have satisfactory final thrombolysis in myocardial infarction (TIMI) flow[4], it is more important to identify high-risk parameters in these patients by using more detailed methods.

The soluble suppression of tumorigenicity 2 (sST2), a member of the interleukin (IL)-1 family, is considered to play a role in cardiac remodelling and in the inflammatory process[5]. sST2 levels are thought to increase with cardiovascular stress and cardiac fibrosis, which ultimately create a substrate for fatal arrhythmia[6,7]. Circulating sST2 prevents the positive effects of IL-33 to be felt on myocardial fibrosis, hypertrophy, apoptosis, and myocardial function[8]. sST2 has been shown to be an independent predictor of both short- and long-term follow-up and is independent of myocardial infarction (MI) type[9,10]. In addition, a higher increase of sST2 in patients with lower initial TIMI flow[11] suggests that this marker may be associated with post-procedural TIMI flow[11].

There is insufficient evidence in the literature on the early predictors of poor outcome in patients who cannot achieve satisfactory final TIMI flow. In addition to this, we do not know if the sST2 and N Terminal-Pro Brain Natriuretic Peptide (NT-proBNP) levels are related to cardiac mortality either separately or together in STEMI patients with poor final TIMI flow. Therefore, we aimed to evaluate the additive short-term prognostic value of the combination of NT-proBNP and sST2 in STEMI patients with poor post-procedural TIMI flow.

PATIENTS and METHODS

In this study, 472 patients who were admitted to a large-volume centre with a diagnosis of STEMI and who underwent primary percutaneous coronary intervention (PCI) between April 2017 and November 2018 were evaluated as potential study participants. Five of these patients were excluded from the study because of death before PCI. The remaining 467 patients were evaluated for TIMI flow and 109 patients with TIMI flow grade < 3 were planned as study participants. Five more patients were further excluded from the study: 2 due to active malignancy and 3 due to chronic dialysis. Following this exclusion, 104 patients with post-procedural TIMI flow grade < 3 were included in the study. STEMI patients were defined as patients with typical chest discomfort or other ischaemic symptoms, who had developed new ST-segment elevations in two or more contiguous leads or new bundle branch blocks with ischaemic repolarisation patterns on the standard 12-lead electrocardiogram. All primary PCI procedures were performed by operators who routinely performed more than 100 PCIs in one year at a single centre (> 3.000 PCIs/year). Informed consent was obtained from all patients and the Declaration of Helsinki requirement was provided, and ethical committee approval was obtained from our university for all patients.

Information regarding patient demographic parameters, past medical histories, and medical therapies was collected. Five millilitres of peripheral venous blood were taken from all patients and placed in ethylenediamine tetra acetic acid (EDTA)-coated vacutainer tubes at the time of hospital admission. Immediately after that, the blood was separated by centrifugation and eventually stored at -70°C. sST2 levels were measured using the sandwich enzyme immunoassay using enzyme-linked immunosorbent assay (ELISA) kits (Shanghai YL Biotech, Shanghai, China) according to the manufacturer's protocol. The coefficients of intra-assay and inter-assay variation of sST2 were 8-10% and the correction was used to reach standard value. The sensitivity of the sST2 assay for plasma samples was 0.13 ng/L. First, the study population was divided into two groups according to the sST2 and NT-proBNP levels (low sST2 = 53 points, mean age: 61.9 ± 12.8 years; high sST2 = 51 points, mean age: 64.5 ± 9.2 years; low NT-proBNP = 51 points, mean age: 60.5 ± 8.7 years; and high NT-proBNP = 53 points, 65.8 ± 12.8 years). In addition, patients were divided into two groups according to the presence of 30-day mortality: group 1 (n= 15, mean age: 65.5 ± 4.3 years) consisted of patients with cardiac mortality and group 2 (n= 89, mean age: 62.8 ± 11.9 years) consisted of surviving patients.

The patients' angiographic data were reached by assessing catheter laboratory records. Blood flow was calculated using the TIMI classification[12], and patients with TIMI 3 were excluded from the study. Primary angioplasty was performed only for infarct-related artery (IRA) occlusion (either total or partial). Each patient was classified under The Killip classifi-

cation[13]. Short-term mortality was considered if death due to MI, arrhythmia, or heart failure occurred within 30 days after the first hospital admission.

Statistical Analysis

Statistical analysis were performed using the SPSS software version 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The normal distribution of the data was determined by using visual and analytical methods. Descriptive analyses were considered as the mean and standard deviations for variables with normal distribution. Similarly, median and interquartile range were used to represent non-normal distribution. The categorical variables are expressed as numbers and percentages. Multivariate logistic backward stepwise regression that included variables with p< 0.1 on univariate analysis was carried out to identify independent predictors of the 30-day mortality. Nagelkerke r-squared values for logistic regression were recorded. To identify the interaction effect between sST2 and NT-proBNP level, we created two dichotomised variables as high/low sST2 and high/low NT-proBNP. We have used age-related cut-off values since NT-proBNP can vary significantly with age as a general acceptance. The age of the patients determining the low and high NT-proBNP group was < 50, NT-proBNP > 450 pg/mL; age 50-75, NT-proBNP > 900; and age > 75, NT-proBNP > 1800 pg/mL, respectively[14]. Since different methods and kits were used for sST2, the cut-off value was not clearly stated. However, it was determined that a value of > 35 ng/mL accurately predicted mortality in patients with heart failure[15]. It has also been shown that 35 ng/mL can be used to predict the 30-day mortality in both non-STEMI and STEMI patients[10]. In addition, Kohli et al. stated that high sST2 values (> 35 ng/mL) predicted the 30-day and one-year cardiovascular mortality and heart failure with a three-fold risk in patients with ACS[5]. Therefore, 35 ng/mL was used to determine the high sST2 group in our study. A p-value of less than 0.05 was considered statistically significant.

RESULTS

After excluding inappropriate cases, a total of 104 patients were included. The prevalence of the 30-day mortality was 14.4%. There was no statistical difference in terms of traditional risk factors and laboratory values, except in the sST2 (mortality group = 46.9 ± 23.8 ng/mL vs. survival group= 32.5 ± 12.0 ng/mL, p= 0.001) and NT-proBNP levels (mortality group = 2387.2 ± 2255 pg/mL vs. survival group= 1217.1 ± 1588 pg/mL, p= 0.015) (Table 1). Patients with mortality had a Killip > 1 class (40.0% vs. 12.4%, p = 0.007) and had lower systolic and diastolic blood pressure as compared to those who survived (102.8 ± 14.7 mmHg vs. 125.3 ± 23.7 mmHg, p< 0.001; 63.9 ± 8.7 mmHg vs. 73.0 ± 12.8 mmHg, p= 0.010, respectively). Nevertheless, the IRA, severity of coronary artery disease, baseline TIMI grade, and final TIMI grade did not differ between the groups (Table 2).

When the groups were examined according to the sST2 and NT-proBNP levels, patients with pre-procedural TIMI flow 0 were found to be more frequent in the group with a high sST2 value (84.3% vs. 66.0%, p= 0.031) (Table 3). Groups examined according to the NT-proBNP level, revealed that the high NT-proBNP group was older (65.8 ± 12.8 vs. 60.5 ± 8.7, p= 0.007). In addition, the female sex and the ratio of the left anterior descending artery (LAD) as the culprit artery were higher in the high NT-proBNP group as compared to the low NT-proBNP group (29.3% vs. 9.8%, p= 0.017; 66.0% vs. 37.3%, p= 0.008, respectively) (Table 4). Finally, when the mortality rates of

Table 1. Baseline characteristics by sST2 groups, mean ± SD or n (%)

Variables	Low sST2 (n= 53)	High sST2 (n= 51)	p
Age, years	61.9 ± 12.8	64.5 ± 9.2	0.109
Male, n (%)	42 (79.2)	42 (82.4)	0.688
HL, n (%)	18 (33.9)	22 (43.1)	0.345
DM, n (%)	18 (34.0)	16 (31.4)	0.865
HT, n (%)	19 (35.8)	20 (39.2)	0.723
Smoking, n (%)	22 (41.5)	27 (52.9)	0.243
LAD culprit, n (%)	29 (54.7)	25 (49.0)	0.844
Base TIMI grade= 0, n (%)	35 (66.0)	43 (84.3)	**0.031**
NT-proBNP	1294 ± 1864	1482 ± 1607	0.584

DM: Diabetes mellitus; HL: Hyperlipidaemia; HT: Hypertension; sST2: Soluble ST2, NT-proBP: N Terminal-pro Brain Natriuretic Peptide; LAD: Left anterior descending; SD: Standard deviation.

Table 2. Baseline characteristics by NT-proBNP groups, mean ± SD or n (%)

Variables	Low NT-proBNP* (n= 51)	High NT-proBNP* (n= 53)	p
Age, years	60.5 ± 8.7	65.8 ± 12.8	**0.009**
Male, n (%)	46 (90.2)	38 (71.7)	**0.017**
HL, n (%)	15 (29.4)	20 (37.7)	0.369
DM, n (%)	18 (35.3)	16 (30.2)	0.579
HT, n (%)	17 (33.3)	22 (41.5)	0.389
Smoking, n (%)	23 (45.1)	26 (49.1)	0.686
LAD culprit, n (%)	19 (37.3)	35 (66.0)	**0.008**
Base TIMI grade= 0, n (%)	36 (66.0)	42 (79.2)	0.308
sST2, ng/mL	32.8 ± 13.3	36.3 ± 16.5	0.244

DM: Diabetes mellitus; HL: Hyperlipidaemia; HT: Hypertension; sST2: Soluble ST2, NT-proBP: N Terminal-pro Brain Natriuretic Peptide; LAD: Left anterior descending; SD: Standard deviation.

Table 3. Baseline characteristics of study population according to 30-day mortality, mean ± SD or n (%)

Variables	Total (n= 104)	Mortality (+) (n= 15)	Mortality (-) (n= 89)	p
Age, years	63.2 ± 11.1	65.5 ± 4.3	62.8 ± 11.9	0.114
Male, n (%)	84 (80.8)	13 (86.7)	71 (79.8)	0.531
HL, n (%)	35 (33.7)	6 (40.0)	29 (32.6)	0.574
DM, n (%)	34 (32.7)	8 (53.3)	26 (29.2)	0.065
HT, n (%)	39 (37.5)	6 (40.0)	33 (37.1)	0.829
Smoking, n (%)	49 (47.1)	10 (66.7)	39 (43.8)	0.101
BMI, kg/m^2	25.7 ± 2.5	24.9 ± 1.4	25.8 ± 2.6	0.226
Creatinine, mg/dL	0.98 ± 0.69	0.93 ± 0.19	0.99 ± 0.74	0.737
HDL, mg/dL	40.6 ± 8.7	38.8 ± 9.1	41.6 ± 8.6	0.241
Triglyceride, mg/dL	159.6 ± 115.3	132.1 ± 63.6	135.8 ± 63.6	0.833
Peak CK-MB, IU/L	152.8 ± 114.4	149.4 ± 99.1	153.4 ± 117.8	0.902
Peak troponin, ng/mL	4.08 ± 3.0	5.01 ± 2.5	3.9 ± 3.0	0.198
WBC, count (10^3/L)	14.0 ± 4.9	16.1 ± 4.1	13.6 ± 4.9	0.070
HGB, g/dL	13.3 ± 2.2	12.9 ± 2.4	13.4 ± 2.1	0.412
sST2, ng/mL	33.9 ± 16.9	46.9 ± 23.8	32.5 ± 12.0	**0.001**
NT-proBNP, pg/mL	1386.5 ± 1737.4	2387.2 ± 2255.5	1217.1 ± 1588.8	**0.015**

DM: Diabetes mellitus; HL: Hyperlipidaemia; HT: Hypertension; BMI: Body mass index; WBC: White blood cell; HDL: High density lipoprotein; HGB: Haemoglobin; sST2: Soluble ST2; NT-proBP: N Terminal-Pro Brain Natriuretic Peptide; SD: Standard deviation.

the combined sST2 and NT-proBNP were examined, the highest mortality was detected in the high sST2/high NT-proBNP group (Figure 1).

Lower systolic blood pressure and high frequencies of Killip > 1 were identified as independent predictors of short-term mortality in the logistic regression analysis. Moreover, the high sST2 group was found to be an independent predictor of the 30-day mortality (OR 5.024, 95% CI 1.132-22.308, p= 0.034), whereas the high NT-proBNP group could not reach statistical significance (OR 4.059, 95% CI 0.894-18.427, p= 0.070) (Table 5). In another model, the combination of these two markers was evaluated in terms of their relationship with 30-day mor-

Table 4. Angiographic and procedural characteristics of the study population according to 30-day mortality, mean ± SD or n (%)

Variables	Total (n= 104)	Mortality (+) (n= 15)	In-hospital mortality (-) (n= 89)	p
SBP, mmHg	122.0 ± 23.4	102.8 ± 14.7	125.3 ± 23.7	**< 0.001**
DBP, mmHg	71.5 ± 12.7	63.9 ± 8.7	73.0 ± 12.8	**0.010**
HR, bpm	80.4 ± 14.3	85.7 ± 9.9	79.5 ± 14.8	0.124
Killip Class > 1, n (%)	17 (16.3)	6 (40.0)	11 (12.4)	**0.007**
Culprit lesion, n (%)				0.466
LAD	54 (51.9)	10 (66.7)	44 (49.4)	
CX	23 (22.1)	3 (20.0)	20 (22.5)	
RCA	27 (26.0)	2 (13.3)	25 (28.1)	
Extent of CAD, n (%)				0.259
1-vessel	42 (40.4)	4 (26.7)	38 (42.7)	
2-vessel	37 (35.6)	5 (33.3)	32 (36.0)	
3-vessel	25 (24.0)	6 (40.0)	19 (21.3)	
Baseline TIMI grade= 0, n (%)	78 (75.0)	11 (73.3)	67 (75.3)	0.873

LAD: Left anterior descending; CX: Circumflex; RCA: Right coronary artery; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; bpm: Beat per minute; SD: Standard deviation.

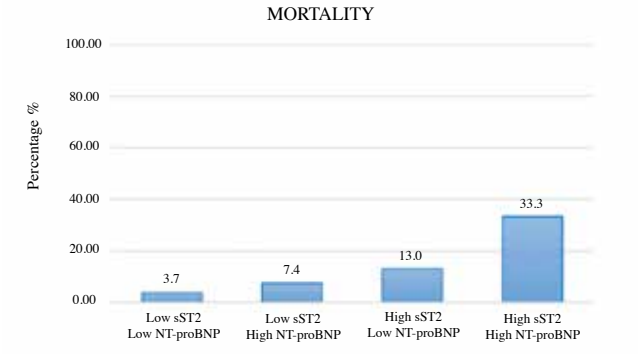

Figure 1. Bar graph showing 30-day mortality in the groups according to sST2 and NT-proBNP levels.

sST2: Soluble ST2; NT-proBNP: N Terminal-Pro Brain Natriuretic Peptide.

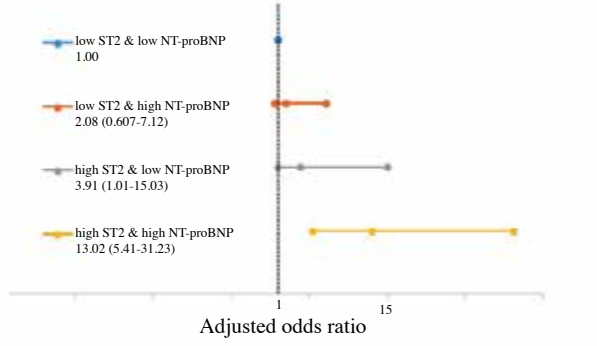

Figure 2. Adjusted odds ratios for 30-day mortality according to sST2 and NT-proBNP groups. Low sST2/Low NT-proBNP group accepted as the reference point.

sST2: Soluble ST2; NT-proBNP: N Terminal-Pro Brain Natriuretic Peptide.

tality. The lower level in both groups of markers was accepted as the baseline. High sST2/low NT-proBNP was associated with increased 30-day mortality (adjusted odds ratio 3.91 95% CI 1.01-15.03, p= 0.048). However, it was not possible to specify the same relationship for the high NT-proBNP/low sST2 group (adjusted odds ratio 2.08 95% CI 0.607-7.12, p= 0.114). It was interesting to note that the synergistic effect of these two markers on mortality in both the high sST2 group and the high NT-proBNP group showed 13 times higher odds for short-term mortality as compared to the low sST2/low NT-proBNP group and was independent of other risk factors (Figure 2).

DISCUSSION

We can summarise the findings of our study as follows: (a) among STEMI patients who underwent unsuccessful primary PCI, 14.4% had 30-day mortality, (b) patients with 30-day mortality had higher levels of sST2 and NT-proBNP in STEMI patients with poor post-procedural TIMI flow, and (c) after

Table 5. Multivariate regression analysis for potential predictors of 30-day mortality

Variables	Univariate analysis HR (CI 95%)	p	Multivariate analysis[c] HR (CI 95%)	p
Age, years	1.011 (0.962-1.063)	0.662	-	-
DM, yes	2.769 (0.910-8.424)	**0.073**	1.961 (0.479-8.026)	0.349
LAD artery, yes	2.045 (0.647-6.467)	0.223	-	-
SBP, mmHg	0.953 (0.925-0.981)	**0.001**	0.950 (0.91-0.986)	**0.005**
Baseline TIMI= 0, yes	0.903 (0.261-3.125)	0.872	-	-
Killip > 1, yes	4.727 (1.409-15.862)	**0.012**	6.051 (1.294-28.305)	**0.022**
WBC, count (10^3/L)	1.094 (0.989-1.210)	**0.082**	1.085 (0.941-1.252)	0.261
Peak Troponin, ng/mL	1.101 (0.941-1.333)	0.200	-	-
High ST2, yes[a]	5.128 (1.353-19.441)	**0.016**	5.024 (1.132-22.308)	**0.034**
High NT-proBNP, yes[b]	3.077 (0.911-10.400)	**0.070**	4.059 (0.894-18.427)	0.070

CI: Confidence interval; LAD: Left anterior descending; DM: Diabetes mellitus; SBP: Systolic blood pressure; WBC: White blood cell; sST2: Soluble ST2; NT-proBP: N terminal-pro Brain Natriuretic Peptide; OR: Odds ratio.
[a]: The classification was made based on the cut-off value of 35.0 ng/mL according to previous studies.
[b]: The classification was made based on age and sex related cut-off values.
[c]: Nagelkerke R square of the model was 44.6%

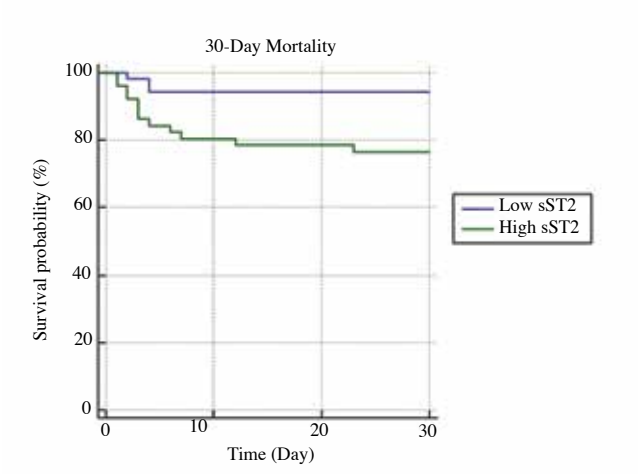

Figure 3. Kaplan-Meier analysis showing 30-day cardiovascular mortality ratio according to sST2 level.

adjustment for potential confounders, it was found that the high sST2 group was one of the independent predictors of short-term mortality, whereas the NT-proBNP group did not reach statistical significance. Another remarkable aspect of the study was the investigation of the additive prognostic value of sST2 and NT-proBNP on short-term prognosis in STEMI patients with poor post-procedural TIMI flow grade. Furthermore, low systolic blood pressure and presence of Killip class > 1 were the other independent predictors of the 30-day mortality.

In spite of the significant advances in medical technologies, short- and long-term undesirable results in STEMI patients are not uncommon. The early mortality risk may vary considerably in STEMI patients undergoing percutaneous coronary intervention. One of the most important parameters used in risk classification is the success of the primary percutaneous procedure. Considering that the early prognosis of patients who cannot provide satisfactory TIMI flow is worse[16], it is more important to determine the high-risk population in this group. Besides, an immediate increase in sST2 levels in patients with MI suggests that they may play a key role in the early pathophysiological mechanisms after MI by releasing proinflammatory cytokines and free radicals and causing poor post-procedural TIMI flow. Although there are many different risk classifications for STEMI patients, there is currently no study in the literature on the risk classification in patients with unsuccessful reperfusion, to the best of our knowledge. Furthermore, the cause or resultant linkage of sST2 with unsatisfactory final TIMI flow remains unclear. Therefore, we felt it was necessary to perform this study to clarify this situation.

Since the contractility and relaxation capacities of both the necrotic and penumbral 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 myocardial function, and sST2 is one of these molecules[17]. The fact that sST2 blocks its cardioprotective effects by binding to IL-33 suggests that sST2 may have a prognostic value, which has led to studies being conducted on this subject. Other studies have found a poor association

between sST2 and other clinical features of MI, which indicates that sST2 elevation reflects a separate mechanical pathway from other known biomarkers[18]. So, sST2 can provide us with new information about the course of MI. Shimpo et al. showed that high sST2 levels were associated with increased major cardiovascular adverse events during the short-term follow-up after STEMI[19]. It has been shown that sST2 is a predictor of mortality and is independent of parameters such as age, heart rate, blood pressure, and Killip classification during the 30-day period after PCI. In a study conducted by Williams et al., 1401 patients with MI were followed-up for five years and an increased relationship between mortality and sST2 (HR 1.73 95% CI 1.22-2.45 and 3.57 95% CI 2.57-4.96 for sST2 tertiles 2 and 3, respectively, trend < 0.001) was found[20]. In another large study, the multi-marker model was examined in the post-MI risk classification, and this study indicated that sST2 predicted short-term mortality both alone and in combination with other biomarkers (alone (2.88; 1.72-4.81)/multimarker (2.88; 1.72-4.81 5.12)[21]. In addition, Liu et al. determined that the highest quartile sST2 (> 58.7 ng/mL) could predict 1-year mortality in STEMI patients (HR 5.01, 95%CI 1.02-16.30, p = 0.048)[22]. We carried out our study in a more specific group of patients with post-procedural poor TIMI flow and observed that the presence of high sST2 predicted short-term mortality, a result that is parallel to those of the above-mentioned studies.

sST2 may be considered a new prognostic marker because it has a poor association with known prognostic risk factors such as cardiac troponin, Killip class, C-reactive protein, and comorbidity[20], whereas NT-proBNP is thought to be more closely linked to the above-mentioned clinical features, which may suggest chronic increased wall stress in the left ventricle. To this end, studies have been conducted to determine whether the combination of NT-proBNP, which is another biomarker that can be used to predict cardiac mortality[23] with sST2 provides additional information about prognosis. In one of these studies, the highest predictive of 1-year adverse events was obtained by the combination of sST2 and NT-proBNP values in 323 STEMI patients (adjusted hazard ratio 7.93, 95% CI 2.97 ± 20.38, p< 0.001)[24]. In a study by Tolppanen et al., it was determined that the combination of sST2 and NT-proBNP in patients with cardiogenic shock after ACS may correctly reclassify 11% of patients above the CardShock risk score to predict short-term mortality[25]. In another study examining the association of NT-proBNP and sST2, Barbarash et al. found that sST2 could predict by a1.7-fold, NT-proBNP could predict a 1.2-fold unfavourable outcome during hospitalisation, and a combination of these two could predict a 1.9-fold unfavourable outcome. Consequently, sST2 has been claimed to be a more sensitive indicator than NT-proBNP[26]. However, cardiovascular mortality was not mentioned and the conditions such as recurrent angina and rhythm disturbances were considered as unfavourable outcomes in this study. Nevertheless, in parallel with our study, sST2 was found to be a more important predictor than NT-proBNP, and in addition, it was found that a combination of these two markers had the highest predictive capacity.

sST2 is associated with cardiac injury and subsequent necrosis and inflammation due to its inability to facilitate coronary flow, whereas NT-proBNP reflects increased cardiac mechanical stress[11,27]. Hence, it can be assumed that sST2 may be a more important predictor than NT-proBNP in the poor post-procedural TIMI flow. For this reason, considering the intense inflammation and free O_2 radicals associated with tissue damage in patients with insufficient TIMI flow, it would not be surprising that sST2 is one step ahead of NT-proBNP in this patient group. In one of the largest studies on this subject, Sabatine and his colleagues found that sST2 levels above the median value predicted short-term mortality[11]. This study showed that the combination of sST2 and NT-proBNP had an additive effect in predicting short-term mortality. The data that examined the relationship of sST2 levels with angiographic parameters were remarkable in ways other than the final result of this study. Patients with low TIMI flow grade and low TIMI myocardial perfusion grade had higher sST2 levels as compared to NT-proBNP levels, whereas NT-proBNP levels were significantly higher in patients with decreased systolic function[11]. Both the pre-process and post-process TIMI flow grade was lower in patients with high sST2 levels as compared to the low sST2 group in our study as well. Nonetheless, we showed that LAD as the culprit artery was more frequent in the high NT-proBNP group. This suggests that the NT-proBNP levels may increase proportionally with the extent of the affected area. In addition, there was no correlation between sST2 and NT-proBNP in our study. Consequently, sST2 was superior to NT-proBNP in determining prognosis, in cases where successful percutaneous intervention could not be performed. However, the combination of these two markers provided the highest predictability for short-term mortality. A weak correlation between these markers, but a greater correlation of the combination of these two markers with cardiac mortality confirms that these molecules have emerged through different mechanisms.

There are some limitations to our study. First, this was a single-centre study that may cause selection bias. Nevertheless, the study population was homogeneous and all participants were STEMI patients who had undergone primary PCI using the same protocol. Second, it was difficult to compare our results with other studies on this subject due to the differences

in the pre-analytical medical therapy, storage techniques, and ELISA kits. Third, since our primary aim was to identify early prognostic markers for STEMI in the emergency room setting, all blood tests and samplings were performed upon admission to the emergency service, however, repeated measurements of sST2 were not calculated, therefore, changes that may have affected the result could not be derived. Fourth, the absence of left ventricular function and the other inflammatory markers may change the interpretation of our results. Finally, there were no data regarding the admission time and pain duration of the patients, which could have affected both the success of the procedure and the mortality rates.

CONCLUSION

sST2, especially in combination with NT-proBNP, can help physicians to predict short-term mortality after unsuccessful primary PCI in STEMI patients. The choice of treatment becomes very limited after the TIMI flow is unsatisfactory, so it is important to recognise patients who may develop adverse events in this group. As STEMI patients with high levels of sST2 had lower successful procedure rates and consequently more frequent adverse events, the use of curative methods, such as more intensive follow-ups or more supportive treatment to prevent adverse events, should be considered in this group of patients. Further studies are needed to understand the effect of sST2 on poor TIMI flow pathogenesis and to identify protective strategies in high-risk patients.

CONFLICT of INTEREST

The authors declare that there was no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MS, BK
Analysis/Interpretation: AA, NS
Data Acquisition: TA, HK
Writting: MS, TA
Critical Revision: BK, TA
Final Approval: All of authors

REFERENCES

1. Gaziano JM. Global burden of cardiovascular disease. In: Braunwald E, Zipes DP, Libby P (eds). Heart Disease: A Textbook of Cardiovascular Medicine. 6th ed. Philadelphia: WB Saunders Company, 2001:1-17.
2. The GUSTO Angiographic Investigators. The effect of tissue plasminogenactivator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615-22.
3. Ndrepepa G, Tiroch K, Fusaro M, Keta D, Seyfarth M, Byrne RA, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. J Am Coll Cardiol 2010;55:2383-9.
4. Resnic FS, Wainstein M, Lee MK, Behrendt D, Wainstein RV, Ohno-Machado L, et al. No-reflow is an independent predictor of death and myocardial infarction after percutaneous coronary intervention. Am Heart J 2003;145:42-6.
5. Kohli P, Bonaca MP, Kakkar R, Kudinova AY, Scirica BM, Sabatine MS, et al. Role of ST2 in non-ST-elevation acute coronary syndrome in the MERLIN-TIMI 36 trial. Clin Chem 2012;58:257-66.
6. Pascual-Figal DA, Januzzi JL. The biology of ST2: the international ST2 consensus panel. Am J Cardiol 2015 Apr 2;115(7 Suppl):3B-7B
7. Lepojaervi ES, Piira OP, Paeaekkoe E, Lammentausta E, Risteli J, Miettinen JA, et al. Serum PINP, PIIINP, galectin-3, and ST2 as surrogates of myocardial fibrosis and echocardiographic left ventricular diastolic filling properties. Front Physiol 2015;6:200.
8. Seki K, Sanada S, Kudinova AY, Steinhauser ML, Handa V, Gannon J, et al. Interleukin-33 prevents apoptosis and improves survival after experimental myocardial infarctionthrough ST2 signaling. Circ Heart Fail 2009;2:684-91.
9. Manzano-Fernández S, Mueller T, Pascual-Figal D, Truong QA, Januzzi JL. Usefulness of soluble concentrations of interleukin family member ST2 as predictor of mortality in patients with acutely decompensated heart failure relative to left ventricular ejection fraction. Am J Cardiol 2011;107:259-67.
10. Eggers KM, Armstrong PW, Califf RM, Simoons ML, Venge P, Wallentin L, et al. ST2 and mortality in non-ST-segment elevation acute coronary syndrome. Am Heart J 2010;159:788-94.
11. Sabatine MS, Morrow DA, Higgins LJ, MacGillivray C, Guo W, Bode C, et al. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation 2008;117:1936-44.
12. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, et al. Thrombolysis in myocardial infarction (TIMI) trial. Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142-54.
13. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol 1967;20:457-64.
14. Hildebrandt P, Collinson PO, Doughty RN, Fuat A, Gaze DC, Gustafsson F, et al. Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. Eur Heart J 2010;31:1881-9.
15. Ky B, French B, McCloskey K, Rame JE, McIntosh E, Shahi P, et al. High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure. Circ Heart Fail 2011;4:180-7.
16. Stone GW, Peterson MA, Lansky AJ, Dangas G, Mehran R, Leon MB. Impact of normalized myocardial perfusion after successful angioplasty in acute myocardial infarction. J Am Coll Cardiol 2002;39:591-7.
17. Weinberg EO, Shimpo M, De Keulenaer GW, MacGillivray C, Tominaga S, Solomon SD, et al. Expression and regulation of ST2, an interleukin 1 receptor family member, in cardiomyocytes and myocardial infarction. Circulation 2002;106:2961-6.
18. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov 2008;7:827-40.
19. Shimpo M, Morrow DA, Weinberg EO, Sabatine MS, Murphy SA, Antman EM, et al. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. Circulation 2004;109:2186-90.
20. Jenkins WS, Roger VL, Jaffe AS, Weston SA, AbouEzzeddine OF, Jiang R, et al. Prognostic value of soluble ST2 after myocardial infarction: a community perspective. Am J Med 2017;130:1112.e9-1112.e15.
21. O'Donoghue ML, Morrow DA, Cannon CP, Jarolim P, Desai NR, Sherwood MW, et al. Multimarker risk stratification in patients with acute myocardial infarction. J Am Heart Assoc 2016;5.

22. Liu X, Hu Y, Huang W, Zhang G, Cao S, Yan X, et al. Soluble ST2 for prediction of clinical outcomes in patients with ST-segment elevation myocardial infarction receiving primary PCI. Int Heart J 2019;60:19-26.

23. Kontos MC, Lanfear DE, Gosch K, Daugherty SL, Heidenriech P, Spertus JA. Prognostic value of serial N-terminal pro-brain natriuretic peptide testing in patients with acute myocardial infarction. Am J Cardiol 2017;120:181-5.

24. Yu J, Oh PC, Kim M, Moon J, Park YM, Lee K, et al. Improved early risk stratification of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention using a combination of serum soluble ST2 and NT-proBNP. PLoS One 2017;12:e0182829.

25. Tolppanen H, Rivas-Lasarte M, Lassus J, Sadoune M, Gayat E, Pulkki K, et al. Card shock investigators. Combined measurement of soluble ST2 and amino-terminal Pro-B type natriuretic peptide provides early assessment of severity in cardiogenic shock complicating acute coronary syndrome. Crit Care Med 2017;45:e666-e673.

26. Barbarash O, Gruzdeva O, Uchasova E, Dyleva Y, Belik E, Akbasheva O, et al. Prognostic value of soluble ST2 during hospitalization for ST-segment elevation myocardial infarction. Ann Lab Med 2016;36:313-9.

27. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998;135:825-32.