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

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Abstract

Background

Although soluble suppression of tumorigenicity 2 (sST2) in serum is known to be associated with ischemic heart disease and heart failure, data regarding its prognostic impact in ST-segment elevation myocardial infarction (STEMI) is limited. We evaluated the prognostic impacts of serum sST2 and other serum biomarkers in STEMI patients undergoing primary percutaneous coronary intervention (PCI).

Methods

Consecutive all 323 patients with STEMI that underwent primary PCI were enrolled. Blood tests and samples were obtained in an emergency room. The primary endpoint was 1-year major adverse cardiovascular and cerebrovascular events (MACCEs), defined as a composite of cardiovascular death, non-fatal MI, non-fatal stroke, and ischemia-driven revascularization.

Results

Mean age was 59.1±13.1 years (men 84%). MACCE (20 cardiovascular deaths, 7 non-fatal MI, 4 non-fatal stroke, 7 ischemia-driven revascularizations) occurred in 38 patients (12%). After adjusting for confounding factors, Cox regression analysis revealed that high serum sST2 (>75.8 ng/mL mean value, adjusted hazard ratio 2.098, 95% CI 1.008–4.367, p = 0.048) and high serum NT-proBNP level (>400 pg/mL, adjusted hazard ratio 2.606, 95% CI 1.086–6.257, p = 0.032) at the time of presentation independently predicted MACCE within...
a year of primary PCI. Furthermore, when high serum sST2 level was combined with high serum NT-proBNP level, the hazard ratio of MACCE was highest (adjusted hazard ratio 7.93, 95% CI 2.97–20.38, p<0.001).

**Conclusion**

Elevated serum levels of sST2 or NT-proBNP at the time of presentation were found to predict 1-year MACCE independently and elevated serum levels of sST2 plus NT-proBNP were associated with even poorer prognosis in patients with STEMI undergoing primary PCI.

**Introduction**

ST-segment elevation myocardial infarction (STEMI) is associated with significant morbidity and mortality. Early diagnosis and proper management, especially at time of presentation in emergency room (ER), are essential for long-term prognosis. However, even after timely management, including primary percutaneous coronary intervention (PCI), patients with STEMI are still at increased risk of major adverse cardiovascular and cerebrovascular events (MACCE) [1, 2]. Therefore, early risk stratification at the time of presentation in ER is of considerable clinical importance.

Many studies have been conducted to identify more powerful predictors of the short- and long-term prognoses of STEMI, and as a result, cardiac biomarkers, such as, troponins, creatine kinase-myocardial band (CK-MB), and natriuretic peptides are widely used to diagnose and predict prognosis in patients with STEMI [3–5].

Soluble suppression of tumorigenicity 2 (sST2), a member of the interleukin-1 receptor family, is known to be associated with ischemic heart disease and congestive heart failure (CHF). Several studies have reported sST2 is closely related with diagnosis and prognosis in patients with acute coronary syndrome, including non-STEMI [6–8]. However, data regarding the usefulness of sST2 as a prognostic marker in patients with STEMI is limited and results obtained to date conflict [9–12]. Therefore, we evaluated the prognostic impact of serum sST2 and the impacts of other biomarkers, including serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), at presentation in STEMI patients undergoing primary PCI.

**Methods**

**Study design and patient selection**

This trial was conducted as a single center, prospective, observational study. STEMI patients aged 20 years or older treated by primary PCI from January 2011 to January 2015 were included. STEMI was diagnosed based on clinical findings, such as chest pain, 12-lead electrocardiography findings, and cardiac markers in ER setting. A well-trained study coordinator collected data using a standard protocol. The Institutional Review Board of Gachon University Gil Medical Center approved this study, which also complied with the Declaration of Helsinki (6th revision). All patients provided written informed consent prior to enrollment. Key exclusion criteria were as follows: thrombolytic therapy (n = 6), myocardial infarction (MI) caused by stent thrombosis (n = 12), history of allergy or anaphylaxis to antiplatelet agents, steel, or heparin. Patients with a history of coronary artery disease, cardiomyopathy, valvulopathy (> moderate), CHF or pericardial disease were also excluded (n = 84). After applying the
above-mentioned inclusion and exclusion criteria, a total of 323 patients (84.0% male, mean age 59.1±13.1 years) of the originally considered 425 patients were included in the present study.

Primary PCI
All procedures were performed according to current standard guidelines. Before PCI, patients were pre-medicated with aspirin (at least 100 mg), and a loading dose of P2Y12 receptor antagonist. Heparin was administered throughout PCI to maintain an activated clotting time of ≥250 seconds. A glycoprotein IIb/IIIa receptor blocker was administered at the discretion of the operator. Coronary angiography was performed using standard techniques. Decisions to use thrombectomy devices, intravascular ultrasound, an intra-aortic balloon pump, or percutaneous cardiopulmonary support were made by the operator. Second generation drug eluting stents were implanted in all patients. Primary success was defined as no in-hospital death, no emergency bypass surgery, and the achievement of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 in the distal portion of the infarct-related artery and the presence of <30% residual stenosis.

Blood tests and sampling in the ER
Most blood tests were performed and recorded in accord with routine ER care of STEMI patients. Blood for two biomarkers, that is, sST2 and copeptin, was sampled in the ER and stored at -70°C. Laboratory determinations were performed by investigators unaware of patients’ clinical characteristics or outcomes. To assess sST2 and copeptin levels in serum, all ELISA reagents, working standards, and samples were prepared according to the manufacturer’s instructions (R&D Systems, Minneapolis, MN, USA). Samples were added to wells of antibody precoated microplates and were incubated adding conjugate. Substrate TMB (3,3′,5,5′-tetramethylbenzidine) solution was then added, incubated for 5–10 minutes, and then an equal volume of stop solution (2N H₂SO₄) was added. Optical densities were measured at 450 nm. For the sST2 assay, mean intra-assay and inter-assay coefficients of variance were 1.5% and 3.2%, respectively. Serum NT-proBNP was measured using an electrochemiluminescence sandwich immunoassay and an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany); coefficients of variation were 1.2% for intra-assay and 3.0% for inter-assay. Serum troponin I was measured using the ADVIA Centaur System (Bayer Diagnostics, Tarrytown, New York, USA).

Follow up
After primary PCI, all patients were monitored in a coronary care unit for at least 24 hours. Two-dimensional transthoracic echocardiography was performed within 12 hour of the index procedure. Standard medical management including dual antiplatelet agents, beta blockers, statins, nitrates, angiotensinogen converting enzyme inhibitors or angiotensin II receptor blockers was provided by responsible physicians according to the up-to-date guidelines. After discharge, patients were followed up regularly at outpatient clinics. To assess outcomes, all medical records were reviewed and in cases lost to follow-up, families of patients were contacted by telephone.

Study endpoint
The primary endpoint was 1-year MACCE, defined as a composite of cardiovascular death, non-fatal MI, non-fatal stroke, and ischemia-driven revascularization.
Statistical analysis
Continuous variables are presented as means ± standard deviations for the normally distributed data or as medians (interquartile ranges) for skewed data and the significances of inter-group differences were determined using the Student’s t-test or Mann-Whitney U test. Normality of variables was evaluated using Shapiro-Wilk test (p > 0.05 as normal). Categorical variables are expressed as absolute numbers and percentages, and were analyzed using the Chi-square test or Fisher’s exact test. Cox multiple regression analysis was performed to quantify relationships between MACCE and potential risk factors. The Kaplan–Meier method was used to determine cumulative MACCE-free survival rates. The analysis was performed using a computer-based statistical software package (Statistical Package for Social Sciences [SPSS®], Ver. 18.0 for Windows®; SPSS, Chicago, IL, USA). Two-sided p-values of < 0.05 were considered statistically significant.

Results
Baseline characteristics and intergroup comparisons
Patient baseline characteristics determined in the ER and intergroup comparisons between the MACCE (+) and MACCE (−) groups are summarized in Table 1. Mean study subject age was 59.1±13.1 years and 84% were male. Of the 323 study subjects, 38 (12%) experienced MACCE. These 38 patients were significantly older and had a lower left ventricular ejection fraction (LVEF) than the 285 patients in the MACCE (-) group. However, risk factor profiles and MI severities (e.g., Killip class), or the presence of anterior MI were not significantly different in the two groups. The prevalence of diabetes mellitus tended to be higher in the MACCE (+) group.

Table 2 showed laboratory findings according to presence or absence of the MACCE. The MACCE (+) group had significantly higher plasma random glucose and HbA1c levels at presentation. In the subgroup with a history of diabetes mellitus (n = 73), random plasma glucose was significantly higher in the MACCE (+) group than in the MACCE (-) group (224.0

Table 1. Demographic characteristics at the time of presentation in the two groups.

|                | Total (n = 323) | MACCE (+) (n = 38) | MACCE (-) (n = 285) | p-value |
|----------------|-----------------|--------------------|--------------------|---------|
| Age, years     | 59.1±13.1       | 63.7±14.4          | 58.5±12.8          | 0.020   |
| Male, n (%)    | 272 (84.0)      | 29 (76.3)          | 243 (85.3)         | 0.155   |
| BMI, kg/m²     | 24.4±3.5        | 23.2±4.0           | 24.5±3.4           | 0.039   |
| Systolic BP, mmHg | 127.6±29.4     | 120.1±41.2         | 128.6±27.4         | 0.225   |
| Diastolic BP, mmHg | 76.6±18.5     | 72.9±27.3          | 77.1±16.9          | 0.362   |
| Heart rate, per min | 75.9±20.0     | 76.4±30.5          | 75.9±18.2          | 0.912   |
| Hypertension, n (%) | 148 (46.0)    | 17 (44.7)          | 131 (46.0)         | 0.887   |
| Diabetes mellitus, n (%) | 73 (22.6) | 13 (34.2)          | 60 (21.0)          | 0.069   |
| Smoking, n (%)  | 183 (57.0)      | 19 (51.4)          | 164 (58.0)         | 0.460   |
| Dyslipidemia, n (%) | 36 (11.1)    | 4 (10.5)           | 32 (11.2)          | 0.897   |
| Killip class, n (%) |              |                    |                    | 0.444   |
| 1              | 261 (80.8)      | 32 (84.2)          | 229 (80.3)         |         |
| 2              | 9 (2.8)         | 2 (5.3)            | 7 (2.5)            |         |
| 3              | 42 (13.0)       | 4 (10.5)           | 38 (13.3)          |         |
| 4              | 11 (3.4)        | 0 (0.0)            | 11 (3.9)           |         |

MACCE: major adverse cardiovascular and cerebrovascular events, BMI: body mass index, BP: blood pressure

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vs. 185.5 mg/dL, respectively, p = 0.015), however, there was no significant difference of HbA1c between the MACCE (+) and MACCE (-) groups (7.9 ± 1.6 vs. 7.3 ± 1.3%, respectively, p = 0.293). The mean level of sST2 was not different between subjects with and without diabetes (75.6 ± 26.9 vs. 76.4 ± 31.4 ng/mL, respectively, p = 0.826). Furthermore, there were no significant correlations between the levels of sST2 and random plasma glucose or HbA1c. The levels of troponin I, CK-MB, and NT-proBNP at the time of presentation were significantly higher in the MACCE (+) group than in the MACCE (-) group. Initial sST2 level tended to be higher in the MACCE (+) group. Although there were no significant difference of serum transaminase levels between the two groups, hypoxic liver injury (serum transaminase level > twice the upper limit of normal [13]) tended to be more frequent in the MACCE (+) group.

### Primary PCI findings

A summary of angiographic, procedural, and echocardiographic data is provided in Table 3. Although baseline characteristics, including extent of coronary artery disease, infarct-related artery, and baseline TIMI flow grade were similar in the two groups, final TIMI flow grade, primary success rate, and LVEF were significantly lower in the MACCE (+) group. Serum sST2 levels were not significantly different among the groups according to the number of affected coronary arteries (75.9±27.6 ng/mL for 1 vessel disease, 74.2±29.7 ng/mL for 2 vessels disease, 77.9±26.1 ng/mL for 3 vessels disease, p = 0.664). Serum sST2 levels according to IRA (infarct-related artery) were also not statistically significant. (74.8±29.0 ng/mL for left main or left anterior descending artery, 77.0±29.6 ng/mL for left circumflex or right coronary artery, p = 0.471).

### Table 2. Laboratory findings at the time of presentation in the two groups.

|                      | Total (n = 323) | MACCE (+) (n = 38) | MACCE (-) (n = 285) | p-value |
|----------------------|----------------|-------------------|---------------------|---------|
| Glucose, mg/dL       | 151.0 (127.0–195.0) | 210.0 (151.5–285.5) | 148.0 (125.0–184.0) | <0.001  |
| HbA1c, %             | 6.4±1.5        | 7.5±2.3           | 6.27±1.2            | 0.022   |
| AST, U/L             | 30.0 (22.0–64.3) | 36.0 (24.0–102.0)  | 29.0 (22.0–57.0)    | 0.090   |
| ALT, U/L             | 26.0 (18.0–45.3) | 26.0 (19.0–49.0)   | 26.0 (18.0–44.5)    | 0.785   |
| Hypoxic liver injury† | 74 (23.0)      | 13 (35.1)         | 61 (21.4)           | 0.062   |
| Total protein, g/dL  | 7.0±0.6        | 7.0±0.7           | 7.0±0.6             | 0.758   |
| hs-CRP, mg/dL        | 0.17 (0.08–0.53) | 0.41 (0.12–1.3)   | 0.16 (0.07–0.45)    | 0.004   |
| sST2, ng/mL          | 75.8±27.8      | 84.0±29.7         | 74.7±27.6           | 0.052   |
| Copeptin, pg/mL      | 0.59 (0.44–0.79) | 0.60 (0.37–1.17) | 0.59 (0.46–0.77)    | 0.610   |
| Hemoglobin, g/dL     | 14.4±2.2       | 13.8±3.0          | 14.5±2.1            | 0.058   |
| Total bilirubin, mg/dL| 0.7±0.3        | 0.7±0.4           | 0.7±0.3             | 0.620   |
| Creatinine, mg/dL    | 0.9 (0.8–1.0)  | 0.9 (0.8–1.1)     | 0.9 (0.8–1.0)       | 0.296   |
| HDL-C, mg/dL         | 40.2±10.4      | 39.2±12.8         | 40.3±10.1           | 0.551   |
| LDL-C, mg/dL         | 109.5±34.5     | 106.8±36.7        | 109.8±34.2          | 0.638   |
| NT-proBNP, pg/mL     | 167 (44.9–693.7) | 734.7 (221.9–2346.5) | 145.6 (39.5–564.2) | <0.001  |
| CK-MB, ng/mL         | 2.4 (1.2–7.6)  | 6.9 (1.2–26.9)    | 2.2 (1.1–6.5)       | 0.018   |
| Troponin I, ng/mL    | 0.11 (0.02–0.83) | 0.79 (0.07–5.33)  | 0.10 (0.02–0.55)    | <0.001  |
| Albumin, g/dL        | 4.3±0.7        | 4.5±1.8           | 4.3±0.4             | 0.535   |

MACCE: major adverse cardiovascular and cerebrovascular events, HbA1c: hemoglobin A1c, AST: aspartate transaminase, ALT: alanine transaminase, hsCRP: high sensitivity C-reactive protein, sST2: soluble suppression of tumorigenicity 2, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, NT-proBNP: N-terminal pro-B-type natriuretic peptide, CK-MB: creatinine kinase-myocardial band

†Hypoxic liver injury was defined as an elevation of serum transaminase level more than twice the upper limit of normal [13].

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Symptom to presentation time was adequately reported only in 72 patients (7 with MACCE and 65 without MACCE, 262 [146–633] vs. 239 [125–609] min, respectively, p = 0.64).

Associations between adverse outcomes and biomarkers including sST2 and NT-proBNP

During a year following index PCI, 38 MACCEs occurred (20 cardiovascular deaths, 7 non-fatal MI, 4 non-fatal stroke and 7 ischemia-driven revascularizations), an event rate of 12.0%. Cox multiple regression analysis was used to identify independent predictors for MACCE after index PCI, and results are shown in Table 4. Random plasma glucose level, or sST2 level was categorized into high and low groups according to median or mean level (random plasma glucose level, 151 mg/dL; sST2, 75.8 ng/mL) because the prognostic cut-off values had not been established. However, well-known prognostic cut-off values were used for classifying levels of NT-proBNP, troponin I and high sensitivity C-reactive protein (hsCRP) (400 pg/mL, 0.1 ng/mL, and 1 mg/dL, respectively) [14–17].

After adjusting for age, diabetes mellitus, final TIMI flow grade, hypoxic liver injury, hsCRP level, and troponin I level, high serum sST2 level (>75.8 ng/mL, adjusted hazard ratio 2.098, 95% CI 1.008–4.367, p = 0.048) and high serum NT-proBNP level (>400 pg/mL, adjusted hazard ratio 2.606, 95% CI 0.86–6.257, p = 0.032) at presentation were found to independently predict 1-year MACCE. Of interest, high sST2 combined with high NT-proBNP had the highest adjusted hazard ratio (7.934, 95% CI 2.974–20.381, p < 0.001) (Fig 1). Notably, serum troponin I level, hsCRP level and copeptin level at presentation failed to predict MACCE. The survival probability plots of 1-year MACCE revealed high serum sST2 was associated with poorer prognosis than low sST2 and combined high sST2 and NT-proBNP was associated with even poorer prognosis than any other combinations (Fig 2).

### Table 3. Primary PCI results and transthoracic echocardiographic findings.

|                          | Total (n = 323) | MACCE (+) (n = 38) | MACCE (-) (n = 285) | p-value |
|--------------------------|-----------------|--------------------|---------------------|---------|
| **Extent of CAD, n (%)** |                 |                    |                     |         |
| 1-vessel                 | 123 (38.0)      | 11 (28.9)          | 112 (39.3)          | 0.417   |
| 2-vessel                 | 118 (36.5)      | 17 (44.7)          | 101 (35.4)          |         |
| 3-vessel                 | 82 (25.3)       | 10 (26.3)          | 72 (25.3)           |         |
| Multivessel disease      | 200 (62.0)      | 27 (71.1)          | 173 (60.7)          | 0.217   |
| **Infarct-related artery, n (%)** |              |                    |                     |         |
| Left main artery         | 1 (0.3)         | 0 (0.0)            | 1 (0.1)             | 0.440   |
| Left anterior descending artery | 184 (56.9) | 26 (68.4)          | 158 (55.4)          |         |
| Left circumflex artery   | 25 (7.7)        | 3 (7.8)            | 22 (7.7)            |         |
| Right coronary artery    | 113 (34.9)      | 9 (23.6)           | 104 (36.4)          |         |
| **Baseline TIMI flow grade, n (%)** |              |                    |                     | 0.870   |
| 0–2                      | 269 (83.2)      | 32 (84.2)          | 237 (83.1)          |         |
| 3                        | 54 (16.7)       | 6 (15.7)           | 48 (16.8)           |         |
| **Final TIMI flow grade, n (%)** |              |                    |                     | <0.001  |
| 0–2                      | 28 (8.6)        | 11 (28.9)          | 17 (5.9)            |         |
| 3                        | 295 (91.3)      | 27 (71.0)          | 268 (94.0)          |         |
| **Primary success, n (%)** |              |                    |                     | <0.001  |
| 1–2                      | 286 (88.5)      | 18 (47.3)          | 268 (94.0)          |         |
| **LVEF, %**              | 50.1±11.9       | 43.3±16.8          | 50.9±10.9           | 0.015   |

PCI: percutaneous coronary intervention, MACCE: major adverse cardiovascular and cerebrovascular events, CAD: coronary artery disease, LVEF: left ventricular ejection fraction

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Discussion

Principal findings

The present study was undertaken to evaluate the prognostic impacts of serum sST2 and other serum biomarkers in STEMI patients undergoing primary PCI. Its main findings are as follows. (1) High serum sST2 (>75.8 ng/mL mean value) and NT-proBNP (>400 pg/mL) levels obtained at the time of presentation in the ER independently predicted MACCE during a year following primary PCI. (2) Traditional cardiac markers, such as CK-MB and troponin I level,

Table 4. Cox regression analysis findings for predictors for 1-year MACCE after primary PCI.

| Variables                                      | HR     | 95% CI   | p-value |
|------------------------------------------------|--------|----------|---------|
| **Univariate analysis**                        |        |          |         |
| Age (10-year increase)                         | 1.36   | 1.06–1.74| 0.016   |
| Diabetes mellitus                              | 1.88   | 0.96–3.67| 0.066   |
| Low LVEF (<40%)                                | 3.12   | 1.54–6.30| 0.002   |
| Low final TIMI flow grade (<3)                 | 5.16   | 2.55–10.41| <0.001 |
| High sST2 (>75.8 ng/mL)                        | 1.965  | 1.006–3.842| 0.048  |
| High NT-proBNP (>400 pg/mL)                    | 3.736  | 1.902–7.399| <0.001 |
| High troponin I (>0.1 ng/mL)                   | 2.376  | 1.179–4.791| 0.016  |
| High hsCRP (>1 mg/dL)                          | 2.448  | 1.224–4.895| 0.011  |
| High random plasma glucose level (>151mg/dL)   | 3.344  | 1.578–7.087| 0.002  |
| Hypoxic liver injury (serum transaminase >80 U/L) | 1.946  | 0.991–3.821| 0.053  |
| **Multivariate analysis**                      |        |          |         |
| Low final TIMI flow grade (<3)                 | 2.556  | 1.049–6.228| 0.039  |
| High sST2 (>75.8 ng/mL)                        | 2.098  | 1.008–4.367| 0.048  |
| High NT-proBNP (>400 pg/mL)                    | 2.606  | 1.086–6.257| 0.032  |
| High random plasma glucose level (>151mg/dL)   | 3.737  | 1.586–8.806| 0.003  |

MACCE: major adverse cardiovascular and cerebrovascular events, PCI: percutaneous coronary intervention, HR: hazard ratio, LVEF: left ventricular ejection fraction, sST2: soluble suppression of tumorigenicity 2, NT-proBNP: N-terminal pro-B-type natriuretic peptide, hsCRP: high sensitivity C-reactive protein

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determined at the time of presentation, failed to predict MACCE. (3) Serum sST2 combined with serum NT-proBNP best predicted MACCE. (4) Survival probability plots of MACCE during the first year after PCI revealed that combined high serum sST2 and NT-proBNP was associated with the worst prognosis. Our results indicate high serum sST2 and NT-proBNP levels at the time of presentation in the ER are highly associated with poor prognosis and that they are probably better early prognostic markers than other parameters, including serum CK-MB, troponin I, and copeptin levels in patients with STEMI treated by primary PCI.

Prognostic biomarkers for patients with STEMI

Despite marked improvements in outcomes over the past few decades, relapse rates of adverse events are still unacceptably high for patients with STEMI [1, 2], and thus, it is of considerable importance to continue to develop tools that identify patients at high risk of adverse outcomes who might benefit more from enhanced monitoring or treatment. Moreover, early recognition of these patients at the time of presentation in the ER is crucial to reduce adverse outcomes. Many studies have been conducted to identify prognostic markers in patients with STEMI [6, 10, 11]. One study that included up to 1258 patients with acute MI showed that several candidate markers, that is, NT-proBNP, midregional proatrial natriuretic peptide (MR-proANP), sST2, troponin T, myeloperoxidase (MPO), hsCRP, and pregnancy-associated plasma protein-A (PAPP-A), were significantly associated with 30-day risk of cardiovascular death or CHF after adjusting for clinical predictors [18].

Prognostic value of serum sST2

sST2 was evaluated by Weinberg EO et al. in 2002 [19] and has widely been studied in diabetes mellitus and cardiovascular disease. This notable cardiac biomarker is being increasingly used in patient care, but its clinical and pathophysiologic implications have not been thoroughly determined. Recently, Lin et al demonstrated diabetic patients had significantly higher levels
of sST2 compared with normal subjects and elevated sST2 levels had increased risk of having diabetes. However, in the present study, sST2 levels were not different in patients with or without diabetes and could not reflect glycemic status, suggesting sST2 might have different roles in glucose metabolism and the setting of myocardial injury. Furthermore, sST2 is being actively investigated in the contexts of the prognosis and diagnosis of CHF [20–23], and relatively little information is available about its role in patients with STEMI. Shimpo M et al. measured serum sST2 levels at presentation in 810 patients with STEMI [9]. It was found sST2 levels were higher in patients that succumbed or experienced CHF before 30 days had elapsed after PCI, and multivariate analysis showed sST2 remained predictive of mortality at 30 days after adjusting for age, heart rate, blood pressure, location of infarction, Killip class, and time from symptom onset. However, this independent association disappeared after adjusting for BNP and troponin I. This finding is inconsistent with our findings that high sST2 level at the time of presentation independently predicted MACCE after adjusting for confounding markers. On the other hand, in another cohort in the same study, additional samples were taken at later times and in this cohort serum sST2 at 12 hours after presentation independently predicted mortality. Accordingly, the investigators concluded that sST2 checked at 12 hours after presentation, was associated with mortality after STEMI independently of established clinical indicators. Another point of difference between this previous study and the present study is that the risks of marker combinations, such as, sST2 coupled with troponin I or BNP, were not assessed.

The CLARITY-TIMI 28 trial [11] revealed sST2 and NT-proBNP were found to be complementary in STEMI. In this trial, patients with STEMI were enrolled regardless of primary PCI and it was found serial changes of blood levels of sST2 and NT-proBNP after MI differed. Blood samples were drawn at presentation and several days after MI during angiography, and whereas sST2 modestly decreased between samplings, mean NT-proBNP increased by several folds. In the same study, angiographically determined low TIMI flow grade and TIMI myocardial perfusion grade were found to be more associated with higher sST2 levels than NT-proBNP levels, whereas NT-proBNP levels were more closely associated with LVEF. These findings suggest serum sST2 level reflects the amount of injured tissue and is associated necrosis and inflammatory events, whereas NT-proBNP is associated cardiac mechanical stress. Accordingly, this previously published data indicated these two markers might act in a complementary manner to predict adverse events in STEMI. Mean serum concentrations of sST2 and NT-proBNP in patients that later experienced cardiovascular death or CHF were higher than those of patients that did not experience these outcomes [11], and similarly, these marker levels were higher in patients that experienced stroke than in those that did not [24]. Thus, it would appear that high sST2 and NT-proBNP in combination might be reasonably expected to predict MACCE after STEMI.

Interestingly, although serum copeptin is a well-known cardiac marker with a high negative predictive value in patients with STEMI [18, 25, 26], we found initial serum copeptin measured in the ER setting did not predict long-term prognosis in STEMI patients.

Limitations

Several limitations of the present study should be considered. First, this single center, observational study was conducted using a relatively small Korean cohort. Nevertheless, the cohort was homogeneous and all study subjects were STEMI patients that underwent primary PCI and were managed using the same protocol. Second, all blood tests and samplings were performed at the time of ER presentation, and thus, no subsequent blood tests were performed for sST2 or copeptin, because our primary aim was to identify early prognostic markers for
STEMI in the ER setting. However, this prevented investigating associations between serial changes in sST2 and copeptin levels and clinical outcomes. Third, the time from the first symptoms of MI to presentation in the hospital or PCI would be important, because it might affect sST2 or NT-proBNP levels and has a considerable impact on clinical outcomes. Unfortunately, the time interval was reported only in a portion of subjects and thus its prognostic implication could not be determined in this study. Finally, the cut-off values for sST2 suggested by the present study cannot be compared directly with those of previous studies, because sST2 measurement methods differed.

**Conclusion**

In conclusion, high sST2 and NT-proBNP levels obtained at the time of presentation in the ER were found to independently predict MACCE during a year following PCI, and combined high sST2 and NT-proBNP was associated with the worst prognosis.

**Author Contributions**

**Conceptualization:** Woong Chol Kang.

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