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Original Article

Prognostic value of plasma ST2 in patients with non-ST segment elevation acute coronary syndrome

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ABSTRACT

Objective: The aim of this study is to detect plasma ST2 levels in patients who were admitted to emergency department with chest pain and diagnosed with non st segment elevation myocardial infarction (NSTEMI) and to research the relationship between 28-day mortality and ST2 levels.
Methods: The present study was conducted at Emergency Department of Celal Bayar University Hafsa Sultan Hospital between September 2015 and January 2016 as a prospective, single-center, cross-sectional study. Plasma ST2 levels were detected in patients who were diagnosed with NSTEMI based on physical examination, ECG and troponin. The eligible patients were followed up with regard to mortality during 28 days.
Results: A total of 88 patients diagnosed with NSTEMI were included in the study and followed up for 28 days. While 18 (20.5%) patients died at the end of 28 days, 70 (79.5%) patients survived. Mean ST2 level of surviving 70 patients was 651.37 ± 985.66 pg/mL and mean ST2 level of dying 18 patients was 2253.66 ± 1721.15 pg/mL ($p < 0.001$). ST2 value was higher among the dying (non-survivors) compared to the survivors at the end of 28 days and this was found related to mortality. ST2 cut-off value was found as 1000 pg/mL with 72.2% sensitivity and 20.0% specificity.
Conclusion: Among the patients who were diagnosed with NSTEMI at the emergency department, ST2 levels on admission were found significantly higher among the non-survivors compared to the survivors. ST2 level was accepted as a reliable biomarker for prediction of 28 mortality in patients diagnosed with NSTEMI.

1. Introduction

Acute coronary syndromes (ACS) constitute a heterogeneous group with regard to clinical findings, degree of ischemia, coronary anatomy and prognosis. This large spectrum includes more than one clinical problem and requires rapid decision and intervention.

The term “acute coronary syndrome” encompasses ST-segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), and unstable angina pectoris (UA).[1] ACS has a very high mortality rate. Various guidelines, clinical grading tools, and biomarkers have been developed to predict mortality in patients with ACS. Electrocardiography (ECG) findings of NSTEMI patients may include ST depression and T wave inversion, however, these findings are seen in only 30–50% of the patients.[2] Biomarkers are the cornerstones for diagnosing these patients. Biomarkers which indicate myocardial necrosis and myocardial dysfunction [cardiac troponin I-T, B type natriuretic

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peptide (BNP)] have proven to be useful not only for selecting the proper treatment but also for cardiac risk assessment, and thus, they are accepted as useful clinical tests.[3,4] Suppression of tumorigenicity-2 (ST2), which is a tumor-suppressing biomarker originating from the inflammatory system, has been shown to have prognostic value in ACS patients. ST2, which is a member of the interleukin-1 (IL-1) receptor family, plays an important role in the regulation of the immune and inflammatory responses by binding to IL-33. Soluble ST2 (sST2) is the soluble form of the enzyme which does not have *trans*-membrane and intracellular domains. ST2 levels were found to be elevated in patients who died from severe heart failure.[5–12] The aim of this study was to compare plasma ST2 levels of the surviving and non-surviving patients who were diagnosed with NSTEMI in the emergency department and to determine the relationship between ST2 levels and 28-day mortality.

2. Methods

2.1. Study setting and population

This prospective study was carried out between September 2015, and January 2016, in the emergency department of Celal Bayar University, Faculty of Medicine, which receives 50,000 patients/year. The study was approved by the institutional ethics committee.

Patients who were diagnosed with NSTEMI in the emergency department were included in the study and evaluated prospectively. Patients older than 18 years who presented to the emergency department with the complaint of chest pain and were diagnosed with NSTEMI according to the ECG findings, troponin values and cardiology consultations were included in our study.

Patients with any of the following were excluded from the study: 1) Diagnosed with STEMI, 2) Transferred to the emergency department after out-of-hospital arrest, 3) History of major surgery or trauma within the last 4 weeks, 4) Pregnancy, 5) Underwent coronary artery bypass grafting (CABG) within the last week, 6) Refusal to participate.

Age, gender, comorbid diseases, medications, date of admission, and hemodynamic parameters like blood pressure, heart rate, respiratory rate, body temperature and peripheral oxygen saturation were recorded. Laboratory results and 28-day outcomes (survivor/non-survivor) were recorded.

All participants were followed up and treated in accordance with the Turkish Association of Cardiology (TAC), American Heart Association (AHA) and European Society of Cardiology (ESC) evidence-based NSTEMI management guidelines. Patients were followed-up for 28 days. Patients or relatives were contacted by phone 28 days after admission to ask about the patient's condition. The dates of death of the deceased were checked from the Central Population Management System. The primary end-point was 28-day all-cause mortality.

2.2. Definitions

Patients who presented with chest pain, who did not have ST-segment elevation but whose cardiac markers were elevated were defined as NSTEMI. These patients could have completely normal ECGs or findings such as ST segment depression, T wave negativity or flattening. The diagnosis of acute NSTEMI was established using The joint European Society of Cardiology, American College of Cardiology Foundation, the American Heart Association, and the World Heart Federation (ESC/ACCF/AHA/WHF) committee definition of NSTEMI. Treatment and follow-up strategies for these patients include cardiac monitoring, frequent ECG control, cardiac marker testing, and initiating treatment for ischemia and other symptoms.[13]

The terminology of the new guidelines (2014 AHA/ACC Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes) has been updated from UA/NSTEMI to NSTE-ACS. This new term encompasses both NSTEMI patients and UA patients. In our study, we used the NSTEMI definition in the 2011 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.

2.3. Suppression of tumorigenicity 2 (ST2) assay

Patients who presented to the emergency department of Celal Bayar University Hafsa Sultan Hospital with the complaint of chest pain and who were diagnosed with NSTEMI according to the physical examination, ECG and troponin results were included in the study after written informed consent was obtained. Approximately 2 mL of blood was drawn by the nurse in the emergency department for determining plasma ST2 levels. Venous blood samples were drawn from the antecubital vein immediately after obtaining the ECG. Hemolytic, icteric or lipemic blood samples were not included. The samples were centrifuged at 4000 rpm for 10 min to separate the serum. After centrifugation, blood samples were taken into Eppendorf tubes, frozen at −80 °C and stored until the time of analysis. The samples were thawed at room temperature before analysis. ST2 levels were examined using the automated Eti-Max 3000 (Diasorin SpA, Italy) micro-ELISA (Enzyme-Linked Immunosorbent Assay) device with the sandwich ELISA method. A commercially available IL-1 receptor-like 1 (IL-1 RL-1) human Elisa kit (Cusabio & Cusab Elisa kit) was used in accordance with the instructions of the manufacturer. The value limits of these kits are 32–2000 pg/mL and range of detecting ST2 levels are 70.2–4500 pg/mL.

2.4. Statistical analysis

Patients were divided into two groups as survivors and non-survivors according to the 28-day follow-up outcomes. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) ver 22.0 program. The normality of data distribution was analyzed with the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation or median (Inter-quartile Range [IQR] according to normal or non-normal distribution. Categorical variables were expressed as numbers and percentages (%). The two groups were compared with regard to demographic, clinical and laboratory variables. Fischer's Exact test was used to compare categorical variables and Mann Whitney *U* test was used to compare continuous variables. The correlation between ST2 and clinical scores was analyzed using Spearman rank correlation. Receiving Operating Characteristic (ROC) curve analysis was used for the detection of the optimal cut-off value for ST2 with respect to 28-day mortality. The diagnostic accuracy of the scoring systems was analyzed by calculating the area under the ROC curve (AUC). The cumulative survival rate was calculated using the Kaplan-Meier method, and the differences in survival between the groups were compared using the Mantel-Cox log-rank test. A p-value <0.05 was accepted as statistically significant. The sample size was calculated using power analysis. A sample size of 88 participants was determined based on a power of 84% and an effect size d = 0.40 (d = effect size) of $\alpha_2 = 0.05$.

2.5. Outcome measures

Our primary outcome was to determine the relationship between 28-day mortality and ST2 levels in NSTEMI patients. The

secondary outcome was to find the cut-off value for ST2 in terms of 28-day mortality in NSTEMI patients.

3. Results

A total of 104 patients were diagnosed with NSTEMI in our emergency department during the study period. Of these, 6 who experienced out-of-hospital arrest, 2 who underwent CABG within the last week, 6 who underwent major surgery within the last 4 weeks and 2 who refused to participate were excluded from the study. The remaining 88 patients were followed-up for 28 days. At the end of 28 days, 18 (20.5%) patients died, and 70 (79.5%) patients survived. Table 1 presents the baseline characteristics of the patients at the end of the 28-day follow-up.

The mean ST2 values of the surviving (n = 70) and non-surviving (n = 18) patients were 651.37 ± 985.66 pg/mL and 2253.66 ± 1721.15 pg/mL, respectively (p < 0.001). The median ST2 value of non-survivors was significantly higher than the survivors (1971.43 [3110.84] vs. 184.83 [623.56], p < 0.001). Higher ST2 levels were found to be associated with mortality (Fig. 1).

According to the ROC curve analysis, the optimal ST2 cut-off value for 28-day mortality in NSTEMI patients was 1000 pg/mL, with 72.2% sensitivity and 80.0% specificity (95% confidence interval, AUC = 0.827; p < 0.001) (Fig. 2).

Thirteen patients (72.2%) died within 28 days. According to Kaplan Meier survival analysis, mortality was found to be higher among patients whose ST2 cut-off value was higher (log-rank test = 20.28, p < 0.001) (Fig. 3).

4. Discussion

The aim of this study was to investigate the relationship between plasma ST2 concentrations and 28-day mortality in patients who were diagnosed with NSTEMI in the emergency department. Recent studies have focused on the relationship between ST2 and acute/chronic heart failure, and compared ST2 and BNP as prognostic markers in coronary artery disease.[14–16] ST2 is shown to be an important independent predictor of heart failure and STEMI. However, there are a limited number of studies available which assess its prognostic value in NSTEMI. In this study, we investigated the relationship between ST2 and 28-day mortality in patients diagnosed with NSTEMI.

Sabatine et al. have studied 1239 STEMI patients and Shimpo et al. have studied 810 STEMI patients with regard to their ST2 levels, and revealed that 30-day mortality is higher among patients with higher ST2 levels.[9,17] In the study by Shimpo et al., 362 patients were diagnosed with STEMI. ST2 levels were found to be significantly higher in STEMI patients who died within 30 days (0.379 vs 0.233 ng/mL, p < 0.001) or in those with acute-onset heart failure (0.287 vs 0.233 ng/mL, p = 0.009). ST2 levels were shown to increase within the first day after myocardial infarction, peaking at 12 h. In addition, ST2 level at 12 h was shown to be a significant marker for 30-day mortality (p < 0.001).

In the study by Sabatine et al., ST2 levels of 1239 patients who were diagnosed with STEMI and who underwent angiography within 2–8 days were analyzed and the patients were followed-up for 30 days. The study revealed that, unlike BNP, ST2 levels were independent of increased left ventricle wall tension, age, blood pressure and early stage heart failure (r = 0.14). In addition, BNP and ST2 levels above median values were found to be associated with a higher risk for cardiovascular death or heart failure (3rd quarter odds ratio 1.42; 95% confidence interval, 0.68–3.57; 4th quarter odds ratio 3.57; 95% confidence interval, 1.87–6.81; p < 0.001).

In their study on 403 NSTEMI patients, Eggers et al. have shown that serum ST2 levels are related to one-year mortality.[12] ST2 levels were measured 24, 48 and 72 h after the diagnosis of NSTEMI and patients were followed up for mortality for one year. Maximum ST2 values were obtained at 6th-17th hours after symptom onset. A significant relationship was found between ST2 levels and BNP levels (p < 0.001). However, no relationship was found between ST2 levels and cardiovascular risk factors, comorbid conditions, myocardial necrosis, and inflammation. ST2 was found to be associated with one-year mortality in NSTEMI patients (Odds ratio 2.3 [95% CI; 1.1–4.6], p = 0.03).

Hollander et al. have investigated the levels of ST2 in potential ACS patients who presented to the emergency department with chest pain. Patients who were diagnosed with ACS were followed up in terms of 30-day mortality and recurrent cardiovascular events. Patients who were 25 years and older, who presented to the

Table 1
Baseline characteristics of the patients.

Variables	Survivors n = 70	Non-survivors n = 18	P
Demographic characteristics			
Age (year)	64.20 ± 13.56	64.28 ± 12.49	0.226
Male/female	38/32	12/6	0.344
Previous medical history			
Chronic renal failure	8 (11.4)	3 (16.7)	0.542
Hypertension	54 (77.1)	12 (66.7)	0.360
Conjestive heart failure	14 (20.0)	8 (44.4)	**0.033**
Coroner arterial diseases	33 (47.1)	6 (33.3)	0.293
Diabetes mellitus	23 (32.9)	5 (27.8)	0.680
Hemodynamic parameters			
Systolic blood pressure (mm Hg)	140.87 ± 31.15	140.87 ± 31.15	0.601
Diastolic blood pressure (mm Hg)	80.29 ± 19.88	89.17 ± 22.12	0.156
Heart rate (bpm)	93.79 ± 22.84	101.89 ± 26.31	0.192
Forehead temperature (°C)	36.50 ± 0.67	36.85 ± 0.85	0.091
Respiratory rate (breaths/min)	18.96 ± 6.15	21.28 ± 7.40	0.153
Oxygen saturation (SaO2%)	93.25 ± 8.67	90.56 ± 9.92	0.538
Laboratory test results			
White blood cell count ($\times 10^3$/uL)	10,9 ± 3,6	14,1 ± 6,0	**0.024**
GFR	74,07 ± 28,23	61,85 ± 56,17	**0.009**
Troponin I (ng/mL)	0,9 ± 2,4	0,9 ± 1,5	0.162
ST2 (mean + SD)	651,37 ± 985,66	2253,66 ± 1721,15	**<0.001**

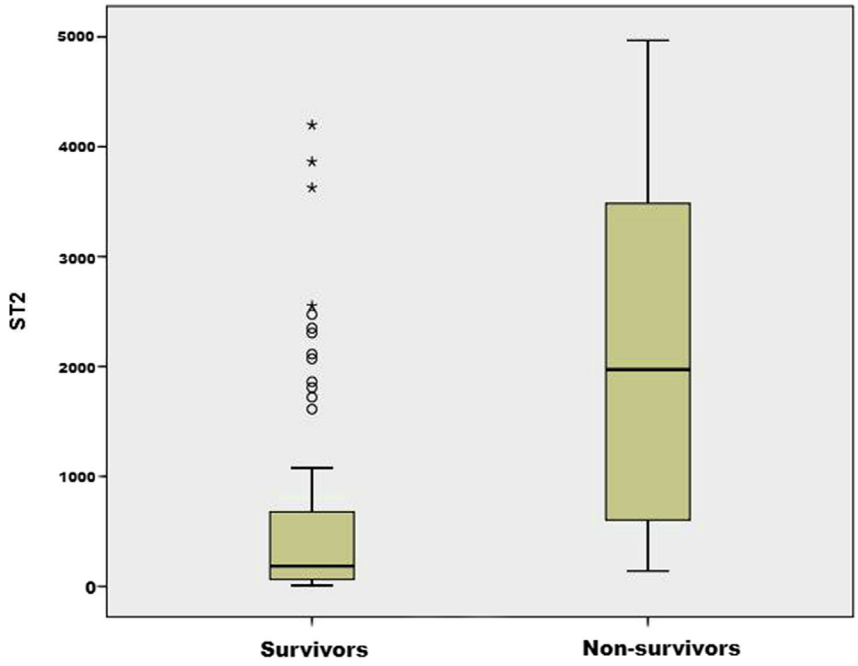

Fig. 1. Graphical comparison of ST2 levels.

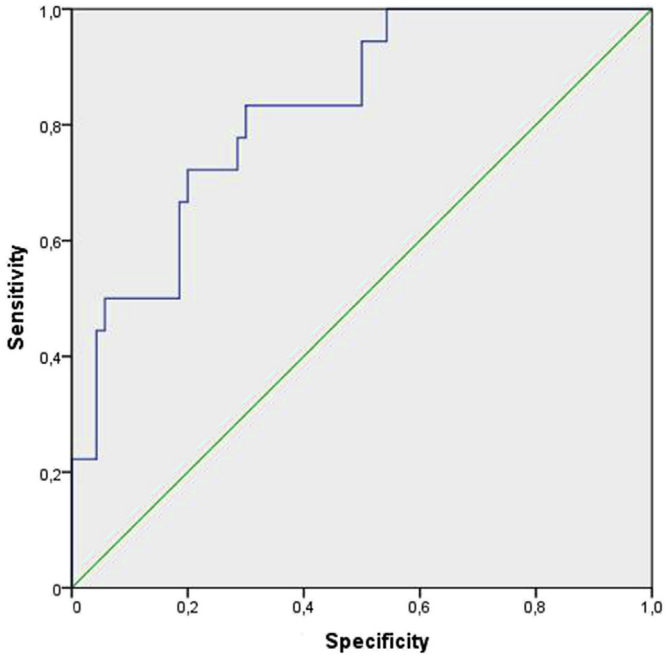

Fig. 2. ROC curve analysis.

emergency department with chest pain and whose ECGs were obtained were included in the study. ST2 levels on admission were measured and the patients were followed-up for ACS, mortality, and other cardiac events for 30 days. A total of 348 patients were included in the study. Within 30 days, the number of acute myocardial infarctions (AMI) was 17 (4.9%), ACS was 39 (11.2%) and cardiac events (death, acute myocardial infarction or revascularization) was 23 (6.6%). The AUCs for AMI, ACS and cardiac events within 30 days were 0.636, 0.630, 0.579, respectively. ST2 did not predict AMI. ST2 levels were found to be higher in patients with pulmonary disease, pulmonary embolism, systemic infection and in alcohol users. Consequently, ST2 was not found to have a prognostic value in patients with ACS.[18]

4.1. Limitations

The present study has indicated a positive relationship between serum ST2 levels and mortality. However, it has some limitations. The first is the limited number of patients. Further prospective studies conducted with larger populations are needed to verify the results of our study. The second is the single-center design of the study. Thus, the results we obtained cannot be generalized. The third limitation is not knowing the ST2 levels before admission, during hospitalization or after discharge. The results of our study were based on a single ST2 measurement, so we were not able to assess the changes in ST2 levels over time. The fourth limitation is using an old guideline for the definition of NSTEMI. We used the NSTEMI terminology in the "2011 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation". Using a more current guideline instead (2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes) would have yielded more actual results. Finally, the influence of parameters such as the duration of heart failure, body mass index, ethnic origin, socio-economic status, and smoking on patients was not investigated.

5. Conclusion

Serum ST2 levels and 28-day mortality were compared in 88 patients who were diagnosed with NSTEMI in the emergency department in the present study. Of the patients, 20.5% died within 28 days. ST2 values were higher among patients who died, and ST2 elevation was shown to be associated with mortality. The cut-off value for ST2 was found to be 1000 pg/mL with a 72.2% sensitivity and 80.0% specificity. In conclusion, there is a positive

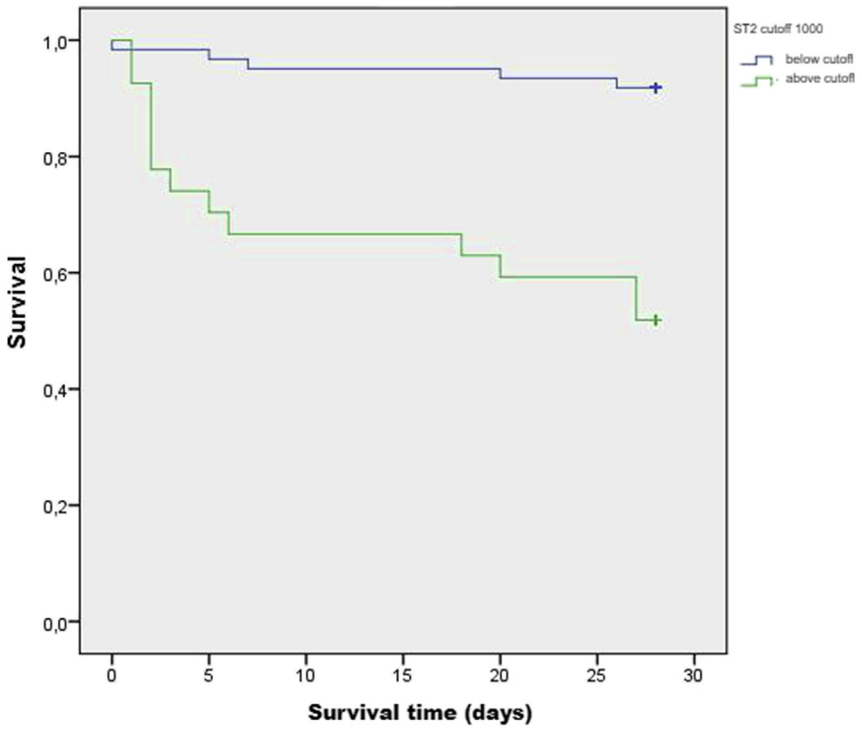

Fig. 3. Kaplan-Meier survival curve according to ST2 level above and below optimal cutoff value for 28 days.

correlation between serum ST2 levels and 28-day mortality in NSTEMI patients. Further studies are required for verifying the results of our study.

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