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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

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