DIAGNOSTIC VALUE OF ST2 IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Acute Myocardial Infarction (AMI) is a major problem threatening Indonesia and many countries. Each year AMI patients are increasing. ST2 is a novel cardiac marker for diagnosis and prognosis of acute myocardial infarction. The purpose of this study is to seek the diagnostic value of serum ST2 in patients with AMI. This cross sectional study was conducted in 46 patients with main complaint of chest pain at the Emergency Department, Dr. Soetomo Hospital from 20 April to 20 July 2013. Sera were examined for ST2, and then the diagnostic value was determined using the clinical criteria of AMI according to the Universal Definition of Myocardial Infarction (2007) as the gold standard. The results of ST2 serum levels measurement showed a sensitivity of 83% and specificity of 70% at a cut-off value of ST2 16.64 ng/mL and AUC 0.878, p = 0.000. The concordance examination between using cTn-T levels and ST2 was 48.1%. A significance correlation was obtained with correlation coefficient r = 0.489, p = 0.001 between the levels of cTn-T and ST2. In result, ST2 serum levels can be used for screening to aid the diagnosis of AMI. There is a weak correlation and concordance between cTn-T with ST2. Further research is needed to determine the diagnostic value of ST2 for the detection of AMI. (FMI 2015;51:106-109)

Keywords: ST2, cTn-T, AMI

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INTRODUCTION

The incidence of acute myocardial infarction is increasing every year in Indonesia and the western world. Coronary heart disease (CHD) is the number one cause of death in the Western world so it is an important public health problem (Roger, 2007). National Household Health Survey mentions that in the last 10 years the death rate from coronary heart disease (CHD) tends to increase. In 1991, the number of death of CHD was 16 percent. That number increased to 26.4 percent in 2001. It is estimated, the death rate of CHD reaches 53.5 per 100 thousand populations in Indonesia (Arief, 2012). ST2 (growth stimulation Expressed gene 2) is a member of interleukin receptor member of IL-1 which have a central role in the regulation of immune and inflammatory responses. It consists of two isoforms, transmembrane form (ST2L) and a soluble form (sST2). Transmembrane form of (ST2L) expressed in heart muscle cells and contains three extracellular IgG domains, a single transmembrane domain and an intracellular domain homologous to toll-like receptors. Soluble form (sST2) circulates in the blood and only consists of the extracellular domain and that transmembrane and intracellular domain are not present (Kakkor and Lee, 2008). Troponin is a complex protein found in skeletal muscle and cardiac muscle. Troponin
has the function to regulate or inhibit contractility of striated muscle. Cardiac troponin (CTN) is troponin found in cardiac muscle and it is released into the circulation during a myocyte damage. Therefore, serum of troponin is a marker of myocardial injury which is important in the diagnosis of myocardial infarction. In this study, troponin is used as the gold standard for the diagnosis of patients with AMI (Sarco, 2002).

The role of ST2 in heart disease was found in 2002 by Richard Lee and his colleagues at Brigham Women’s Hospital, Boston. In an effort to simulate the stress on the myocardium as seen in heart failure, they cultured monolayer myocytes of neonatal rat and applied mechanical strain to myocytes. Messenger RNA levels were measured before and after the application of mechanical stress. From 7000 mRNA transcripts which were examined, it turns out Interleukin 1b upregulated ST2 (4.7 and 2.0-fold increases, respectively, compared to before the initial strain). The authors also showed a temporary increase in serum ST2 in rats which had coronary artery ligation for simulating acute myocardial infarction. At the time of this invention, the ligand for ST2 is unknown. So the function of ST2 is still not known. In 2005, ligand IL-33 was discovered and named ST2 (Kakko and Lee, 2008).

The role of IL-33 and ST2 investigated in an experimental study of heart failure by Sanada et al. showed that in mice which had transverse aortic constriction to induce cardiac hypertrophy, the administration of IL-33 has a cardioprotective effect by reducing fibrosis, hypertrophy, and maintain left ventricular function. But, the mice which not given by IL-33, there is no protection against heart failure after aortic constriction, indicating the importance of ST2L. The addition of soluble ST2 inhibits IL-33/ST2L effect. ST2 is said to now as a decoy receptor. ST2 levels were higher in the serum will bind to IL-33 so there is no binding ST2L (Sanada, 2007).

AMI is associated with loss of myocardial function and to produce cytokines. Pro-inflammatory cytokines include IL–1, IL–6, and TNF–α also participates in the initial response to myocardial injury and cardiac load. In this study, ST2 levels increased after the incident of AMI (Shimpo et al., 2004). Myocardial infarction illustrated cardiac muscle cell death caused by ischemia conditions. Ischemia occurs because perfusion which not balanced between supply and needed. The form of soluble ST2 will quickly secreted by heart muscle cells when the heart muscle cells get such undue burden on the state of Myocardial infarction. Pro-inflammatory cytokines secreted in a state of cardiac muscle cells that undergo ischemia and cardiac muscle cells will enable others to produce ST2 (Shimpo et al., 2004). As consensus criteria to diagnose AMI, the criteria of the Universal Definition of 2007 was used in which AMI can be identified from an increase of troponin, patient complaints and typical electrocardiogram overview (ECG) (Thygesen, 2007). The complaints of patient included chest pain which spread to the neck and epigastrium at rest or activity. These complaints usually last at least 20 minutes. ECG may be a pathological Q waves, ST changes and Left Bundle Branch Block (LBBB) (Thygesen, 2007).

The general objective of this study was to determine the diagnostic value of ST2 in patients with acute myocardial infarction to determine the cut-off value of ST2 with optimal sensitivity and specificity, to determine the suitability of the results of the examination and the value of the correlation coefficient between ST2 with CTN-T in patients with acute myocardial infarction. The benefits of this study were to determine whether the ST2 can be used as a new diagnostic tool for the diagnosis of acute myocardial infarction.

MATERIALS AND METHODS

This type of research was a diagnostic test with a cross-sectional study design. The sample in this study used serum specimens which is examined on its ST2 levels in the laboratory of Clinical Pathology Research and Development section of Dr. Soetomo Hospital using a Quantikine Human ST2 ELISA from R&D systems. The sample size was 36 patients with acute myocardial infarction and 10 patients with complaints of chest pain as a control in the Emergency Ward, Dr. Soetomo Hospital. The study was performed from 20 April – 20 July 2013.

ST2 examination used ELISA (Enzyme Linked Immunosorbent Assay) which used reagents biotinylated anti-ST2 antibody (Biotinylated Antibody) and Streptavidin-HRP conjugate. Absorbance was measured at a wavelength of 450 nm with an ELISA reader after 15 minutes after the addition of a stop solution. Determination of AMI patients use the criteria of the Universal Definition of 2007 in which the AMI could be identified from the increase of troponin, patient complaints and description of typical electrocardiogram (ECG).

Statistical analysis was conducted using the statistical program of SPSS version 20. It was determined of cut-off values with optimal sensitivity and specificity. Then we determine the AUC of the ROC curve. Determined specified percentage of conformity with the test results
of kappa and correlation between ST2 and CTN-T which mentioned the significant value if $p < 0.01$.

RESULTS
These subjects’ age was $57.78 \pm 10.92$ years (Table 1) with an age range 20 - 82 years. Most (65.2\%) research subjects were men. Serum levels of ST2 and CTN-T were examined in all subjects, and the average value for each parameter was as follows: 35.98 ng/mL and 0.69 ng/mL. Of the 46 samples examined, 36 patients had levels of CTN-T > 0.1 ng/mL and were diagnosed as AMI which is consistent with the consensus of Universal Definition in 2007 and 10 patients with complaints of chest pain and CTN-T levels < 0.1 ng/mL were diagnosed unstable angina as a control. Both patients with AMI and unstable angina, all of them were examined their levels of ST2.

To find out the data came from a normally distributed population or not, we used Kolmogorov Smirnov test (Landis and Koch, 1977). There was obtained the results with the test that the data came from a population that was not normally distributed, so that it was used non-parametric Spearman correlation test to determine the relationship of ST2 with CTN-T in patients with infarction Acute myocardial.

There was obtained the sensitivity 83\%, a specificity of 70\% at the cut-off of 16.64 ng/mL and AUC of 0.878. The conformity (kappa) examination between ST2 and CTN-T was 48.1\%. The Spearman correlation between ST2 and CTN-T with significant association of correlation coefficient were $r = 0.489$, $p = 0.001$.

Table 1. Research subject characteristic

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Results</th>
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<tbody>
<tr>
<td>Age (Year)</td>
<td>$57.78 \pm 10.92$</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>30/16</td>
</tr>
<tr>
<td>ST2 (ng/mL)</td>
<td>$35.98 \pm 22.73$</td>
</tr>
<tr>
<td>cTn-T (ng/mL)</td>
<td>$0.69 \pm 0.65$</td>
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All the data above was expressed as mean ± SD, except for gender was expressed in number of each gender.

DISCUSSION
ST2 as a cardiac marker had been used to determine the prognosis of heart failure. On PRIDE study, sST2 levels could give a strong prediction of death within 1 year. When it was grouped by decile, patients in the lowest decile had a mortality rate of 5\%, while the highest decile has a very high risk, with approximately 45\% risk of death at 1 year. Patients with sST2 levels above the median value of the group had a mortality risk 11 times higher with those who had value under the average. The study concluded that sST2 levels at the time of initial presentation may be a good marker for risk stratification in patients with stable Acute Heart Failure (Januzzi et al., 2005).

ST2 in patients with acute myocardial infarction on previous research was obtaine the results AUC of ROC curve of 0.636, so that ST2 could not be used as a diagnostic tool because of the low accuracy of the diagnosis (Brown et al., 2007). In this study, the results AUC of the ROC curve was 0.878 which mean that it was good either in distinguishing patients with AMI or not. We obtained the optimal results of ST2 levels 16.64 ng/mL with a sensitivity 83\% and a specificity 70\%. The differences were likely due to the different number of samples (348 vs 46 patients) and the distribution of the data.

Conformity (kappa) between ST2 with CTN-T was 48.1\% was categorized as moderate. So that on a certain level was obtained CTN-T conformance with ST2 levels at 48.1\%. The relationship between ST2 levels with CTN-T was obtained a significant association, so that the levels pf ST2 in patients with acute myocardial infarction will also increase.

The limitedness of this study was the number of samples that was small, so we need a larger study with more number of samples to obtain a normal distribution of the data. Another limitedness of this research was the process of freeze-thawing specimens before ST2 levels measurement. We recommended to use fresh specimens.

CONCLUSION
The results showed that the category of AUC in this study included both, so that it can be used as a diagnostic tool. Suitability was moderate and significantly relationship was exists between the value of ST2 levels and CTN-T. It can be concluded ST2 can be used to determine a person experiencing AMI or not.

REFERENCES