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Original Research Article

Evaluation of soluble ST2 as a novel cardiovascular biomarker in patients with acute myocardial infarction

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ABSTRACT

Background: Soluble ST-2 has considerable prognostic value and is used as an aid for risk stratification in identifying patients who are at high risk of cardiovascular disease. The main objective of the study was to analyze the level of soluble ST-2 biomarker in patients with acute myocardial infarction and chronic stable angina patients and secondly to evaluate the cardiovascular outcomes after 30 days.
Methods: A total of 71 patients were enrolled into the study, patients were divided into two groups of which 50 patients were in test group (AMI patients) and the remaining 21 patients were in the control group (chronic stable angina). Then, 5ml of blood was collected from the patients and plasma soluble ST-2 was estimated from the sample using ELISA technique. Patients were then followed up to 30 days to ascertain the development of major adverse cardiovascular outcomes.
Results: The median concentration of soluble ST-2 in test group was found to be 213.46pg/ml and in control group was found to be 124.53 pg/ml. Soluble ST-2 correlated significantly with left ventricular ejection fraction (LVEF) between the two groups (P value=0.01). Measurement of soluble ST-2 early after MI assists in the prediction of adverse cardiovascular events. In this study, soluble ST-2 was found to be higher in patients with acute myocardial infarction and also in patients with poor ejection fraction.
Conclusions: Soluble ST-2 is a novel cardiovascular biomarker that is elevated in patients with acute myocardial infarction.

Keywords: Acute myocardial infarction, Cardiac biomarkers, Cardiovascular events, LVEF, Morbidity, Soluble ST-2

INTRODUCTION

Myocardial infarction continues to be one of the killer diseases with high morbidity and those patients with the most severe form of this illness succumb to it even before reaching the hospital in certain instances.[1] The prognosis of patients with myocardial infarction is dependent on several clinical characteristics and laboratory features. It is possible to predict the in-hospital mortality as well as 30 day and long term mortality of these patients to a reasonable extent using tools such as the GRACE and TIMI score that incorporate several variables.[2-4] Some of these variables include age, creatinine, heart rate and blood pressure at the time of admission and elevation of cardiac biomarkers. Cardiac biomarkers such as troponin, CK-MB have shown to reflect both the short term as well as the long term mortality of MI patients.[5] Besides these established biomarkers, a number of novel biomarkers have come into the spotlight in recent years in myocardial infarction such as B-type natriuretic peptide, copeptin,

ischemia- modified albumin, heart-type-fatty acid-binding protein, myeloperoxidase, choline, placental growth factor, soluble CD40 ligand, growth differentiation factor-15.[6] One such biomarker is the soluble ST-2 which is also termed as IL-1 receptor 4.[7]

ST-2 is a member of the Toll-like/IL-1-receptor superfamily.[8] Soluble ST-2 has been extensively studied as a prognostic tool among patients with both acute and chronic heart failure.[9-12] Increased concentrations of soluble ST-2 in patients with acute destabilized heart failure at their initial presentation indicate increased risk of future mortality.[13] Soluble ST-2 is independently associated with worsening heart failure.[14]

Two primary isoforms of ST-2: ST-2 ligand (ST-2L), which is a membrane-bound receptor, and soluble ST-2 (sST-2), a circulating form detected in serum, both have receptor function, with the latter peptide being a non-functional "decoy".[15] It is known the ligand for ST-2 (IL-33) which functions as a cardioprotective hormone. IL-33 has anti-hypertrophic and anti-fibrotic benefits for the myocardium: these effects are in part due to reduction in pro-apoptotic pathways.[16] In turn, sST-2, being a decoy receptor, suppresses this cascade, resulting in excessive cardiomyocytes apoptosis and myocardial fibrosis.[17] Both ST-2 isoforms are induced when cardiomyocytes and cardiac fibroblasts undergo mechanical strain, making sST-2 a promising biomarker that reflects fibrosis, inflammation and remodeling, across the full spectrum of cardiovascular diseases.[18] There are limited studies which have assessed the utility of soluble ST-2 as a biomarker. The objective of the study was to determine the concentration of soluble ST-2 in patients with acute myocardial infarction and compare it with chronic stable angina population. The study also assessed the relationship between soluble ST-2 and other baseline characteristics.

METHODS

The study used a cross-sectional design and the study was approved by the institutional ethics committee. The subjects were divided into two groups, comprising of patients with myocardial infarction (test group) and those with chronic stable angina (control group). Patients were included into the study based on age group between 40-75years of either gender, able to provide written, informed consent, presentation within 24 hours of onset of chest pain, patients with a diagnosis of acute myocardial infarction as diagnosed by twelve lead ECG. Exclusion criteria were pregnant women, lactating women and the patients who were not willing to give informed consent. The control group included patients with chronic stable angina who visited to the hospital for evaluation of chest pain and who did not have elevated.

After obtaining informed consent from the patients, the patient details like age, gender, family history and past medication history laboratory parameters, angiographic findings and treatment were collected. Prior to angiography, blood was collected in 2ml vacutainer tubes coated with ethylene diamine tetra acetic acid for soluble ST-2. Samples were centrifuged at 2,500 rpm for 10 minutes at room temperature, and the plasma sample was separated. The collected samples were frozen and stored at -20˚C. Plasma soluble ST-2 was estimated from the sample using human IL-1 R4 enzyme-linked immunosorbent assay technique (RayBiotech, GA, United States of America). Patients were followed up to 30 days to ascertain the development of major adverse cardiovascular events such as death, recurrent infarction, and stroke and CABG surgery.

Statistical analysis

Data were expressed as mean ± SD or median with interquartile range or frequency with percentages. The baseline characteristics of the study subjects were compared between the two study groups, using student t test for continuous variables and chi square test for categorical variables. Spearman Rank correlation was performed between the concentration of soluble ST-2 and the various study variables. The concentration of soluble ST-2 between the groups was compared using Mann Whitney test and the concentration with respect to the type of lesion on angiography was compared using Kruskal Wallis test. $P<0.05$ was considered statistically significant. Data were analyzed using SPSS v.17.0.

RESULTS

A total of 71 patients participated in the study, comprising of patients with MI (n=50) and patients with chronic stable angina (n=21). The baseline characteristics of patients were described in (Table 1).

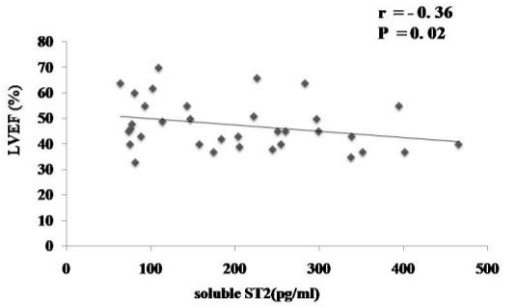

Figure 1: Correlation of soluble ST2 vs left ventricular ejection fraction in MI patients.

Age groups between 51-60 years were found to be at higher risk of developing myocardial infarction. The distribution of Myocardial infarction, Coronary artery disease, and chronic stable angina was found to be higher in males than females which show that male gender were more prone to develop cardiovascular diseases than female gender. Patients with Diabetes mellitus,

Hypertension, Dyslipidemia were more prone to develop Myocardial infarction. Soluble ST-2 was found to be higher in test group than control group and also in patients with poor ventricular ejection fraction.

Table 1: Baseline characteristics of study patients.

Variables	MI (n=50)	CSA (n=21)	P Value
Age (in years)	50.84±10.24	53.90±10.65	0.27
BMI	23.784±3.97	27.60±4.37	0.01*
Hb (gm/dl)	13.931±2.30	12.98±2.60	0.13
CPK (U/L)	230 (150.50-1115.5)	105 (71.25-390)	0.06
CPK MB (U/L)	38 (22.50-139.50)	13.50 (11.75-57.25)	0.01*
Urea (mg/dl)	25.01±8.25	24.67±10.20	0.89
Creatinine (mg/dl)	1.02±0.32	1.07±0.35	0.71
LDL (mg/dl)	115.51±52.10	80.09±39.14	0.03*
HDL (mg/dl)	35.49±9.96	43.09±28.92	0.18
VLDL (mg/dl)	41.77±67.42	46.45±38.82	0.81
TG (mg/dl)	140.49±66.56	119.27±56.28	0.33
TC (mg/dl)	201.57±57.01	165.11±47.54	0.08
DM	21 (42%)	9 (42.8%)	0.43
HTN	9 (18%)	9 (42.8%)	0.16
Smoking	17 (34%)	5 (23.8%)	0.28
Alcohol	7 (14%)	8 (38.1%)	0.23
F/H/O CAD	7 (14%)	7 (33.3%)	0.108
Thrombolysed	37 (74%)	NA	-

BMI- body mass index, CPK – creatinine phospho kinase, CPK-MB creatinine phospho kinase - muscle bone, DM – diabetes mellitus, F/H/O CAD – family history of coronary artery disease, Hb – hemoglobin, HDL – high density lipoprotein, HTN – hypertension, LDL – low density lipoprotein, TC – total cholesterol, TG – triglycerides, VLDL – very low density lipoprotein.; * statistically significant < 0.05.

There was significant correlation between soluble ST-2 and LVEF between the two groups (r=-0.31; P=0.01) (Figure 2). In the test group, a negative correlation was observed between soluble ST-2 and LVEF (r= - 0.36; P= 0.02) (Figure 1).

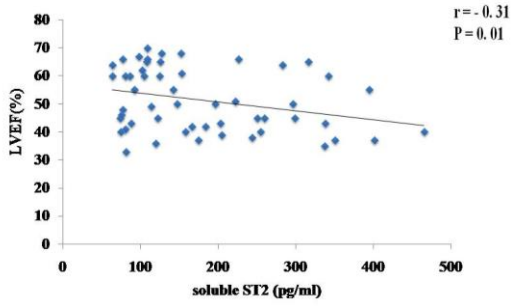

Figure 2: Correlation of soluble ST2vs left sentricular ejection fraction in study patients.

In the control group, there was no correlation observed between soluble ST-2 and LVEF. There was no correlation found between soluble ST-2 and age, haemoglobin, CPK, CPK- MB, HDL, LDL, VLDL, TG, TC, Urea, and Creatinine in both the groups. Patients in the test group had lower BMI (p<0.01), higher CPK-MB (p<0.01) and higher LDL (p<0.03).

There was no difference in any other cholesterol indices between the two groups. Although the concentration of soluble ST-2 was highest in individuals with single vessel disease (SVD), there was no significant difference between the groups (Table 2).

Table 2: Soluble ST-2 concentration based on severity of lesion in coronary angiogram.

Angiogram lesion type	Soluble ST-2 concentration (pg/ml)	P value
Normal coronary angiogram	212.68 (94.93-327.08)	0.609
Single vessel disease	115.84 (97-255.03)	
Double vessel disease	152.16 (125.21-205.11)	
Triple vessel disease	226.08 (95.11-323.71)	

DISCUSSION

We have reported the concentration of soluble ST-2, a novel biomarker in patients with Myocardial infarction and to the best of our knowledge this is the first such report in the Indian population. The median concentration of soluble ST-2 in test group was found to be 213.46pg/ml and in control group was found to be 124.53pg/ml. In a study by Weir et al, performed in 100 patients with AMI, median sST-2 level was 263.3pg/ml.[19] A study was performed by Shimpo et al, in which sST-2 levels were measured in serum of 810 patients with acute myocardial infarction and the median sST-2 was 235 pg/ml.[4] (Table 3). Thus our findings are consistent with these studies (Shimpo et al, Weir et al). In contrast, in the study by Zhang K et al, the median concentration of soluble ST-2 in acute myocardial infarction patients was found to be 29.06 ng/ml.[3]

Table 3: Soluble ST-2 concentration from studies performed in patients with myocardial infarction.

Author	Median conc. of sST-2 in MI (pg/ml)	Timing of sample	Sample size	ELISA Kit used	Population	Age	Male gender (%)
Weir RA, et al.[19]	263.3	AMI within 1-14 days	100	R&D systems, Abingdon, UK	Scotland, UK	58.9±12.0	77
Shimpo M et al.[4]	235	AMI within 12 hours	810	Medical & Biological Laboratories Co, Ltd.	Boston, USA	58±10	79
Zhang K[3]	29,060	AMI within 24 hours	59	ELISA kit , R & D	Beijing, China	Not available	Not available
Demyanets S et al	453	Before angiography	98	R&D Systems, Minneapolis, MN, USA	Vienna, Austria	62.9±13.7	66

One possible explanation for these differences could be that the earlier studies were done in Caucasian population, while the study by Zhang et al was done in the Chinese population.[3,4,19] Present data was similar to the one obtained in the Caucasian population. The high soluble ST-2 concentration in the study by Zhang et al could also be influenced by the lower sample size. There was no influence of the kit used on the soluble ST-2 concentration. In present study we have used RayBio® Human IL-1 R4 enzyme-linked immunosorbent assay, GA, USA. In contrast most of the other studies have used R&D systems.[3,20] In present study the blood sample was collected within 48 hours after onset of MI. There is considerable variation in the timing of sample collected in the earlier studies. However the timing of sample did not appear to have any direct impact on the soluble ST-2 concentration. For instance the study by Weir et al had samples collected even as late as 14 days after MI, yet the median obtained was comparable to that seen with our study.[19] It appears that there is a stable soluble ST-2 concentration in the first 14 days after MI, nevertheless this needs to be explored in future studies.

Present study showed a negative correlation between the soluble ST-2 concentration and left ventricular ejection fraction. Kaspar Broch et al, observed the levels of soluble ST-2 in 1449 patients ≥60 years of age with left ventricular ejection fraction (LVEF) ≤40% due to ischaemic heart disease with a median concentration of 17.8 ng/mL. The study concluded that soluble ST-2 biomarker is associated with adverse outcomes in older patients with systolic, ischaemic HF and in particular, sST-2 is independently associated with worsening HF.[14]

No difference in severity of the disease with respect to angiographic findings in present study. Patients with STEMI showed the highest serum levels of soluble ST-2 in a study performed by Demyanets S et al.[20]

Limitations

The small sample size of the study precluded us from making definitive conclusions about the value of soluble ST-2 as a cardiac biomarker. We did not perform long term follow–up of these patients to assess cardiovascular outcomes.

CONCLUSION

Soluble ST-2 is a novel cardiovascular biomarker that is elevated in patients with acute myocardial infarction. Its role as a prognostic biomarker requires further exploration using prospective cohort studies.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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