Original Article

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Correlation of Suppression of Tumourigenicity 2 with hsCRP, NT-proBNP and Left Ventricular Ejection Fraction in Patients with Myocardial Infarction

Internal Medicine Section

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ABSTRACT

Introduction: Soluble Suppression of Tumourigenicity 2 (sST2) represents a clinically relevant biomarker and has predictive evidence in acute Myocardial Infarction (MI) and predicts cardiovascular death and risk of heart failure development in these patients. The data about the correlation of sST2, N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) and high-sensitivity C-reactive protein (hsCRP)in the Indian population is lacking.

Aim: To find a correlation of ST2 level at the time of admission with NT-proBNP, hsCRP and Left Ventricular Ejection Fraction (LVEF) in patients with MI, and the association of ST2 levels with mortality.

Materials and Methods: This longitudinal observational study was conducted at Poona Hospital and Research Centre, Pune, Maharashtra, India, between June 2018 and August 2019, among 75 myocardial infarction patients above 18 years of age. ST2, NT-proBNP and hsCRP levels were checked within 6 hour of hospitalisation. The primary outcome measures were to study the correlation of ST2 levels at the time of admission with hsCRP, NT-proBNP and LVEF. The secondary outcome measures were to study the association of ST2 levels with in-hospital and one-month mortality. The medians of continuous variables of two groups and three groups were-tested using the Mann-Whitney U test and Kruskal-Wallis H test respectively. The correlation analysis was performed using Spearman's method.

Results: The mean age of the study population was 57.8±7.2 years. The mortality rate was 60% (12/75). ST2 levels showed a statistically significant positive correlation with NT-proBNP (r =0.703, p-value=0.001) and hsCRP (r=0.873, p-value=0.001), whereas, ST2 levels showed a negative correlation with LVEF (r=-0.711, p-value=0.001) in MI patients. The median ST2 levels were significantly higher in-hospital (215.3 ng/dL vs 94 ng/dL) and one month (219.5 ng/dL vs 92.0 ng/dL) mortality as compared to survived MI patients.

Conclusion: ST2 levels showed a statistically significant positive correlation with NT-proBNP and hsCRP and were associated with in-hospital and one month mortality in MI patients.

Keywords: Association, High-sensitivity c-reactive protein, Left ventricular ejection fraction, Mortality, N-terminal pro-B-type natriuretic peptide

INTRODUCTION

High sensitivity C-Reactive Protein (hsCRP), a marker of inflammation, is well-established for risk stratification in Coronary Artery Disease (CAD) [1]. Suppression of tumourigenicity 2 (ST2) is emerging as a powerful and reliable prognostic biomarker in cardiology. Its soluble form (sST2) in the blood signifies pathological cardiac remodelling [2,3]. The interleukin-1 receptor family has numerous members. In 1989, one member of the family, ST2, was recognized as an orphan receptor [4]. ST2 has a role in the inflammatory processes, mainlyin relation to mast cells, type 2 CD4+ T-helper cells, and the production of Th2-associated cytokines [5].

Clinical and investigational explanations led to the association of ST2 with disease entities such as asthma, pulmonary fibrosis, rheumatoid arthritis, collagen vascular diseases and septic shock [6-10]. The discovery of Interleukin-33 (IL-33) as an ST2 ligand provided novel understandings of ST2 signalling [11]. IL-33 is obviously a possible mediator of various inflammatory diseases [12]. IL-33 has now also been shown to contribute in cardiovascular pathophysiology. Also, the IL-33/ST2 system probably plays a part in the development of atherosclerotic vascular disease [13]. Beyond its role as a therapeutic target, the sST2 has also emerged as a biomarker for disease. For example, serum levels of ST2 are raised in patients with acute exacerbations of bronchial asthma [6], and in emergency-room patients presenting with shortness of breath, serum levels of ST2 can discriminate between Heart Failure (HF) and non-cardiovascular aetiologies [14]. Therefore, ST2 signifies a promising biomarker for cardiac injury.

The elevations of ST2 levels in the blood are observed in patients after Myocardial Infarction (MI). The elevated ST2 levels in patients are associated with a higher risk of death on short and long-term follow-up [14-19]. The prognostic value of ST2 seems to be additive to natriuretic peptides among patients with MI [14,16-18,20]. A previous general population research has shown that sST2 were elevated in blacks and predict increased all-cause and cardiovascular mortality [21]. In patients with acute and chronic HF, sST2 levels are strongly predictive of death, and Left Ventricle Ejection Fraction (LVEF), and contribute pertinent evidence in addition to other predictors and biomarkers, as natriuretic peptides or troponins. sST2 also retains prognostic evidence in acute MI and predicts cardiovascular mortality and risk of HF development in these patients. sST2 might be a promising tool to stratify the risk of sudden cardiac death in patients with low LVEF. Thus, sST2 signifies a biomarker that reflects the pathophysiological processes, and predicts about several cardiovascular diseases, particularly in patients with HF [22].

The data on the utility of ST2 in the Indian population are lacking. Also, there are no data about the correlation of ST2, N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) and hsCRP in the Indian population. The aim of the present study was to find the correlation of ST2 level at the time of admission with NT-proBNP, hsCRP and LVEF in patients with MI, and the association of ST2 level with mortality.

MATERIALS AND METHODS

This longitudinal observational study was conducted between June 2018 and August 2019. After approval from the Institutional Ethics Committee (Letter No. RECH/EC/2018-19/183), written informed consent was obtained from all the patients prior to enrolment explaining the risks and benefits of the procedure.

Inclusion criteria: Patients above 18 years of age who had only fresh MI presented within 12 hour of symptom onset were included.

Exclusion criteria: Patients who had liver cirrhosis, chronic obstructive pulmonary disease, bronchitis, asthma, pulmonary fibrosis, chronic heart failure due to rheumatic valvular heart diseases, collagen vascular diseases, rheumatoid arthritis and sepsis were excluded from the study.

Sample size calculation: Barbarash O et al., reported a significant correlation between NT-proBNP and ST2 levels (r-value=0.50, p-value=0.001) [23]. The sample size was calculated by formula:

$N=[(Z_\alpha+Z_\beta)/C]^2 + 3$

where $C=0.5 * \ln[(1+r)/(1-r)]$ [24]

$Z\alpha$ was considered at 1% type 1 error (2.58)

$Z\beta$ the standard normal deviate for β power 90 % at type II error (1.28).

Total sample size of 52 was calculated by above method. In the present study, 75 patients were included to validate the results.

Myocardial infarction: MI was defined as detection of rise and/or fall of cardiac biomarkers (preferably cardiac troponin I value >99th percentile of upper reference limit) plus atleast one of the symptoms of ischaemia (chest pain, irregular heart rate, malaise), new or presumed new significant ST-segment and T wave changes or new Left Bundle Branch Block (LBBB), development of pathological Q waves on Electrocardiogram (ECG), imaging evidence of new loss of viable myocardium or new regional wall motion abnormality and identification of intracoronary thrombus by angiography [25].

Data collection: Detailed clinical history and examination findings were noted for each patient. The ECG changes were noted such as ST elevation/depression, T wave inversion or Q waves and new LBBB. A 2D-ECHO was done to determine LVEF. Haemogram, serum urea, serum creatinine, serum electrolytes, blood sugar levels along with chest X-ray were done on admission. ST2, NT-proBNP, hsCRP and Troponin I levels were checked within 6 hours of hospitalisation.

- ST2 was checked by Sandwich monoclonal lateral flow immunoassay, on Aspect Reader (cut-off value 35 ng/dL);
- High-sensitivity C-reactive protein (hsCRP) was measured by Nephelometry method on BN ProSpec;
- NT-proBNP was measured by Enzyme-linked Fluorescent Assay, on VIDAS and
- Troponin-I was measured by Chemiluminescent microparticle immunoassay method on ARCHITECT.
- The duration of hospital stay, in-hospital mortality and status on discharge were recorded for each patient. At one month follow-up, mortality, if any was noted.
- The primary outcome measures were to study the correlation of ST2 with hsCRP, NT-proBNP levels and LVEF at the time of admission in MI patients. The secondary outcome measures were to study the association of ST2 levels with in-hospital mortality and mortality on one month follow-up.

STATISTICAL ANALYSIS

Data collected were entered in Excel 2007 and analysis of data was done using Statistical Package for Social Sciences for Windows, Version 20.0 from IBM Corporation, Armonk, NY, USA. The data on categorical variables are shown as n (% of cases). The parametric data on continuous variables are presented as mean and Standard Deviation (SD), whereas non-parametric data are presented as median and Interquartile Range (IQR). The intergroup comparison of medians of continuous variables was done using the Mann-Whitney U and Kruskal-Wallis H test for two groups and three groups respectively. The correlation analysis was performed using Spearman's method. The confidence limit for significance was fixed at a 95% level with a p-value <0.05.

RESULTS

The demographic and clinical characteristics are depicted in [Table/Fig-1]. The mean ± SD of the age of the study population was 57.8±7.2 years. The majority (49,65.3%) of the population was comprised of males. The median ST2 level on admission was 109.6 ng/dL.

Variables	n, %
Age group in years	
<50	12 (16.0%)
50-59	35 (46.7%)
≥60	28 (37.3%)
Gender	
Male	49 (65.3%)
Female	26 (34.7%)
Days of hospitalisation	
1-7	65 (86.7%)
8-13	10 (13.3%)
In-hospital outcome	
Survived	65 (86.7%)
Died	10 (13.3%)
Outcome at one month follow-up	
Survived	63 (96.9%)
Died	2 (3.1%)

[Table/Fig-1]: Demographic and clinical characteristics.

There was a statistically significant positive correlation between ST2 and NT-ProBNP levels and ST2 and hsCRP levels. ST2levels on admission showed a statistically significant negative correlation with LVEF. The lower LVEF on admission was significantly associated with the higher ST2 levels and vice-versa [Table/Fig-2]. The median ST2 levels were significantly higher in patients who died in hospital (in-hospital mortality) as compared to survived patients. The median ST2 levels did not differ significantly according to the duration of hospital stay. The median ST2 levels were significantly lower in patients who had LVEF ≥50%.The median ST2 levels were significantly higher in patients who died as compared survived patients at one month follow-up [Table/Fig-3].

	Myocardial infarction (n=75)	
Variables	r-value	p-value
ST2 with NT-ProBNP	0.703	0.001
ST2 with hsCRP	0.873	0.001
ST2 with LVEF	-0.711	0.001

[Table/Fig-2]: Correlation analysis of ST2level with NT-proBNP,hsCRP, and LVEF. Spearman's correlation was used; ST2- Suppression of tumourigenicity 2; NT-proBNP—N-terminal pro-B-type natriuretic peptide; hsCRP- high-sensitivity C-reactive protein; LVEF- Left ventricular ejection fraction

DISCUSSION

There was a statistically significant positive correlation between ST2 and NT-ProBNP levels and hsCRP levels in patients on admission of MI. ST2 levels on admission showed a statistically significant negative correlation with LVEF in patients of MI. The median ST2 levels were significantly higher in patients who died (in-hospital deaths and at one month follow-up) as compared to survived patients. This is the first Indian study that has compared well established cardiac biomarkers, NT-proBNP and hsCRP with a novel biomarker ST2.

Outcome	ST2 level		p-value
	Median (ng/dL)	IQR	
In-hospital outcome			
Survived	94.0	80.5	0.001*
Died	215.3	53.0	
Duration hospital stay (in days)			
1-7	117.0	103.5	0.508*
8-13	149.0	123.0	
LVEF (in %)			
<40	177.0	74.5	0.001**
40-49	89.9	75.0	
≥50	57.5	49.8	
Outcome at one month follow-up			
Survived	92.0	82.7	0.004*
Died	219.5	-	

[Table/Fig-3]: Median ST2 level according to outcome.
*Mann-Whitney U test was used; **Kruskal-Wallis H test was used; IQR-Inter quartile range; ST2- Suppression of tumourigenicity 2; LVEF- Left ventricular ejection fraction.

Various studies have reported higher levels of ST2 in MI. In studies by Sabatine MS et al., Barbarash O et al., Jenkins W et al., and Dhillon OS et al., median levels of ST2 levels were 80 ng/dL, 57 ng/dL, 70.0 ng/dL and 78.2. ng/dL respectively which was much higher than the baseline levels and it was associated with the poor outcome [20,23,26,27]. In the present study, the median ST2 level in the MI patients was 117.00 ng/dL much higher than reported previously. This was likely due to more severely ill patients in the present study.

The positive correlation of ST2 and NT-proBNP has been reported by Shimpo M et al., and Sabatine MS et al., for ST-elevation Myocardial Infarction (STEMI) [15,20]. Sabatine MS et al., and Barbarash O et al., reported that the correlation between baseline ST2 levels and NT-proBNP was slight (r-value=0.14, p-value <0.001) and (r-value =0.50, p-value=0.001) respectively [20,23]. O'Donoghue ML et al., reported a positive correlation (r=0.34) between ST2 and NT proBNP [28]. The present study substantiated these findings. Studies directly correlating ST2 and hsCRP in MI are lacking. O'Donoghue ML et al., and Wang TJ et al., in the Framingham offspring study and using the multimarker model in MI had reported a positive correlation of ST2 and hsCRP [28,29].

Kohli P et al., reported that in patients with LVEF, higher ST2 concentration was weakly but significantly associated with lower ejection fraction (r-value=0.12, p-value=0.0001) [30]. In the present study, ST2 level was inversely related (r-value=-0.711) to LVEF in MI patients. This is likely due to more damaged and poorly functioning myocardium in STEMI cases with lower LVEF.

Sabatine MS et al., reported that the baseline ST2 level was significantly higher in patients who suffered cardiovascular death [20]. Jenkins W et al., reported that persons with elevated sST2 had a 2.4-fold increased risk of death {Hazards ratio (HR) 2.38; 95% CI 1.46-3.86; p-value=0.005} and a 2.1-fold increased risk of Heart Failure (HF) (HR 2.11; 95% CI 1.18-3.76; p-value=0.01) [26]. Barbarash O et al., reported that median sST2 (ng/mL) of 35.5 and 70.0 had favourable and unfavourable outcome respectively after MI [23].

Dhillon OS et al., reported that ST2 independently predicts 30-day mortality (HR: 4.43, p-value=0.02) [27]. Kohli P et al., reported that high ST2 was associated with increased risk for Cardiovascular Death (CVD)/HF at 30 days (6.6% vs 1.6%, p-value=0.0001) and 1 year (12.2% vs 5.2%, p-value=0.0001) [30]. Wang TJ et al., reported that the concentrations of sST2, predict the future risk of death {HR=1.32 (1.20-1.46)} [29]. O'Donoghue ML et al., reported that after adjustment for clinical variables and using a dichotomous cut point, ST2 was significantly associated with the higher odds CVD or HF (Odds ratio adj, 2.87; 1.61-5.12) [28]. In the present study, the median ST2 levels were significantly higher in patients who died (in-hospital deaths and at one month follow-up) as compared to survived patients.

The present study showed that high levels of ST2 levels at admission were associated within-hospital and one month follow-up mortality in MI patients. Therefore, it is recommended that ST2 levels should be checked at admission in all the patients of MI.

Limitation(s)

The sample size, study duration and follow-up period were small. This study was conducted in MI patients only, and no control group was taken. Authors only assessed ST2, NT-proBNP and hsCRP at baseline. Repeated testing was not done on follow-up, due to the costs, which would have given information on the degree of change in biomarkers following treatment. The details of the patients such as STEMI/non- STEMI) and the therapy offered to patients were not noted.

CONCLUSION(S)

Suppression of Tumourigenicity 2 levels showed a statistically significant positive correlation with NT-proBNP and hsCRP, whereas ST2 levels showed a statistically significant negative correlation with LVEFin MI patients. The median ST2 levels were significantly higher in in-hospital mortality and mortality at one-month follow-upin MI patients.

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