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ORIGINAL PAPER

ROLE OF ST2, AN INTERLEUKIN-1 FAMILY RECEPTOR, AS A PROGNOSTIC MARKER IN ACUTE CORONARY SYNDROME (AN ORIGINAL PROSPECTIVE OBSERVATIONAL STUDY CONDUCTED IN A TERTIARY CARE HOSPITAL IN INDIA)

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ABSTRACT

BACKGROUND:

An important sequelae post myocardial infarction is left ventricular remodelling, which determines the long term outcome and occurrence of heart failure. Biomarkers are used as a tool to identify high risk individuals, to diagnose disease conditions promptly/accurately and to effectively prognosticate and treat patients with disease. ST2 is one such promising relatively new biomarker. Myocytes that are subjected to mechanical stress secrete ST2 and the ST2 level has been found to be an independent predictor of heart failure and adverse outcome in patients with acute myocardial infarction.

METHODS:

We checked the Serum ST2 level on admission of 102 patients admitted with acute myocardial infarction in our hospital. In 34 patients out of these a discharge time ST2 level was also measured. The ST2 levels obtained on presentation, were correlated with the clinical severity of the disease on presentation and subsequent acute complications during hospital stay. ST2 level at discharge was correlated with readmission and occurrence of heart failure or cardiovascular event after discharge for a follow up period of 6 months.

RESULTS:

In our study high ST2 levels on admission significantly correlated (P values < 0.05) with disease severity in the form of high TIMI score and low LV systolic function. High ST2 level had a statistically non-significant

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negative association with blood pressure (lower blood pressures having higher ST2 values) and a positive association with duration of symptoms (longer duration had higher values), 'in hospital' adverse events. In our study none of the patients from low ST2 group had 'in hospital' adverse events or mortality. Majority of patients readmitted were from high ST2 group (statistically non-significant).

CONCLUSION:

ST2 is a promising biomarker for prognostication and can be included in routine biomarkers for risk stratification of acute myocardial infarction and heart failure. Patients admitted with acute MI or heart failure who have high ST2 levels should be followed up closely to prevent the occurrence of adverse cardiovascular events.

KEYWORDS: Acute, infarction, ST2, mortality, readmission, correlation

INTRODUCTION:

Cardiovascular diseases (CVD) are the leading cause of mortality and morbidity in today's world. Rising age of global population and higher prevalence of comorbidities makes Coronary artery disease (CAD) one of the important causes of mortality & morbidity amongst CVD. CAD caused ≈ 1 of every 6 deaths in the United States in 2010.[1]

An important sequelae post myocardial infarction is left ventricular remodeling. Cardiac remodeling is an important determinant of the long term outcome and occurrence of heart failure. Although clinical assessment is the keystone of patient management such evaluation has its limitations. Many times one requires additional tools to aid clinical assessment.

Biomarkers are one such tool. Biomarkers are used as a tool to identify high risk individuals, to diagnose disease conditions promptly/accurately and to effectively prognosticate and treat patients with disease. A biomarker may be measured on a bio-sample (as a blood, urine, or tissue test), it may be a recording obtained from a person (blood pressure, ECG, or Holter), or it may be an imaging test (echocardiogram or CT scan).

ST2 is one such novel biomarker. ST2 (suppression of tumourogenesis 2) is a member of the interleukin (IL)-1 receptor family and exists in two forms, a trans-membrane receptor (ST2L) as well as a soluble decoy receptor (sST2).[2] The ligand of ST2 is IL-33, which is involved in reducing fibrosis and hypertrophy in mechanically strained tissues.[3]

The role of ST2 in cardiovascular disease, including ventricular remodeling and heart failure (HF) progression has been suggested by both experimental and clinical studies. Serum soluble ST2 is a novel biomarker for neurohormonal activation in patients with heart failure. In patients with severe chronic NYHA class III to IV heart failure, the change in ST2 levels is an independent predictor of subsequent mortality or transplantation.[4] ST2 has also been found to be an independent predictor of heart failure and adverse outcome in patients with acute myocardial infarction.[5] Myocytes that are subjected to mechanical stress secrete ST2, that is associated with HF after ST elevation myocardial infarction (STEMI). Thus ST2 level can indirectly tell about the extent of pathophysiological changes going on at molecular level leading to LV remodeling and eventually clinically present as heart failure.

This study is being done with an aim to establish correlation, if any, between the ST2 level and the presentation as well as the course of patients with acute coronary syndrome. A high ST2 level may indicate adverse LV remodeling at molecular level even before the clinical presentation with LV dilatation and heart failure. Establishing such a relationship will help guide therapy in future. Patients with higher ST2 levels can be observed closely and treated with maximally tolerated doses of beta blocker, ACE-I/ARB, Aldosterone antagonists at the time of discharge even in absence of overt clinical signs of LV remodelling.

METHODS:

This is a prospective observational study which has been conducted in Apollo Hospital, Chennai in India from February 2014 to June 2015. Patients admitted with acute coronary syndrome fulfilling the inclusion criteria of the study (as outlined in Table) were included in the study.

There are literature that say about the cut off value of ST2 as 35ng/ml.[5] Also literature supports that patients with ≥ 35ng/ml ST2 value had 1.77 times (Odds Ratio) higher chance of adverse outcome.[6] With this knowledge we worked out the sample size with two tailed distribution, effect size of 0.13, level of significance

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at 5%, power of 80% and the constant proportion of 0.5, the required sample size was derived as 102 cases. The sample size is derived using the software G*power 3.1.9.2

Definition of Acute MI was as per 'The third universal definition of MI'-Expert consensus document (2012). Data was collected and recorded according to a preformed study proforma (Annexure).

The study included taking blood samples for ST2 on presentation (for all patients) and at discharge (in as many as possible). The sample was analyzed using the 'Presage kit' provided by Critical diagnostics. Detailed history, including onset of pain, co-morbidities (Diabetes mellitus, hypertension, dyslipidemia, previous CAD), personal history of alcohol consumption, smoking, drug intake (anti-platelets) was taken. Clinical examination of CVS was done. Blood investigations like Serum creatinine and Troponin was documented. Echocardiogram to assess LV systolic function was done on admission and discharge. TIMI risk score was calculated to assess the clinical severity/mortality. Prediction as a standard for comparison. Significant events during hospital stay like pulmonary oedema, arrhythmias, shock and the intervention done (IABP, temporary pacing, mechanical ventilation) were documented. The treatment received by the patient whether medical management, thrombolytic therapy or intervention was documented. The duration of stay and outcome in the form of recovery and discharge or death was recorded. Patients were followed up for a period of 6 months to note occurrence of heart failure, re-infarction or death due to cardiovascular causes during this period.

Method of statistical analysis:

All the continuous variables were assessed for the normality using Shapiro-Wilk's test. If they were normally distributed they were expressed as mean ± SD. All categorical variables were expressed as percentages.

Comparison of categorical variables were done by Chi square test or Fisher's exact test. Data entry was done in MS Excel spread sheet. Data analysis was carried out by SPSS version 16.0. All 'P' values < 0.05 were considered statistically significant.

Table No. 1: Inclusion and exclusion criteria

Inclusion criteria:
1. Age more than 30 years
2. Presenting within 24 hours of onset of symptoms
3. Fulfilling the criteria for diagnosis of Acute MI (as per the 'Third Universal definition of AMI-2012')
Exclusion criteria:
Patients with PCI related and CABG related acute MI have been excluded

RESULTS:

Results of 102 patients was analysed. Out of these 34 patients had paired samples with one taken at the time of presentation and another at the time of discharge. The Mean age of study population was 56.2 years (SD ±12.08), 81.4 % were males, 50% were known Diabetics and 49% were known hypertensive. The Demographic profile if the population is shown in Table No. 2

Table No.2: Demographic data

Demographic Data	Mean	SD
Age	56.2years	12.08
Duration of symptoms	7.8 hours	6.96
Serum Creatinine	1.04mg/dl	0.18
TIMI score	3.8	2.51
Systolic BP	129.9mmHg	24.96
Heart Rate	85.4bpm	18.25

Demographic data	n	%

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Male	83	81.4
AW-STEMI	47	46.1
Known Diabetic	51	50
Known Hypertensive	50	49
Previous CAD	6	5.9
Known Dyslipidaemia	8	7.8
High ST2 (>35ng/ml) on admission	74	72.5
Patients discharged	96	94.1
Patients expired	6	5.9
Readmission	11	11.5

We also correlated the demographic and clinical parameters with the ST2 level obtained on presentation. (Table No. 3)We found no significant correlation between high ST2 levels and age more than 65 years, although there was a positive correlation between age and ST2 level on admission. Also ST2 level did not show any statistically significant correlation with gender. 83% of the patients with anterior territory ACS (Acute coronary syndrome) had high ST2 level. Also there was a positive correlation between duration of symptoms in hours and the ST2 level on admission.

There was a negative correlation between the blood pressure on admission and the ST2 levels, with patients having lower blood pressure having higher ST2 levels on admission. Presence of co-morbidities like Diabetes mellitus, hypertension, previous CAD or dyslipidaemia did not have any statistically significant correlation with the ST2 level on admission. Also Serum creatinine level did not seem to influence the ST2 level. Calculated TIMI score had a statistically significant positive association with ST2 levels, with higher TIMI scores having higher ST2 levels (Figure No.1). The left ventricular ejection fraction assessed by echo showed a strong statistically significant negative association with the ST2 levels (Figure No. 2).

Figure 1: Positive association between TIMI score and ST2 level

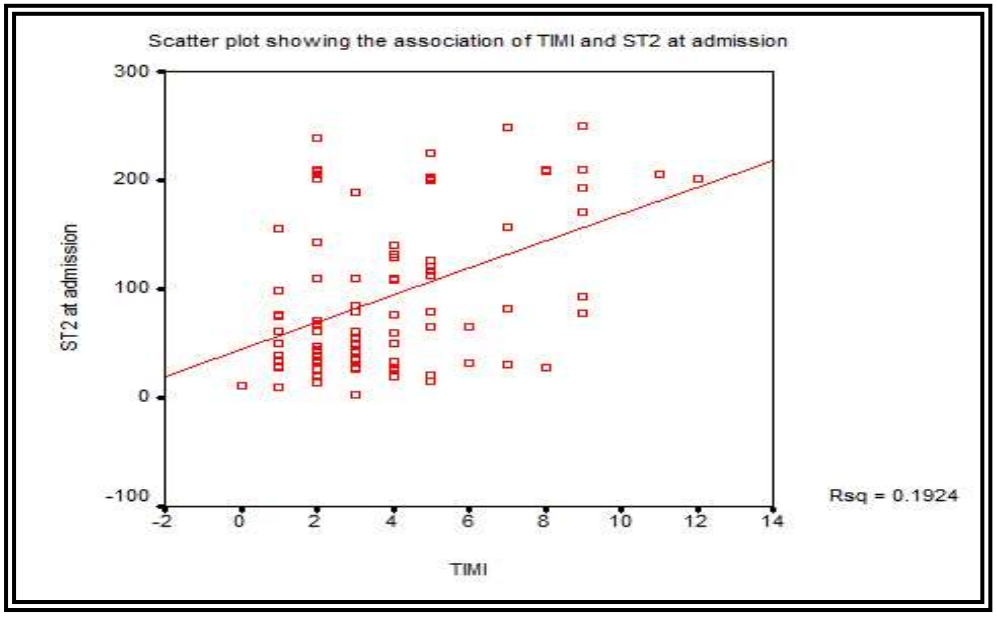

Figure 2: Negative association between LVEF and ST2 level

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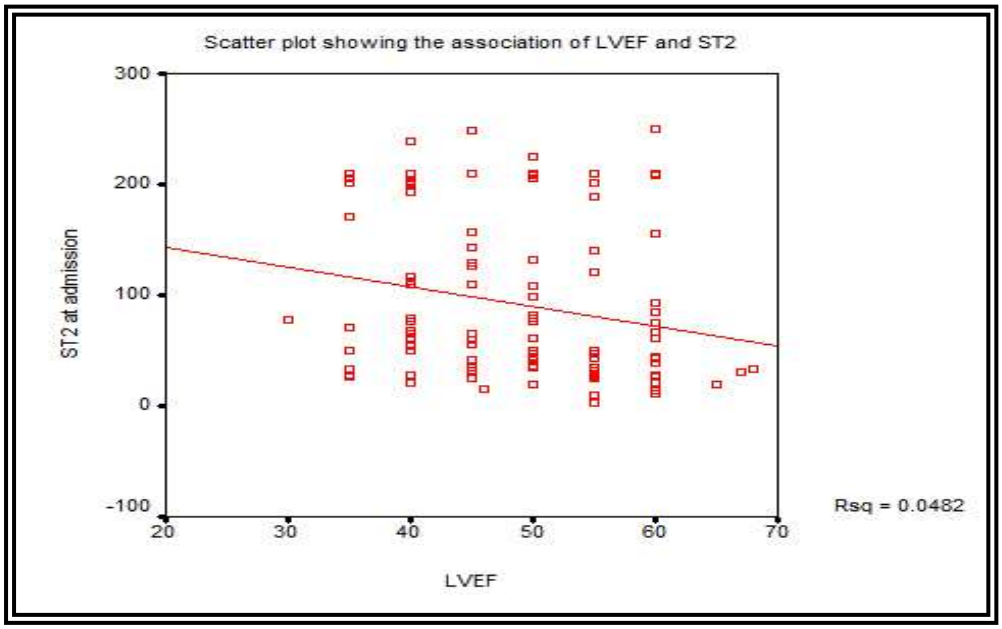

Table No. 3:

Correlation analyzed	'p' value	Coefficient of correlation 'r'
Age> 65yrs and high ST2 (≥35ng/ml)	0.46	
Gender and high ST2 level	0.15	
Duration of symptoms and ST2 on admission	0.419	0.081
Diabetes mellitus and high ST2 level	0.506	
HTN and high ST2 level	0.659	
Previous CAD and high ST2 level	0.665	
Dyslipidemia and high ST2 level	1	
BP and ST2 level	0.180	-0.135
TIMI score and ST2 level	**0.0001**	0.439
LVEF and ST2 level	**0.027**	-0.219

All the patients who required invasive mechanical ventilation due to pulmonary oedema and those who had associated adverse events like arrhythmias, shock had high ST2 levels (greater than 35ng/ml). Also the 6 patients who died in the study group had ST2 level >35ng/ml on admission (Table No. 4). Although statistical significance could not be established, none of the patients with low ST2 level had in hospital adverse events.

Table No. 4:

Adverse event	n	% of total study sample	% having high ST2 (≥ 35ng/ml)
Mechanical ventilation	8	7.8%	100%
Shock	8	7.8%	100%
Arrhythmia	9	8.8%	100%
Death	6	5.8%	100%

In the 34 patients with two serial ST2 samples (one on admission and one at discharge) we studied the shift of ST2 levels and correlated it with the occurrence of adverse events. Shift in ST2 levels was considered adverse when on admission ST2 level was high (≥35ng/ml) which remained high on the day of discharge, or

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when ST2 levels were low on admission (< 35ng/ml) but became high on the day of discharge. The shift was considered favourable when low values on admission, remained low on the day of discharge or when high value on admission became low on discharge.

In the study population of 34 patients, 16 showed adverse shift, while 18 showed favourable shift. 7 out of 16 patients (43.8%) in the adverse shift group had an event (in hospital shock, arrhythmia, heart failure or death). While only 3 out of 18 patients (16.7%) in the favourable group had event.

DISCUSSION:

Our study population showed predominance of male patients (81.4%). The mean age of the study population was found to be 56.2 years (SD 12.08). The mean age is lesser than that of western population as observed by Joshi P et al, in their study.[7] This profile is similar to that described by Singh PS et al when they studied 200 patients to describe the clinical profile and risk factors of Acute coronary Syndrome.[8]

Morrow DA, et al. in 2000 developed and evaluated a convenient bedside clinical risk score for predicting 30-day mortality at presentation of fibrinolytic-eligible patients with STEMI. They concluded that TIMI risk score for STEMI captures the majority of prognostic information offered by a full logistic regression model but is more readily used at the bedside. This risk assessment tool is likely to be clinically useful in the triage and management of fibrinolytic-eligible patients with STEMI.[9] We recorded TIMI score for all the patients (STEMI and Non-STEMI). The mean TIMI score of the population was 3.8.

In our study higher number of males (75.9%) had elevated ST2 levels compared to females (57.9%). Also 78.6% patients more than 65 years of age had higher ST2 levels. Age and ST2 levels showed positive association, with higher age group patients having higher ST2 level.

This is in concurrence with the studies by Kohli P, Bonavca MP et al in the MERLIN-TIMI36 trial where they observed that patients with ST2 concentrations in the top quartile (≥35 ng/ml) were more likely to be older and males.[10]

However in our study these variables did not show any statistical significance.

Left ventricular systolic function expressed as LV ejection fraction on echocardiogram showed a statistically significant negative association with ST2 values at admission (P value= 0.027). This correlates with the studies done by Sanada et al and Weinberg EO et al. describing the release of ST2 by cardiac myocytes in response to biomechanical stress.[11, 12]

Presence of co-morbidities like Diabetes mellitus, hypertension, previous coronary artery disease did not have any correlation with the ST2 levels. Also ST2 level was found to be independent of serum creatinine level.

We found a negative association between blood pressure and ST2 values, with patients with lower blood pressure at presentation having higher ST2 level. In the various prognostic risk scores low systolic BP has been an important variable carrying more weight. In TIMI score systolic BP less than 100mmHg carries 3 points.[9] In a study by Gonclaves et.al of various risk scores, in GRACE score the lower the systolic BP, higher is the points given and hence worse the prognosis.[13]

We calculated TIMI score of patients in our study population. Although the mean TIMI score in both the groups (high ST2 and low ST2) did not show significant difference, it was observed that all the patients with TIMI score ≥ 8 belonged to the group with high ST2 levels (≥35ng/ml). TIMI score showed a statistically significant positive correlation with ST2 values at admission (P value = 0.0001). Higher the TIMI score, higher were the ST2 values. This is in line with the studies of Dhillon OS et al, who observed that ST2 level is useful in predicting STEMI patients who are at risk of early mortality when compared with other risk predicting scores.[14]

Acute pulmonary oedema is an important manifestation of heart failure (left ventricular failure). Killip class II and above is defined by clinical signs of heart failure. In our study majority of patients with Killip class II and above had high ST2 level ≥ 35ng/ml. Out of these all the patients who required invasive mechanical ventilation had high ST levels. This is in line with the study done by Shimpo M et.al, who correlated high ST2 levels with higher rates of heart failure in hospital and mortality in acute MI.[15]

In our study out of 102 patients, 9 people developed arrhythmia, and all these 9 patients had high ST2 levels, although this failed to show any statistical significance, future studies with larger sample may bring up this association. There are not much literature highlighting the role of ST2 in predicting arrhythmic risk in acute MI. However a study by Stolen CG et al, in monitoring arrhythmic risk in stable heart failure patients,

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concluded that serial measurement of ST2 can be a useful tool to predict arrhythmic risk in heart failure patients.[16]

In our study population 8 patients were in shock and had systolic blood pressure less than 90mmHg. All these patients had high ST2 levels. A low systolic blood pressure is a sign of extensive myocardial stress/damage and heart failure. This finding is in line with the various studies done by Dhillon OS, et al and by Kohli P, et al in the MERLIN-TIMI trial.[10, 14]

In our study population of 102 patients, there were 6 deaths in hospital. All these 6 patients had high ST2 levels. There were no deaths in the low ST2 group. This is in line with the study by Shimpoo et al where they found that high ST2 levels were associated with in hospital mortality.[15]

If we consider the number of patients readmitted, 81.8% (9 out of 11) had high ST2 levels on first admission.

Out of the patients with high ST2 levels, 13.2% got readmitted with cardiovascular causes.

Although we could not find statistical significance in our study, majority of patients readmitted did have high ST2 levels during first admission and probably warrants a larger study with bigger sample to show statistical significance.

The study by Shimpoo et. al of 810 patients with acute MI, in hospital events (death, heart failure) as well as readmission with cardiovascular causes (recurrent MI, heart failure) were more in patients with high ST2 levels.[15]

The correlation between the shifts in the ST2 levels (in patients with serial samples on admission and discharge) was studied with occurrence of adverse events (shock, arrhythmia, heart failure or death). Shift in ST2 levels was considered adverse when on admission ST2 level was high (≥35ng/ml) which remained high on the day of discharge, or when ST2 levels were low on admission (< 35ng/ml) but became high on the day of discharge. The shift was considered favourable when low values on admission, remained low on the day of discharge or when high value on admission became low on discharge. In our study population 43.8% patients in the adverse shift group had an event (in hospital shock, arrhythmia, heart failure or death). While only 16.7% patient in the favourable group had events. However this correlation lacked statistical significance.

But the observation is in concurrence with studies done in acute heart failure in literature, where Boisot et al determined the prognostic utility of serial sampling of ST2 and concluded that percentage change in the ST2 level during acute treatment is predictive of 90 day mortality.[17]

CONCLUSION:

- In our study high ST2 levels were associated with higher age and male gender, although we could not establish statistical significance.

- High ST2 levels on admission significantly correlated (P values < 0.05) with disease severity in the form of high TIMI score and low LV systolic function.
- High ST2 level had a negative association with blood pressure, with lower blood pressures having higher ST2 values.
- High ST2 level also had positive association with duration of symptoms, with longer duration having higher values, but statistical significance could not be achieved.
- We observed that high ST2 levels were associated with 'in hospital' adverse events like shock, arrhythmia, heart failure, with 100% of these events being from high ST2 group (however this association failed to show statistical significance).
- In our study adverse outcome in the form of mortality was only from the high ST2 group.
- None of the patients from low ST2 group had 'in hospital' adverse events or mortality.

LIMITATIONS:

Following are the limitations of our study:

- Although we observe a positive correlation between disease severity and adverse outcome with high ST2 levels, we could not establish statistical significance in all the variables.

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- Our sample size being 102, a larger sample size may help in establishing statistical significance.
- During our study many patients who were very sick or dying could not be included due to lack of informed consent by patient's family.
- We did not have a discharge day ST2 sample for whole of our study population, which might have helped.

RECOMMENDATIONS

- ST2 is a promising biomarker for prognostication and can be included in routine biomarkers for risk stratification of acute myocardial infarction (MI) and heart failure.
- Serial sampling of ST2 can be used in guiding and optimization of therapy of heart failure patients on follow up.
- Patients admitted with acute MI or heart failure who have high ST2 levels should be followed up closely to prevent the occurrence of adverse cardiovascular events.

STUDY FUNDING
Chennai Medipoint provided research assistance in the form of free Critical diagnostics presage ST2 kits, required in this study. We acknowledge and thank them for their support.

CONFLICT OF INTEREST
None.

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