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"Relationship between serum concentration of the soluble interleukin-1 receptor family member ST-2 and serial change in left ventricular function after acute myocardial infarction"

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Abstract:
Background: *Myocardial infarction continues to be one of the most important cause of mortality and morbidity worldwide. The sequel of infarction may be heart failure, myocardial rupture, various arrhythmias, aneurysm or even death. Early and proper management of myocardial infarction by medical treatment, thrombolysis, percutaneous coronary intervention and coronary artery bypass grafting has improved the outcome to much greater extent in terms of cardiac end point[1]. If we could have such biomarkers which not only would increase the diagnostic accuracy but also provide the prognostic information about the concerned disease promptly and in an effective way, serum soluble ST2 is one such biomarker which has the above mentioned qualities.*
Aim: *To find relationship between serum concentration of the ST-2 and serial changes in left ventricular function.*
Method: *This was an observational study involving 30 new cases of AMI .Serum ST-2 was measured at admission and its relation was seen with left ventricular function.*
Result: *We analyzed the relationship of serum soluble ST2 with the ejection fraction at the time of admission and after an interval of 15 days. The ejection fraction measured at admission and 15 days after admission was having a significant correlation with the measured serum soluble ST2 at the time of admission [having a p value of 0.00(<0.05)].*
Key Word: *Myocardial Infarction, Serum soluble ST2, Left Ventricular Function*

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I. Introduction:

As India is becoming a hub for various cardiovascular events and among them AMI which is gradually becoming one of the major burden on our country health and economical structure thus it is really important to have a study on a biomarker which could be of great value for diagnosing and determining the prognosis in much better, accurate, affordable way in Indian context.

ST2 is an IL-1 receptor like protein which was found to be elevated in serum of heart under stress[2] .ST2 predicts cardiovascular death following ACS[3] .ST2 turned out to be the target for an interleukin called IL-33 which seems to have a cardio protective role and only appears when cardiomyocytes are under biomechanical stress[4] .In mouse studies, IL-33 was found to markedly antagonize angiotensin-II and phenylephrine-induced cardiomyocyte hypertrophy. It is thought that ST2/IL-33 interaction also reduces atheroma burden[5].Investigation into the use of IL33/ST2 pathway activation as a therapeutic target are still ongoing[6] .ST2 is also elevated in asthma and autoimmune disease[7] .There is a tight relationship of ST2 with cardiac function and dysfunction.ST2 action in cardiac muscle is complex and it is tightly related to IL-33 mode of action. Kakkar et.al[8] demonstrated that the mechanical stretch of living cells could enhance the release of IL-33 from the cytoplasmatic vesicles. An increase in serum soluble ST2 could reduce the cardio protective action of IL-33 on cardiac cells and could induce a negative prognostic effect on the overall cardiovascular risk profile[9] .As demonstrated by Weingberg et.al[10] , the increased plasma level of serum soluble ST2 soon after a myocardial infarction event could be considered as a negative prognostic factor. Concentration of serum soluble ST2 correlate positively with parameters of HF severity as ,nor epinephrine levels, natriuretic peptide levels, diastolic filling pressure and C-reactive protein level .it is thus possible that ST2 is not only a biomarker but also a true pathophysiological mediator of disease progression and predisposition to SCD.As per article released by Reuters on Friday July 2014 multiple studies show superiority of critical diagnostics ST2 over BNP, NT-proBNP and other heart failure

biomarkers. It was stated by this article and other journal that along with other cardiac biomarkers the sensitivity and efficacy of serum soluble ST2 as a prognostic marker increase to many fold[11,12,13] .

Aims and objective: measurement of soluble ST-2 early after AMI in the prediction of LV function and to find relationship between serum concentration of the ST-2, also to measure serial changes in left ventricular function.

II. Material and method:

The present study has been done in 30 new cases of AMI admitted in department of medicine RIMS, Ranchi within a duration of one year. (December 2015 – November 2016). All those patients who were above the age of 18years with ECG changes suggestive of ischemia and LVEF<40% on screening echocardiography at the time of admission had been included in our study. Pregnant women, clinical or radiological heart failure (Killip score),Established diabetes mellitus, serum creatinine>220micromol/l, serum potassium>5mmol/l, presence of infectious, inflammatory and neoplastic disease, patients on immunosuppressive drugs, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout and all cases of stable angina were excluded from the study.

Method:

The critical diagnostics presage ST2 Assay is a quantitative sandwich monoclonal ELISA in a 96-well microtitre plate format for measurement of soluble ST2 in serum, EDTA plasma, or heparin plasma. The presage ST2 Assay utilizes two monoclonal antibodies against ST2. A mouse monoclonal anti-human ST2 antibody is coated onto the surface of the microititre plate wells and act as the capture antibody to bind ST2 molecule in solution .A second mouse monoclonal anti-human ST2 antibody is provided in solution and functions as the tracer antibody for detecting ST2 molecules which have bound to capture antibody. The microtitre plate is provided ready to use .Standards, quality control materials, and patient specimens are introduced in to the wells and incubated for 60 minutes. During this incubation period, the ST2 present in standards and specimens bind to the capture antibody coated onto the well surface. After incubation, a wash step removes unbound material introduced with the samples. The tracer antibody, an anti ST2 Biotinylated antibody is introduced in to the well and incubated for 60 minutes. During the time, an antibody-antigen-antibody complex is formed. After incubation a wash step removes unbound materials. Working streptividin-HRP conjugate Reagent is then introduced into the wells and incubated for 30 minutes. During this time, the streptividin HRP conjugate bind to the anti ST2 Biotinylated antibodies. After incubation, a wash step removes unbound material. The Tetramethylbenzidine (TMB) substrate is added, which yields a blue colour in the presence of HRP.The color development is stopped after 20 minutes by addition of stop solution, which changes the color to yellow and which can be read at an absorbance of 450 mm within 15 minutes .The absorbance is proportional to the ST2 levels in the specimens. The test results of the specimen are read from the standard curve.

Specimen collection and storage:

The pesage ST2 assay is validated for use with human serum, EDTA-plasma, and heparin plasma only. The presage ST2 assay is not validated with citrated plasma. Blood should be collected using standard collection techniques. Centrifugation and separation of the serum or plasma from the cellular components should occur as soon as possible following collection. The recommended specimen volume for the presage ST2 assay is 20microlitre which is sufficient volume for duplicate measurements following recommended sample dilution. If necessary, serum or plasma may be stored for the future analysis.

Statistical analysis:

Data obtained from all the admitted cases of myocardial infarction was tabulated in Microsoft excel and then using SPSS version 23 has been statistically analysed using frequency tables, scatter and various tests of significance like independent sample t test and Pearson bivariate correlation analysis and accordingly inference were drawn to establish the statistical significance of work done.

III. Result:

This study involved 30 cases of AMI patients of which 22 were males and 8 were female. The minimum age at which AMI occurred is 30 years while the maximum 77years, occurrence of MI was most common in the age group 50-60years.Frequency of MI was found to be more in males(73.3%) as compared to females(26.7%).In different occupation group house wives(26.7%) among females and serviceman (23.3%) among male were most affected. This can be attributed to the fact that housewives are not very vigilant of their health states and medical problem and avoid routine evaluation of major risk factor.

The most common presenting symptom in AMI in our study was chest pain with diaphoresis (26.7%), followed by chest pain(23.3%) and dizziness and vomiting was the least common symptom.80% of the MI patient were of STEMI(80%) as compared to NSTEMI(20%).According to ECG changes most cases were

having Anterior wall MI (46.7%) ,followed by Anterolateral wall MI(20%).This can be attributed to the fact that bulk of heart tissue is supplied by the LCA and its branches. Occlusion of which can lead to infarction of anterior, lateral or anterolateral wall of heart. Ours study can be inferred that higher the value of serum soluble ST2 more significant was the decrease in the ejection fraction after 15 days of admission on echocardiography. Also this decrement in ejection fraction was present in most of the patients if serum ST2 was higher above the cut off value of 35ng/ml. The patient of NSTEMI generally have low serum soluble ST2 level as compared to STEMI and there was a positive correlation between serum soluble ST2 and cardiac Troponin T.

IV. Discussion:

The ST2 cardiac biomarker is a, novel biomarker of cardiac stress. ST2 signals the presence and severity of adverse cardiac remodeling and tissue fibrosis, which occurs in response to myocardial infarction, ACS, or worsening heart failure. It is a protein that is encoded by the IL1RL1 gene.ST2 is a strong predictor of cardiovascular death and risk of developing new heart failure in STEMI and NSTE-ACS patients. In patients presenting with ACS ,those in the highest quartile (above 35ng/dl) have more than 3 times have higher risk of cardiovascular death and new heart failure at 30 days ST2 has considerable prognostic value and is used as an aid for risk stratification in identifying patients who are at high risk of mortality and rehospitalization in patients diagnosed with heart failure as a consequence of AMI. ST2 is independent of BNP,NT- proBNP and not adversely influenced by age, BMI, therefore provide unique and complementary prognostic information. In present study no significant relationship of serum ST2 with the sex and age has been observed the fact which already has been reported in various studies[14,15] but the occurrence of MI was much higher in males as compared to females this may be of the fact that all the females cases under study were housewives. In the study 80% cases were of STEMI and 20% cases were of NSTEMI. Among all the cases 83.3% were not having any significant or relevant past history.

There was a significant difference in the value of serum soluble ST2 in the patients of STEMI ad NSTEMI (p value 0.00 i.e. <0.05) with the value of ST2 was significantly higher in patients of STEMI as compared to NSTEMI. A study done by Svitlana Demyanets, Walter S.Speidl and Loannis Tentzeris et al in 373 patients was published in 2014 and the results reported are comparable with our present study. There was a positive correlation between ST2 and Cardiac Troponin T.This positive correlation of cardiac Troponin T with serum soluble ST2 was significant (p value 0.041 i.e. <0.05). A similar result has been documented by the work done by Domingo A.et al in which correlation of serum soluble ST2 with various other cardiac biomarkers was studied in 107 patients in a retrospective way.

We analyzed the relationship of serum soluble ST2 with the ejection fraction at the time of admission and after an interval of 15 days. Initially ejection fraction did not drop but after 15 days ejection fraction drop down to a significant value in majority of those patients in which the initial value of ST2 was above the cut off value of 39 ng/ml. Higher the value of ST2 greater was decrease in ejection fraction as compared to previous value irrespective of the fact that whether the initial ejection fraction at the time of admission was normal or decreased. Thus serum ST2 is having a strong and positive correlation with the left ventricular dysfunction within a period of 30 days of AMI and high value of ST2 is associated with bad prognosis in terms of heart failure and mortality. The data observed in present study is corresponding with the results reported in one of the study done by Robin & Miller, which was published in journal of American college of cardiology in 2010[18] and also with results published in various other studies[19, 20, 21]. Limitation of our study was that we included small sample size. More studies and bigger number of sample size need to be included in the study to establish the above fact

V. Conclusion:

All those patients in which serum soluble ST2 at the time of admission was increased above the cut off value of 35 ng/ml had undergone decrement in there ejection fraction below normal as determined by 2D echocardiography 15 days after the occurrence of myocardial infarction and those cases developed heart failure. The correlation was significant having p value of 0.00(<0.05). So the earliest possible measurement of serum soluble ST2 after AMI will be very helpful serological parameter in determining the prognosis as it has been found that it correlates significantly with the adverse outcomes in terms of heart failure and mortality both individually or in combination with other cardiac biomarkers.

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Table (I) showing differences in the value serum soluble ST2 cases of STEMI and NSTEMI

Mi	N	Mean	Std. Deviation	Std. Error Mean
Sst2(ng/ml) STEMI	24	122.43	36.470	7.444
NSTEMI	6	41.95	14.362	5.863

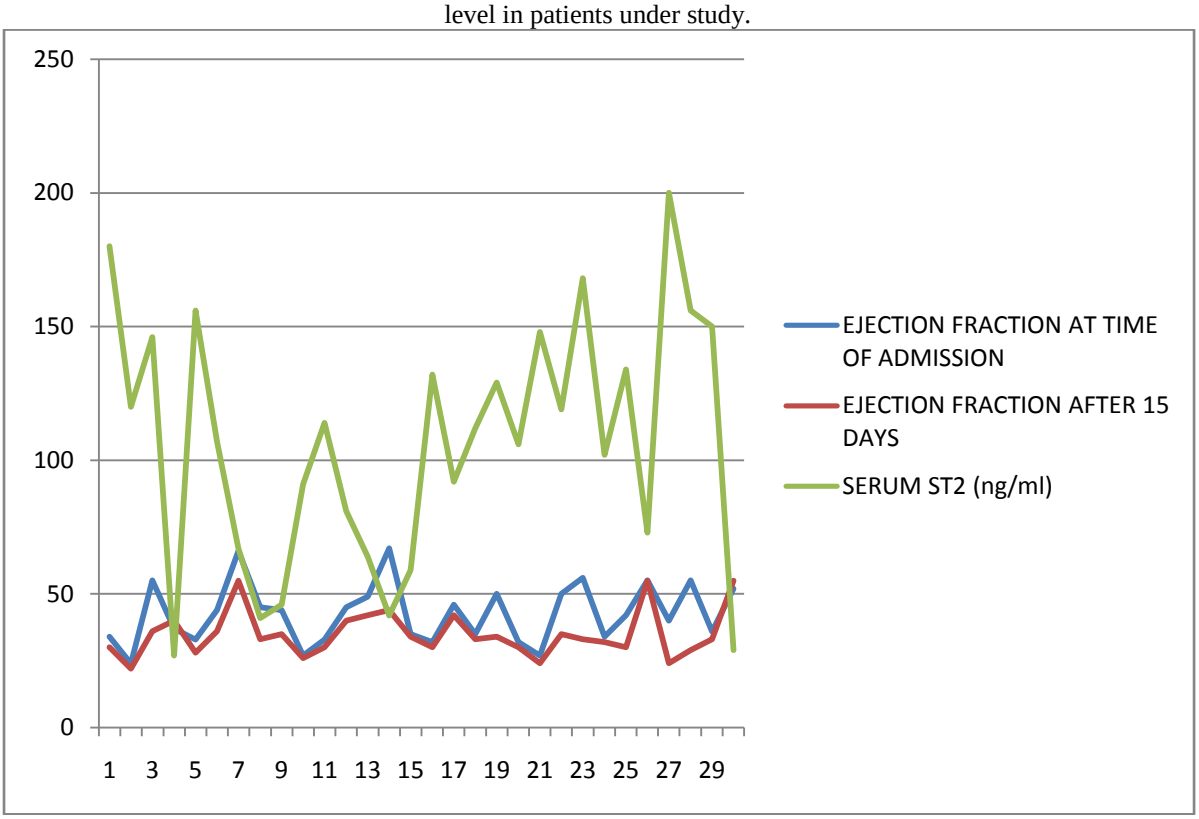
Table (II) Showing independent t test in two different groups of patients i.e STEMI and NSTEMI

t-TEST for Equality of Means						
T	Df	Sig.(2- tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
					Lower	Upper
5.247	28	.000	80.479	15.339	49.059	111.900
8.493	21.800	.000	80.479	9.476	60.817	100.142

Table (III) Showing correlation between serum soluble ST2 and cardiac Troponin T level in patients under study

		Sst2(ng/ml)	Troponin T(ng/ml)
Sst2(ng/ml)	Pearson Correlation	1	.375 *
	Sig. (2-tailed)		.041
	N	30	30
Troponin T(ng/ml)	Pearson Correlation	.375 *	1
	Sig. (2-tailed)	.041	
	N	30	30

FIGURE -1(SCATTER DIAGRAM) Showing correlation between serum soluble ST2 and cardiac Troponin T level in patients under study.



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