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Original Research Article

Prognostic utility of soluble ST2 biomarker in heart failure patients with reduced ejection fraction

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ABSTRACT

Introduction: sST2 is a member of interleukin 1 receptor family biomarker and the concentration of its soluble isoform increases with cardiac stress leading to cardiac fibrosis. It has 2 isoforms the ligand forms sST2L and soluble form. In acute or chronic heart failure the soluble form is highly prognostic and predictive of mortality.

Materials and Methods: It's a prospective study of patients aged 45 to 90 with reduced ejection fraction and cardiomyopathy. Sample collected for day 1,5,30. There outcome assessed at day 30 and mortality on one year follow up.

Results: Total 79 patients studied, 57 LVF cases and 22 healthy controls. 50 males, 29 females, Cardiomyopathy 24 cases. Mean sST2 value 137.7829±89 (SD). At 30 days outcome and one year mortality with significant P value 0.000. As the age increases sST2 levels rises. For cardiomyopathy patients sST2 (141±78). At day 5 and 30 patients improved with decrease in levels where worsened patients had persistent high values. Those patient with more than 250 or implausible values had worse outcome or expired. Most important those responded to appropriate treatment values significantly improved. For cardiomyopathy patients values remained high persistently and ultimately required cardiac transplant or definitive line of treatment.

Conclusions: sST2 is diagnostic and prognostic marker in patients with HFrEF presenting as acute or chronic heart failure. Significant p values for 30 days outcome and mortality. In cardiomyopathy patients with persistent high levels were bad prognostic indicator and suggests consideration of definitive line of treatment.

1. Introduction

Heart failure represents an increasing problem worldwide and has an advancing trend predominantly in elderly patients. At the age of 50 years the prevalence is 1% whereas at the age of 80 or above 1 out of 10 people suffers heart failure.[1,2] Heart failure is complex clinical syndrome caused by structural or functional defect in myocardium resulting in impairment of filling or ejection of blood. It is clinically silent process with progressive cardiac remodeling that eventually leads to the symptomatic presentation late in the course disease progression. The most common cause of heart failure is reduced left ventricular myocardial function. However, dysfunction of pericardium, myocardium, endocardium, heart valves or great vessels alone or in combination is also associated with heart failure. Some of pathogenic mechanism leading to heart

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failure are increased hemodynamic overload, ischemia related dysfunction, ventricular remodeling, abnormal myocyte calcium recycling accelerated apoptosis and genetic mutation.[3]

1.1. Biomarker of heart failure

A biomarker is of a characteristic that can objectively be measured and evaluated as an indicator of normal biological, pathological process, pharmacological response to therapeutic intervention. Biomarker should be cost effective after medical management and outcomes are integrated unto everyday clinical practice. Importance of biomarker is that it should be accurate, reproducible. It should provide information that is not available from clinical assessment or else value of biomarker should correlate with the clinical assessment report. Its value should aid to the clinician in medical decision making. It should have high sensitivity and specificity.

The biomarker for heart failure is BNP, NT pro BNP and sST2 (Soluble suppressive of tumorgenicity 2) level. sST2 was originally identified as marker of IL1 receptor family in 1989. The sST2 gene is located on human chromosome 2 and is a part of human IL-1 gene locus. The sST2 gene encodes two isoforms of sST2 protein, soluble circulating form referred to as sST2, and a membrane bound receptor form referred to as ST2 receptor or ST2L) sST2 is considered a novel biomarker for cardiac strain. sST2L is composed of 3 immunoglobulins viz IgG extracellular domain, a transmembrane segment and an intracellular domain that mediates intracellular signaling.[4,5]

A cardiovascular role for sST2 was first reported by Weinberg et al in 2002 that sST2 could be expressed by cardiac cell in response to myocardial stress. When the myocardium is stretched the sST2 gene is up regulated increasing the concentration of circulating soluble sST2.[3–5] The ligand for sST2 is cytokine Interleukin -33 (IL-33).IL-33 is induced by mechanical strain predominantly in the cardiac fibroblast. Protein interleukin -33 is a functional ligand for sST2. Binding of interleukin 33 to sST2 receptor in response to cardiac strain or injury elicits the cardio protective effect which results in preserved cardiac function. This cardio protective IL-33 signal is counterbalanced by level of sST2 which binds IL-33 and makes it unavailable to the sST2 receptor for cardio protective signaling. The sST2 protein destroys the anti-hypertrophic effect of IL33 since it operates as a soluble decoy receptor by binding IL 33 and in the way, blocks preventing sST2L signaling. Blocking the sST2L receptor by anti sST2 monoclonal antibodies has resulted in blockage of anti-hypertrophic effect of IL33. Increased concentration of sST2 in blood has been found in condition associated with cardiac fibrosis and re-modelling. It emerged as a strong predictor of cardiovascular outcome both acute and chronic heart failure.

1.2. Rationale

Heart failure accounts for > 1,100,000 admissions and 60,000 death per year worldwide at the cost of more than 39 billion/year. Despite advances in therapy outcome after hospitalization remains poor. Although the mortality rate has decreased slightly over last 20 years, the 30 days re-admission rate has gone up. Now a days approximately 1 out of 4 patients hospitalized for heart failure is re-admitted within 30 days.[6] Apart from increased cost heart failure re-admission is also associated with worse prognosis with risk of death increasing after each re-admission. Patient's with more than 4 re-admission for acute HF has more than 40% mortality risk at 6 months.[7] The American Heart Association and American College of Cardiology guideline for management of HF provide a class IIB guideline for measurement of sST2 in patients with acute or ambulatory HF. The guidelines notes that not only sST2 is predictor of hospitalization and death in patient with HF but information acquired from sST2 measures provide additive prognostic value.[8] Higher the sST2 level more aggressive line of treatment can be suggested. Hence in the present study we have studied relationship between serum sST2 levels along with prognosis and risk of mortality in heart failure patients.

2. Aims and Objective

The aim and objective of the present study is to study prognostic value of serial Sr. sST2 levels in patients with cardiomyopathy and reduced EF (HFrEF) and their 1 months and one year follow up. Estimating the sST2 concentration predicts response to treatment, improved, worsened and mortality.

3. Materials and Methods

Study population + design: This study consisted of total 79 patients. 57 diagnosed with HFrEF (among 24 cardiomyopathy patients) and 22 control patients', between group of 45 to 90 years were enrolled. The study was approved by ethics committee and informed consent was taken from patients prior to enrolment. The diagnoses of HFrEF was established on the basis of current guidelines and defined as the rapid or gradual onset of signs and symptoms of heart failure resulting in unplanned hospitalization. 10 ml of whole blood was collected from patient, in 2 plain tubes (5 ml each) for the separation of Serum samples. sST2 was performed using Serum sample on the Aspect plus reader from Skymed Diagnostics (USA) and other parameters like creatinine were performed on the VITROS 4600 clinical chemistry analysis from Ortho clinical diagnostics (USA).

3.1. The test principle

The Aspect Plus sST2 test is a quantitative sandwich monoclonal lateral flow immunoassay. The serum sample is loaded into the sample well where it flows through the anti-sST2 antibody coated strip. Assay buffer is added to the second well. The cassette is then loaded in the aspect reader for incubation and sST2 is quantitatively determined and reported by the reader.

3.2. Inclusion and exclusion criteria

The patient with clinical signs and symptoms of HF with LVEF less than 40% are included in the study. Men or women more than 18 years of age with LVEF < 40 were included. Exclusion criteria were severe renal or liver dysfunction, autoimmune disease, malignant disease and other inflammatory states.

3.3. Clinical data collection

The patient demographics characteristics, significant clinical HF signs and medications history were all obtained at the time of hospitalization. Echocardiography was performed to assess LVEF. Baseline clinical characteristics and hospital events were recorded. All patients received standard HF management as recommend by guidelines. Sample collected for sST2 level on day 1,5, and some patients on day 30. One year follow up was done for outcome and mortality.

4. Results

1. Total 79 patients studied. 57 patients with HFrEF (EF<40) and 22 patients in control group between the age group 45 to 90 years were enrolled in this study. The baseline characteristic of study population was represented in Table 1. Male patients 50 (63%) and female patients were 29 (37%). Mean plus SD Values of sST2 on day 1 is 156.16±88.47, on day 5 is 118.94±85.16, on day 3 is 129.98±108.14. sST2 values reduced significantly on day 5 in patients who responds well to medical or definitive management of patients. Higher persistent levels associated with worse outcome at day 30.(Table 2) Diabetic-31, hypertensive-38, ischemic heart disease-37, cardiomyopathy-24. Total 20 patients undergone CABG (coronary artery bypass Grafting), 2 underwent cardiac transplant as definitive management. 11 undergone CRTD device as symptomatic management. Table 1 Mean sST2 levels in each condition is seen in Table 3.

2. Cardiomyopathy 24 patients followed. Mean and SD sST2 levels a 141.66±94.41. It has very strong relation with sST2 levels. Higher levels were associated with poor outcome and bad prognostic indicator. Persistent higher levels could be marker to opt for definitive line of treatment in such patients. In our study 2 patients ultimately required cardiac transplant and 11 undergone CRTD device. Higher level prompts more aggressive line of treatment in cardiomyopathy patients with HFrEF. (Table 1, Figure 1)

Table 1: Baseline characteristics of patients age, gender, comorbidities, undergone treatment

Characteristic	Patients (n)
Age	45-90 years
Sex	Male - 50 Females - 29
Diabetes	31
Hypertenson	38
Ischaemic heart Disease	37
Cardiomyopathy	24
Improved	35
Worsened	22
Alive	45
Dead	12
Cardiac Transplant required	2
CRTD Device	11
CABG	20

Table 2: sST2 levels measured on day 1,5, 30.

	Day 1 (n=57)	Day 5 (n=50)	Day 30 (n=9)
SST2			
Mean	156.1688	118.9463	129.9811
SD	88.47371	85.16489	108.1453
Median	169.8	91.375	92

Table 3: sSt2 levels mean and SD (standard Deviation) associated with comorbidities, creatinine, improved and worsened condition

Characteristics association with	sST2 levels (Mean ±SD)
Diabetes mellitus	128.43±89.11
Hypertension	137.54±89.58
Ischemic Heart Disease	134.85±87.72
Cardiomyopathy	141.66±94.41
Creatinine levels >1.5	139.59±89.24
Improved	106.48±78
Worsened	190.91±82.70

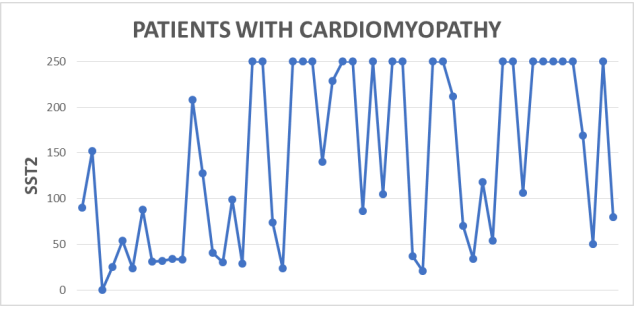

Fig. 1: sSt2 levels association with Cardiomyopathy patients

3. Outcome at day 30 days. sSt2 levels has significant p value 0.000 (less than 0.05). It has very strong relation

with day 30 days outcome. It is strongly correlating those higher values associated with worsened conditions but also prompts aggressive line of management to clinicians and seeks definitive line of treatment for long term patient management. Lower values associated with improved clinical outcome. (Figure 2)

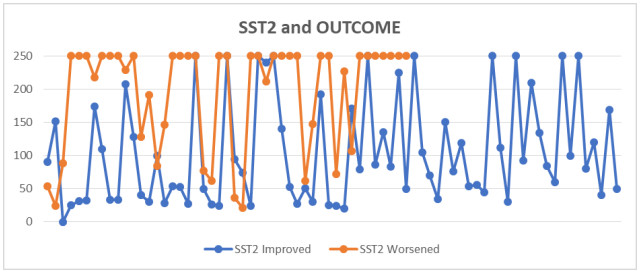

Fig. 2: sSt2 levels showing improved and worsened outcome

4. Patients readmitted: Higher sST2 levels, comorbidities, poor response to medical or surgical management associated with frequent readmissions. (Figure 3)

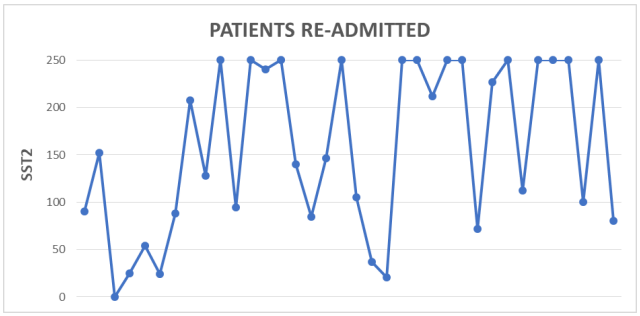

Fig. 3: sSt2 levels showing association with readmission

5. Mortality: out of 57 patients 12 expired (21%). sST2 values > 250 or implausible levels associated with higher mortality and deaths.(Figure 4)

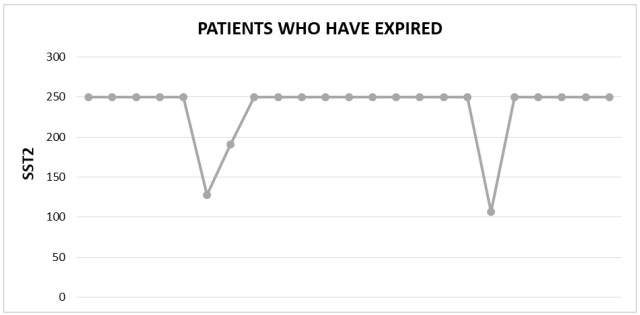

Fig. 4: sSt2 levels showing association in patients whohave expired

6. One year follow up and statistics of mortality suggest significant p value 0.000 (less than 0.05). Hence sST2 levels accurately predicts clinical improved or worsened state as well as 30 days outcome and one year mortality. It also prompts clinician for aggressive and definitive management of patients in case values remains persistent high. In cardiomyopathy patients with HFrEF prompts further escalation for CRTD device, cardiac transplant listing, Left ventricular assist device (LVAD), etc.

5. Observations

1. 22 normal patients who visited the health checkup Department and had normal HR, BP and normal body profile were taken for the study as controls These patients had normal sST2 levels (referred range of sST2 of < 34 ng/ml).
2. 57 patients with decreased EF on 2D echo (HFrEF) were analyzed and had sST2 highly increased than the reference range.
3. Patient's whose sST2 levels decreased on day 5 or day 30 after aggressive treatment were clinical improved and with higher values worsened.
4. However, those patients whose sST2 levels remained high (> 250 ng/ml) or implausible were either not discharged and considered for further management or were re-admitted again with worsening of symptoms has higher mortality and death rates.
5. In cardiomyopathy patients' persistent higher values suggest poor prognostic indicator and prompts clinician for more aggressive and definitive line of treatment like cardiac transplant, Left ventricular assist device or arrythmia management or CRTD device.
6. It has significant P value for 30 days outcome and 1 year mortality. It's a prognostic indicator for patients with reduced left ventricular ejection fraction and cardiomyopathy.

6. Discussion

It has been demonstrated that serial monitoring of sST2 provides additional prognostic information as compared with single measurement. Manzano Fernandes et al. carried out serial measurements of sST2 in acutely decompensated heart failure patients during admission and post treatment 4^{th} day. Their results were in agreement with ours where they stated that sST2 values were prognostic at presentation and during hospitalization.[9]

Our findings were in agreement with Breidthardt et al. which also mention findings similar to us where values significantly decreased from admission to 48 hours with median reduction of 42% in survivors as compared to 25% in non survivors.[10]

Our study supports the study carried out by Socrates et al.[11] where they stated that sST2 levels were higher in dying patients than the survivors., and also in patients with HFrEF when compared with sST2 levels in HFpEF. Hence proving ST2 a strong and independent predictor of 30 day and 1-year

mortality may improve risk stratification already provided by BNP and NT proBNP.

The research data of present author is very much in agreement with the PRIDE study[12] which states that the sST2 levels were high in patients with dyspnea due to heart failure than those with dyspnea due to non-cardiac origin. The PRIDE study also supported the data of the present author stating that patients with highly raised levels of sST2 and NT pro BNP had worst prognosis with high risk of death.

Rehman S.U et al[13] in their research data stated that sST2 levels were highly raised in patients with cardiac fibrosis and hypertrophy. According to them the elevated values of sST2 strongly correlated with the severity of heart failure and decreased left ventricular ejection fraction. Similar to their views about raised sST2 on admission and decreased ejection fraction the present authors views very well correlate.

Ky et al[14] data correlated well with the data of present author who followed their patients with heart failure for three years exhibiting the risk of death for these patients with elevated levels of sST2.

Weinberg et al[15] demonstrated an increase of sST2 levels in two weeks after initial measurement and this rise was associated with risk of death and this data was parallel to the findings of the present author.

Alberto Aimo et al[16] (have opined that SST2 is produced as a result of myocardial stress and have attributed the raised levels as aid in risk stratification. According to them raised levels predict risk of sudden cardiac death in heart failure and have added prognostic significance to Natriuretic peptides. They opine that in arrythmogenic ventricular cardiomyopathy the function of both ventricles is decreased with increased plasma SST2 due to extensive replacement of fibrofatty tissue. Such patients are admitted for prolonged hospital stay and uptitrated heart failure drugs. Such patients are also considered for defibrillator implantation. In the present research work the present authors have also studied that patients with raised SST2 were considered further for cardiac transplant or Cardiac resynchronisation therapy pacemaker implant.

J J Dalal and associates[17] in their studies have evaluated ST2 at ao admission and exhibited sustained raised levels at 2 years with increased mortality in such patients. Thus clinicians should be alerted with raised ST2 levels in patients on admission to intensify aggressive treatment. Upon following the patients for 1 year these patients had to undergo cardiac transplant. The findings of Dalal et al correlate well with those of the present author. Dalal et al also opine that SST2 values less than 35 at admission had no risk death. Patients who had severe hypertension and continuously raised SST predicted death risk.

Study presented by the current authors was in agreement with Villa corta and A Miesel[18] who state that SST2 predicts mortality in patients with heart failure. Higher values correlated with increased mortality rates, and is a superior marker in comparison to NT BNP and hs trop I. They were of the opinion that serial measurement is important for guiding therapy and studying course of the disease in acute decompensate heart failure. Patients with raised levels of SST2 had higher mortality rates at 6 months and hence patients with raised levels can be earnestly considered for implantable cardioverter de fibrillators. Thus studies of Villa Corta and Dr A Miesel are in agreement with the present authors.

Ravi Parikh et al[19] have mentioned SST2 as marker of myocyte stretch and fibrosis and the levels were likewise increased in both subtypes viz preserved and reduced ejection fractions. According to them, raised levels were associated with old age, cardiovascular death with cardiac pathology.

Skvortsov et al[20] categorised patients at risk and very high risk on the basis of threshold value of SST2. By evaluating patients for SST2 level for long period of time they can predict the risk of death in them. Present authors too are of the same opinion that patients who had implausible values of SST2 died and they are also of the opinion that effectiveness of SST2 value should be considered for implementing treatment.

Domingo A, Pascual Figal et al[21] have opined that SST2, NT pro BNP and hs Trop I are predictors of high risk of death. All candidates who have SST2 values below the cutoff were free of death while 53% who had raised values died. They defined SST2 as marker of remodelling, hs Trop I as marker of necrosis and BNP as marker of myocardial stress and stretch.

Rahul Kakkar and Richard Lee[22] have complimented the work of Pascaul Figal[21] saying that these authors have laid foundation for trials on multimarker approach for risk stratification and guiding targeted therapy in acute decompensated heart failure. The vision of present authors is in agreement with that of Kakkar et al.

M Emdin et al[23] exhibited their research findings in collaboration with our studies where they concluded that elevated SST2 had strong correlation with cardiovascular mortality and hospitalization following heart failure. According to them SST2 evaluation should be considered in the multimarker panel along with NT pro BNP and hs Trop T.

MJ Coronado et al[24] have reported raised levels of SST2 in patients with myocarditis due to cardiac inflammation especially in men and have stated that it predicts mortality. These patients were heart failure patients with biopsy confirmed myocarditis. These patients had worse outcome and needed cardiac transplantation. Findings are similar to the findings of present author.

A Grupper et al[25] have reported rise of SST2 post cardiac transplant and have attributed the rise due to antibody

mediated transplant rejection. Present authors have not studied the post cardiac transplant SST2 levels.

7. Conclusion

sST2 is diagnostic and prognostic marker in patients with HFrEF presenting as acute or chronic heart failure. Significant p values for 30 days outcome and mortality. In cardiomyopathy patients with persistent high levels were bad prognostic indicator and suggests consideration of definitive line of treatment.

8. Abbreviations

HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fractions; sST2: Soluble suppressive of tumorgenicity 2; HF, Heart failure; IL- Interleukin; BNP: Brain Natriuretic Peptide; NT proBNP: NT pro Brain Natriuretic Peptide

9. Conflict of Interest

The authors declare no conflict of interest.

10. Source of Funding

No financial support to declare.

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