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Original Research Article

Role of sST2 in prognostication and risk stratification in patients with heart failure

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ABSTRACT

Background: sST2, an interleukin (IL)-1 receptor family member, has been identified as a novel biomarker for cardiac strain. Concentrations of sST2 have prognostic value and found to be predictive of the rate of mortality in the follow-up of patients after an acute heart failure episode. The present study aims to study relationship between serum sST2 levels along with prognosis and risk of mortality in heart failure patients.
Methods: The Study was conducted in A.J. Institute of Medical Sciences, Mangalore, Karnataka, India with 56 heart failure patients in the duration of 1 year. sST2 level of each patient was taken on the day of admission then after one month, six months and one year.
Results: Concentration of sST2 was consistently higher in 55.3% patients. Patients with lower values of ST2 levels were having less number of hospital admissions for heart failure symptoms (44.6%). The patients who were having high ST2 levels died due to cardiac events by the end of one month, six months and one year were 7.1%, 11.5% and 13% respectively ($p<0.001$) which was highly significant. Overall mortality with the patients who were having higher ST2 levels was 28.5% ($p<0.001$ HS).
Conclusions: Elevated sST2 levels are predictive of cardiac events in patients with heart failure and provide complementary information about prognostication and risk stratification of patient. Serial monitoring of sST2 will aid in clinical decision making.

Keywords: CRT-D- Cardiac resynchronization therapy defibrillator, CRT-P- Cardiac resynchronization therapy pacemaker, HF- Heart failure, ICD- Implantable cardioverter defibrillator

INTRODUCTION

Acute heart failure accounts for more than 1,100,000 admissions and 60,000 deaths per year worldwide at a cost of >$39 billion per year.[1] Hospitalization-related charges account for more than half of this cost. Despite advances in therapy, outcomes after hospitalization remain poor. Although the mortality rate has decreased slightly over the last 20 years, the 30-day readmission rate has steadily risen. Nowadays, approximately 1 in 4 patients hospitalized for heart failure (HF) is readmitted within 30 days.[2]

Aside from increased cost, HF readmission is also associated with worse prognosis with the risk of death increasing after each readmission. Patients with ≥4 admissions for AHF have >40% mortality risk at 6 months and a median survival of 0.6 months after the readmission.[3] A substantial proportion of these admissions may be avoidable.[4] This concept is supported by the wide variation in 30-day readmission rates

between comparable hospitals. Given the high costs of short-term readmission in terms of morbidity and dollars, reducing preventable readmissions within 30 days is now a metric for quality of care.[5]; this effort has become a major focus of hospitals and health care systems. Because strategies that have included home tele-monitoring and earlier clinic visits have made only small inroads in the problem, newer, creative strategies should be considered.

ST2 is a member of the interleukin-1 receptor (IL-1) family, existing in both a transmembrane ligand (ST2L) and a soluble, circulating form (sST2).[6] ST2 expression seems to be driven by cardiomyocyte stretch in a dose-dependent fashion,[7] suggesting its applicability as a marker of hemodynamic derangement in acute and chronic HF states.

The American heart association and American college of cardiology guidelines for the management of HF provide a class IIb recommendation for the measurement of ST2 in patients with acute or ambulatory HF.

The guidelines note that not only is ST2 predictive of hospitalization and death in patients with HF, but information gleaned from ST2 measures provides additive prognostic value.[8]

Hence, in the present study we have studied relationship between serum sST2 levels along with prognosis and risk of mortality in heart failure patients.

METHODS

Study was performed in A.J. Institute of Medical Sciences, Mangalore, Karnataka, India with 56 heart failure patients in the duration of 1yr (November 2014 to November 2015). sST2 level of each patient was taken on the day of admission (admission due to Heart Failure symptoms) then after one month (First follow up), six months and one year.

Diagnosis of Heart failure was done on the basis of framingham criteria of heart failure. NYHA classification and presentation of patient with acute pulmonary edema due to cardiac cause were also taken in the consideration.

Serum ST2 levels were measured quantitively by ST2 assay kit by enzyme linked immunosorbent assay (ELISA). Normal limit of ST2 <35ng/ml.

Sudden cardiac death (Out of hospital) was verified by either primary physicians or relatives who had witnessed death.

Sudden cardiac death was defined as[9]: 1) Witnessed death occurring within 60 min from the onset of new symptoms, unless a cause other than cardiac was obvious. 2) An unwitnessed death (<24hrs) in the absence of pre-existing progressive circulatory failure or other causes of death. 3) Death due to attempted resuscitation.

Inclusion criteria

Patients > 18 years of age, patients presenting with heart failure (chronic and acute), left ventricular ejection fraction ≤ 45%, patients who were willing for regular follow up, patients who have given consent for regular contact over phone, Patients willing to give informed consent for the study.

Exclusion criteria

Patients < 18 years of age, patients with known - congenital heart disease, pericardial pathology, rheumatic heart disease, aortic Stenosis (moderate and severe), mitral Stenosis (moderate and severe), acute mitral regurgitation due to any cause, cor pulmonale, chronic kidney disease, bronchial asthma, pulmonary embolism, chronic obstructive pulmonary disease, left ventricular ejection fraction >45% by ECHO, patients not willing to give consent.

Patients were followed up via regular OPD follow-ups and telephonic communication at regular intervals. Patients treated with beta-blockers, ACE Inhibitors or ARBs, calcium channel blockers, diuretics, digoxin, ivabradine, aspirin, clopidogrel, atorvastatin and warfarin whenever necessary. Necessary investigations which includes ECG, echo, chest X-ray, holter monitoring along with routine blood investigations were done whenever indicated. Collected data was analysed by frequency, percentage, mean, standard deviation and Mann-Whitney test.

RESULTS

At the baseline, higher sST2 levels observed in thirty-one (55.3%) patients, at one month higher sST2 levels were observed in twenty-seven (51.9%) patients, at six months twenty-one (45.6%) patients had higher sST2 levels, while at the end of one year six (15%) were having higher sST2 levels.

Over the period of one year, total thirty-three (58.9%) patients had ninety-six hospital readmissions for heart failure symptoms, within first one month 8%, within six months 54% and by the end of one year 38% hospital readmissions were observed.

By the end of one month, four (7.1%) out of fifty-six patients died due to cardiac events ($p<0.001$ HS), all four patients were having high ST2 levels (202 ± 20.3). Out of four patients, three were readmitted twice within the duration of one month. Those who survived at the end of one month were having relatively lower sST2 levels (50.3±11.4), ($p<0.001$ HS). By the end of six months, six (11.5%) out of fifty-two HF patients died due to cardiac events ($p<0.001$ HS), all six patients were having high ST2 levels (150.7±22.4) and those who survived by the end of six months were having lower levels of sST2 (35.9±15.2), ($p<0.001$ HS).

Table 1: Basic characteristics of study population (mean ± standard deviation) and frequency.

Basic characteristics of the study population (n=56)	
Variables	**Value**
Age	66±11
Sex (male)	83%
Diabetes mellitus	22 (39.2 %)
Hypertension	38 (67.8%)
Tobacco use	26 (46.4%)
Alcohol use	22 (39.2%)
Atrial fibrillation	6 (10.7%)
History of prior coronary artery disease	30 (53.5%)
Acute coronary syndrome	32 (57.1 %)
Left ventricular ejection fraction	34±10
NYHA classification- class I	8 (14.2%)
NYHA classification- class II	24 (42.8%)
NYHA classification- class III	18 (32.3%)
NYHA classification- class IV	6 (10.7%)
Non-compliant to medications	4 (7.1%)
Use of beta blockers	48 (85.7%)
Use of ACE inhibitor /ARB	52 (92.8%)
Use of ivabradine	16 (28.5%)
Use of digoxin	20(35.7%)
Use of diuretics	56 (100%)
Use of aspirin	36 (64.2%)
Use of clopidogrel	33 (58.9%)
Use of statins	36 (64.2%)
Use of warfarin	10 (17.8%)
Overall mortality	16 (28.5%)

By the end of one year, six (13%) out of forty-six HF patients died due to Cardiac events (p<0.001 HS), all six patients were having high ST2 levels (125.5±17.2) and those who survived were having lower sST2 levels (34.2±16.7), (p<0.001 HS).

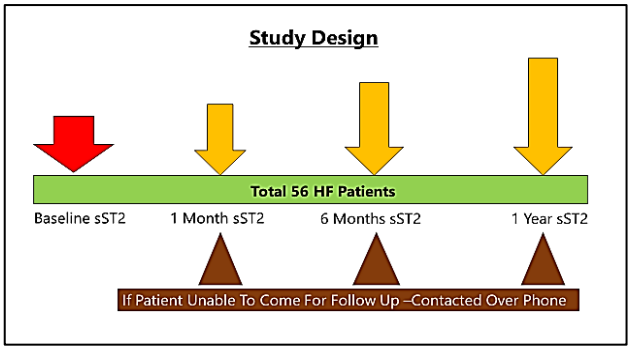

Figure 1: Study design.

By the end of one year overall mortality was sixteen (28.5%) out of fifty-six HF patients. sST2 levels were high in thirty-one (55.3%) HF patients, those who died were having high sST2 levels 28.5% (p<0.001 HS).

Total forty (71.4%) patients survived by the end of one year, in which twenty-five (62.5%) patients had normal sST2 levels and fifteen (37.5%) patients were having high sST2 levels, all the patients with high sST2 levels managed with aggressive diuretics and optimal medical therapy. Nine (60%) out of fifteen patients responded to optimal medical therapy and there subsequent sST2 levels were lower than the baseline levels, six (40%) patients out of fifteen were having repeated hospital admissions even after aggressive medical management and advised for cardiac resynchronization therapy defibrillator (CRT-D) and implantable cardioverter defibrillator (ICD) as per the criteria, five patients were fulfilling criteria for CRT-D out of which two underwent CRT-D insertion and three choose to have medical management. ICD was inserted in one patient who was having documented ventricular tachycardia episode both in ECG and holter monitoring.

Table 2: Relationship between sST2 levels and those who survived/died at one month, six months and at the end of one year.

Duration	Survived/died	Number of patients	sST2 levels, mean ± SD	Mann-Whitney's test
1 Month	Survived	52	50.3±11.4	P=0.000<0.001 HS
	Died	4	202±20.3	P=0.000<0.001 HS
6 Months	Survived	46	35.9±15.2	P=0.000<0.001 HS
	Died	6	150.7±22.4	P=0.000<0.001 HS
1 Year	Survived	40	34.2±16.7	P=0.000<0.001 HS
	Died	6	125.5±17.2	P=0.000<0.001 HS

DISCUSSION

This study shows that sST2 is a marker of increased risk in patients with destabilized HF in the ambulatory setting. sST2 levels correlates with clinical symptoms, and adds prognostic significance with the present data in treatment of HF patients. In consequence, sST2 monitoring emerges as a novel tool for prognostic guidance in HF.

In this study, we found that a decrease in sST2 concentration was associated with more benign outcome at one-year follow-up, while the absence of a reduction

and higher levels of sST2 was associated with a higher risk of cardiovascular events.

There is a need for novel biomarkers whose change during therapy is predictive of outcome. The present study data suggest that the subset of patients who received therapy sufficient to allow their clinical condition to be considered stable but whose sST2 concentrations did not change significantly might be candidates for more aggressive diagnostic and therapeutic manoeuvres.

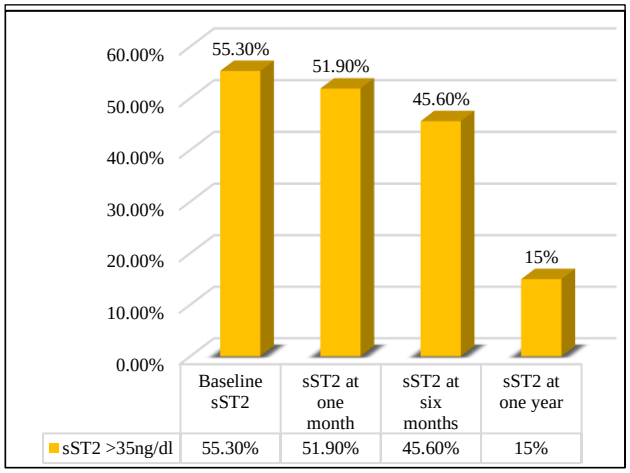

Figure 2: sST2 levels in HF patients at baseline, after one month, after six months and after one year.

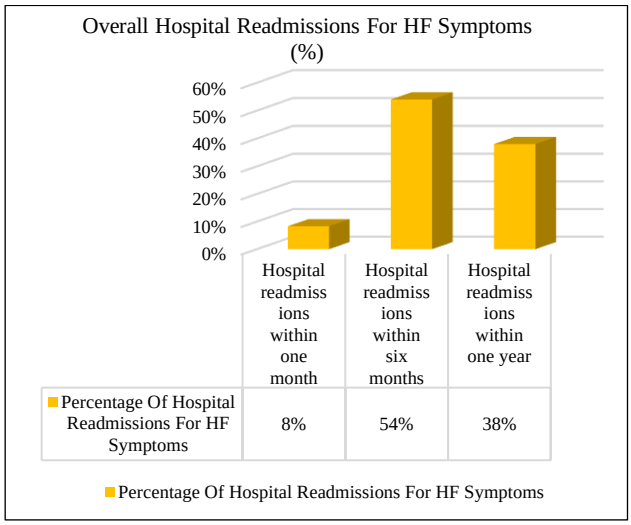

Figure 3: Percentage of hospital readmissions in HF patients within one month, six months and one year.

The above obtained values of sST2 protein aids in prognostication and risk stratification of HF patients, sST2 is an independent variable for the poor prognosis in short term observation after hospitalisation among patients with HF and LVEF ≤ 45%. This study is one of the research in association with the sST2 protein in the Indian population suffering from HF.

Weinberg et al, in their study evaluated 181 patients with CHF (mean age 62 years, mean LVEF 22% and 73% male) and documented that the increase of sST2 concentration of 0.1 ng/mL in two weeks after first measurement was associated with the risk of death or heart transplantation in 47 patients (25.9%, p = 0.048).[10]

Bayes-Genis et al, in their study of 891 CHF patients (mean age 70.2 years, mean LVEF 34% and 71.6% male) found that sST2 protein (OR = 1.04; 95% CI 1.029-1.051; p = 0.001) and NT-proBNP (OR = 1.632; 95% Cl 1.484-1.795; p = 0.001) were independent risk factors for mortality of 244 (27%) patients in a prospective observation (median 33.4 months).[11]

The largest published study on the prognostic value of sST2 protein in CHF was carried out by Ky et al, in a population of 1,141 patients (mean LVEF 32±17%; mean age 56±14 years and 67% male). Patients in this study were followed for nearly three years.[12] Researchers discovered that patients with elevated levels of sST2 in the highest tertile (sST2 > 36.3 ng/mL) had a significantly higher risk of death or heart transplantation, mortality noted was 23% (OR = 3.2; 95% CI 2.2-4.7; p < 0.0001) compared to patients in the lowest tertile (sST2 < 22.3 ng/mL).

In the present study, we found higher concentrations of sST2 protein (sST2 >35 ng/mL) in 55.3% HF patients and by the end of one year mortality in these patients were 28.5% (p<0.001 HS). our findings correlate with Weinberg et al and Bayes-Genis et al.[10-11] However, our findings do not correlate with Ky et al, because of smaller sample size.

Boisot et al demonstrated in their study of serial sampling of sST2 that by the end of 90 days out of 150 patients' 126 were alive while 24 died who were having higher sST2 levels yielding mortality rate of 16%.[13] In current study we found that 30 days and 6 months mortality was 7.1% and 11.5% respectively in the patients with high sST2 levels.

Limitations of the study was observational study, smaller sample size, no control group was created, narrow inclusion criteria used during the study were the limitations of the present study.

CONCLUSION

Elevated sST2 levels are predictive of cardiac events in patients with HF and provide additional information about prognostication and risk stratification. It can give an idea about the need for optimization of medications including use of ivabradine or sacubitril (neprilysine inhibitor) and use of devices (CRT-P or CRT-D or ICD) in heart failure patients. This approach may have an impact on clinical decision-making in individual patient care.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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