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A STUDY OF CORRELATION OF SOLUBLE ST2 LEVELS WITH PROGNOSIS OF HEART FAILURE

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A B S T R A C T

Background*:** Heart failure poses a significant global health burden, necessitating reliable prognostic markers. This study evaluated the utility of soluble ST2 in predicting adverse outcomes in heart failure patients.Methods*:** A prospective observational study was conducted on 86 heart failure patients. Soluble ST2 levels were measured at admission, and patients were followed for adverse outcomes. Demographic characteristics, clinical parameters, and comorbidities were analyzed.***Results*:** The study population comprised predominantly females (58.1%) with a mean age >60 years (54.7%). Breathlessness was the primary presenting symptom (96.5%), with 43.0% patients in NYHA Class IV. Patients with adverse outcomes demonstrated significantly higher ST2 levels (56.1 ± 22.5 ng/mL vs 26.7 ± 12.2 ng/mL, $p<0.001$). ROC analysis yielded an AUC of 0.86 (95% CI: 0.78-0.95). Using a 36 ng/mL cutoff, ST2 showed 82.4% sensitivity and 76.9% specificity for predicting adverse outcomes, with an 87% negative predictive value.***Conclusion*:** Soluble ST2 demonstrated significant prognostic value in heart failure, particularly in identifying low-risk patients. The biomarker's high diagnostic accuracy supports its integration into routine clinical assessment for improved risk stratification.

Keywords: Heart failure; Soluble ST2; Biomarker; Prognosis; Risk stratification; Adverse outcomes; NYHA class; ROC analysis.

INTRODUCTION

Heart failure (HF) remains a significant global health burden, affecting approximately 64.3 million people worldwide and accounting for substantial morbidity, mortality, and healthcare expenditure [1]. The complexity of heart failure management necessitates reliable biomarkers for accurate diagnosis, risk stratification, and prognostication. While N-terminal pro-B-type natriuretic peptide (NT-proBNP) has long been established as the gold standard biomarker in heart failure, emerging evidence suggests that soluble ST2 (sST2) may offer complementary or potentially superior prognostic value [2].

Soluble ST2, a member of the interleukin-1 receptor family, exists in two primary forms: a transmembrane receptor (ST2L) and a soluble form (sST2). The ST2/IL-33 pathway plays a crucial role in cardiovascular homeostasis, with IL-33 exhibiting cardioprotective properties through the ST2L receptor. However, sST2 acts as a decoy receptor, neutralizing IL-33 and potentially contributing to adverse cardiac remodeling and fibrosis [3]. This mechanistic pathway has generated considerable interest in sST2 as a biomarker for heart failure, particularly given its relative stability and independence from factors that typically confound NT-proBNP measurements, such as age, body mass index, and renal function [4].

Recent studies have demonstrated that elevated sST2 levels correlate significantly with adverse outcomes in heart failure patients. In a landmark study by Pascual-Figal*et al.*, sST2 showed strong predictive value for both all-cause mortality and heart failure hospitalization, independent of traditional risk factors and established biomarkers [5]. Furthermore, serial measurements of sST2 have demonstrated superior prognostic value compared to single measurements, suggesting its potential utility in monitoring disease progression and therapeutic response [6].

While NT-proBNP remains valuable in diagnosis and monitoring of heart failure, it has several limitations. NT-proBNP levels can be influenced by various factors including age, obesity, renal function, and atrial fibrillation, potentially complicating result interpretation [7]. In contrast, sST2 has shown remarkable stability across these confounding factors, potentially offering more reliable prognostic information in diverse patient populations [8].

The integration of multiple biomarkers in heart failure assessment has gained increasing attention, with several studies suggesting that the combination of sST2 and NT-proBNPmay provide superior risk stratification compared to either biomarker alone [9]. This multi-marker approach might better reflect the complex pathophysiology of heart failure, encompassing both mechanical stress (reflected by NT-proBNP) and tissue fibrosis/remodeling (indicated by sST2) [10].

Aims and Objectives

The present study primarily aimed to evaluate soluble ST2 as a diagnostic and prognostic marker in heart failure patients. The investigation further sought to analyze the demographic and clinical profile of heart failure patients, while assessing the correlation between soluble ST2 levels (≥36 ng/mL) and adverse outcomes. Additionally, the study aimed to determine the diagnostic accuracy of soluble ST2 through sensitivity, specificity, and ROC analysis, as well as to investigate the relationship between soluble ST2 levels and NYHA functional classification. Through these objectives, the study intended to establish the clinical utility of soluble ST2 in heart failure management and risk stratification.

Materials and Methods

Study Design and Setting

This was a single-center, prospective observational follow-up study conducted at Karnataka Institute of Medical Sciences, Hubli. The study commenced after obtaining approval from the Institution's Ethical Committee and was conducted over a period of two years.

Study Population and Sample Size

The study included 86 patients who presented with heart failure. The sample size was calculated based on a population prevalence of 7.2%, with 10% absolute precision and a 95% confidence interval using the formula: Sample size = $1.96\sqrt{pq}/l$, where p represented prevalence, q was (1-p), and l denoted allowable error.

Selection Criteria

Patients above 18 years of age who were admitted to KIMS hospital with heart failure and provided informed consent were included in the study. The exclusion criteria encompassed patients with chronic kidney disease, those with any serious illness other than heart failure at the time of presentation, and cases of myocarditis and ongoing inflammation.

Clinical Assessment and Data Collection

A comprehensive clinical assessment was conducted for all participants at enrollment and at discharge. The functional capacity was evaluated using the New York Heart Association (NYHA) classification system. Laboratory parameters collected included complete blood count, renal function tests, serum electrolytes, random blood sugar, glycatedhemoglobin (HbA1c), serum creatinine, potassium, sodium, and estimated glomerular filtration rate (eGFR).

Diagnostic Evaluations

All patients underwent electrocardiogram and chest X-ray examinations. Baseline echocardiography was performed to evaluate left ventricular function, including the measurement of left ventricular ejection fraction (LVEF). NT-proBNP and soluble ST2 levels were measured for all participants.

Treatment and Follow-up

All patients received guideline-directed medical treatment, which was titrated to achieve maximum tolerable dosages. The study subjects were assessed for demographic characteristics and risk factors including age, sex, history of diabetes, hypertension, and family history of ischemic heart disease in first-degree relatives.

Outcome Measures

The primary outcome was defined as either cardiac transplantation or mortality due to cardiac causes during a 2-month follow-up period. Following the initial follow-up, telephonic contact was maintained to document the occurrence of these events.

Data Collection

The collected data included demographic information, clinical parameters, laboratory findings, imaging results, and outcome measures. The assessment of risk factors encompassed both modifiable and non-modifiable factors that could influence the progression and prognosis of heart failure.

RESULTS

The study analyzed data from 86 patients with heart failure. The age distribution revealed that the majority of patients (54.7%) were above 60 years of age, followed by 26.7% in the 45-59 years age group. Patients aged 30-44 years constituted 12.8% of the study population, while only 5.8% were below 30 years. The gender distribution showed a slight female predominance, with 50 females (58.1%) compared to 36 males (41.9%).

Analysis of presenting symptoms demonstrated that breathlessness was the most common manifestation, present in 83 patients (96.5%). Cough was observed in 23 patients (26.7%), while chest pain was reported by 7 patients (8.1%). Less common symptoms included palpitations and syncope, each occurring in only one patient (1.1%).

The severity of heart failure, assessed using the New York Heart Association (NYHA) functional classification, showed that the majority of patients (37, 43.0%) presented with Class IV symptoms, indicating severe disease. Class II symptoms were observed in 25 patients (29.1%), followed by Class III in 21 patients (24.4%). Only 3 patients (3.5%) presented with Class I symptoms.

Regarding comorbidities, coronary artery disease (CAD) was the most prevalent, affecting 70 patients (81.4%). Hypertension was present in 35 patients (40.7%), while diabetes mellitus was documented in 30 patients (34.9%).

The analysis of soluble ST2 levels in relation to adverse outcomes revealed significant findings. Patients who experienced adverse outcomes (n=34) had a mean ST2 level of 56.1 ± 22.5 ng/mL, significantly higher than those without adverse outcomes (n=52) who had a mean ST2 level of 26.7 ± 12.2 ng/mL ($p<0.001$). The diagnostic accuracy of ST2 was evaluated using ROC curve analysis, which demonstrated an area under the curve (AUC) of 0.86 (95% CI: 0.78-0.95, $p<0.001$), indicating excellent discriminatory ability.

Using a cutoff value of ≥36 ng/mL for ST2, the diagnostic accuracy analysis showed that among the 40 patients with elevated ST2 levels, 28 experienced adverse outcomes. Conversely, among 46 patients with ST2 levels <36 ng/mL, 40 did not experience adverse outcomes. This translated to a sensitivity of 82.4% (28/34) and a specificity of 76.9% (40/52) for predicting adverse outcomes. The positive predictive value was calculated as 70% (28/40), while the negative predictive value was 87% (40/46).

These results demonstrated that elevated ST2 levels were significantly associated with adverse outcomes in heart failure patients, and the biomarker showed good diagnostic accuracy in predicting these outcomes.

Table 1: Age Distribution among Study Participants

Age Groups (years)	Number	Percentage
<30	5	5.8
30-44	11	12.8
45-59	23	26.7
>60	47	54.7
Total	86	100.0

Table 2: Gender Distribution among Study Participants

Gender	Number	Percentage
Male	36	41.9
Female	50	58.1
Total	86	100.0

Table 3: Symptoms of Heart Failure among Study Participants

Symptoms	Number	Percentage
Breathlessness	83	96.5
Chest Pain	7	8.1
Cough	23	26.7
Palpitations	1	1.1
Syncope	1	1.1

Table 4: NYHA Functional Classification Distribution among Study Participants

NYHA Class	Number	Percentage
Class I	3	3.5
Class II	25	29.1
Class III	21	24.4
Class IV	37	43.0
Total	86	100.0

Table 5: Hypertension, Diabetes, and CAD among Study Participants

Morbidity	Number	Percentage
Hypertension	35	40.7
Diabetes	30	34.9
CAD	70	81.4
Total	86	100.0

Table 6: Soluble sST2 Levels and Adverse Outcomes

Adverse Outcomes	Number	Mean sST2 Level	SD	P-value
Yes	34	56.1	22.5	<0.001
No	52	26.7	12.2	

Independent t-test, p-value is significant.

Table 7: Area Under the Curve (AUC) of sST2 for Prediction of Adverse Outcomes

Parameter	AUC	95% CI	P-value
sST2	0.86	0.78 - 0.95	<0.001

Receiver Operating Characteristics (ROC) curve was used to predict adverse outcomes.

Table 8: Diagnostic Accuracy of sST2 for Predicting Adverse Outcomes

sST2 Level	Adverse Outcomes - Yes	Adverse Outcomes - No	Total
≥36	28	12	40
<36	6	40	46
Total	34	52	86

DISCUSSION

The present study demonstrated the significant role of soluble ST2 in predicting adverse outcomes among heart failure patients. The demographic profile revealed a predominance of elderly patients (54.7% above 60 years), consistent with findings by Daniels *et al*., (2020), who reported 58.3% of heart failure patients were over 65 years in their cohort of 1,023 patients [11]. The female preponderance (58.1%) in our study differs from the PARADIGM-HF trial, which reported male predominance (66.7%) among 8,399 heart failure patients [12].

Breathlessness was the predominant symptom (96.5%) in our study population, comparable to the findings of Mueller *et al*., (2021), who reported dyspnea in 94.2% of 766 heart failure patients [13]. The high prevalence of NYHA class IV patients (43.0%) in our study indicates late presentation, similar to findings from the ASIAN-HF registry, which reported 38.6% class III/IV patients among 5,276 Asian heart failure patients [14].

The substantial presence of comorbidities, particularly CAD (81.4%), aligns with the GUIDE-IT trial, which reported CAD in 77.3% of their cohort [15]. Our study found hypertension in 40.7% of patients, lower than the 68.5% reported in the CHAMPION trial [16], possibly due to regional variations in risk factor prevalence.

The primary finding of our study was the significant association between elevated ST2 levels and adverse outcomes (56.1 ± 22.5 ng/mL vs 26.7 ± 12.2 ng/mL, p<0.001). This aligns with the landmark PRIDE study by Januzzi*et*

al., which demonstrated that ST2 levels >35 ng/mL were associated with increased mortality (HR 3.2, 95% CI 1.8-5.8, p<0.001) [17].

The diagnostic accuracy of ST2 in our study (AUC 0.86, 95% CI: 0.78-0.95) was comparable to findings from the Penn-HF study, which reported an AUC of 0.84 (95% CI: 0.76-0.92) [18]. Our sensitivity of 82.4% and specificity of 76.9% at the 36 ng/mL cutoff were similar to those reported by Pascual-Figal*et al*., (sensitivity 78%, specificity 81%) [19].

The high negative predictive value (87%) observed in our study suggests that ST2 could be particularly useful in identifying low-risk patients, consistent with findings from the Barcelona study, which reported an NPV of 89% for adverse cardiac events [20].

CONCLUSION

This study demonstrated that soluble ST2 serves as a robust prognostic biomarker in heart failure patients. The significant difference in ST2 levels between patients with and without adverse outcomes (56.1 ± 22.5 ng/mL vs 26.7 ± 12.2 ng/mL, p<0.001) validates its utility in risk stratification. The high diagnostic accuracy (AUC 0.86) and excellent negative predictive value (87%) at the 36 ng/mL cutoff make ST2 particularly valuable for identifying low-risk patients. The biomarker's performance remained consistent across different NYHA functional classes and was independent of common comorbidities like hypertension and diabetes. These findings suggest that routine measurement of ST2 levels could enhance current risk assessment strategies in heart failure management. The integration of ST2 measurement into clinical practice could facilitate more targeted therapeutic interventions and improved patient outcomes. Future large-scale, multicenter studies are warranted to further validate these findings and establish standardized protocols for ST2-guided therapy in heart failure patients.

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