Quality in Primary Care
ISSN: 1479-1064

Open access Research Article

Biomarkers in Heart Failure with Reduced Left Ventricular Ejection Fraction, Prognostic Significance

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ABSTRACT

Background: Soluble Suppression of Tumorigenicity 2 (sST2) belongs to the interleiukin-1 receptor family and has been found to be elevated in different cardiovascular conditions. However, its utility in predicting the severity of diseases or mortality outcomes has been a topic of debate. This study explores the relationship between soluble ST2 (sST2) and the prognosis of heart failure patients with reduced ejection fraction.

Methods: The study involved measuring sST2 at baseline (N=111), 1 month and 12 months in heart failure patients with reduced EF. Patients with chronic heart failure with enrolled randomly. The analysis employed a non-linear model to assess the association between sST2 and primary outcomes: Cardiovascular mortality, number of hospitalizations with diagnosis of Acute Decompensated Heart Failure (ADHF), and composite rate of death from cardiovascular disease and hospitalizations with ADHF diagnoses.

Results: The findings reveal a non-linear relationship between sST2 and the risk of cardiovascular, mortality, heart failure hospitalization and composite of cardiovascular, mortality, heart failure hospitalization. However, when considering various clinical variables, including N-terminal pro brain natriuretic peptide (NT-proBNP), only sST2 values below a specific threshold were significantly associated with outcomes.

Conclusion: Despite these findings, the inclusion of sST2 did not notably enhance the predictive ability of a model already incorporating clinical variables. The study suggests further investigation is needed to determine if monitoring sST2 can genuinely improve patients' outcomes. Elevated sST2 concentrations and high NT-proBNP levels are stronger indications of a severe prognosis in chronic heart failure. Therefore, the combination of these two biomarkers ought to be taken into account when creating a multimarker prognostic panel.

Keywords: Heart failure; New biomarkers; Prognosis

INTRODUCTION

The present challenges for scientific study into chronic heart failure include the impact of heart failure on medical systems and society, the need to establish efficient diagnostic and predictive clinical tools, and the need to find innovative treatment techniques. But it's crucial to pick and apply biological markers and sensitive clinical signs to assess the actual results

Received:	04-June-2024	**Manuscript No:**	ipqpc-24-20357
Editor assigned:	06-June-2024	**PreQC No:**	ipqpc-24-20357 (PQ)
Reviewed:	20-June-2024	**QC No:**	ipqpc-24-20357
Revised:	25-June-2024	**Manuscript No:**	ipqpc-24-20357 (R)
Published:	02-July-2024	**DOI:**	10.36648/1479-1064.32.3.13

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Citation Shengelia T (2024) Biomarkers in Heart Failure with Reduced Left Ventricular Ejection Fraction, Prognostic Significance. Qual Prim Care. 32:13.

of medication therapy. Finding fresh, trustworthy biological markers to research is vital significance for the improvement of heart failure care strategies and the modifications to medical care procedures.

Circulating as the cell-surface receptor ST2L, Soluble Suppression of Tumorigenesis 2 protein (sST2) is expressed by cardiomyocytes and vascular endothelial cells when combined with its ligand, interleukin-33, while on cardiovascular damage. Interleukin-33 binding to ST2L is anticipated to reduce unfavorable cardiac remodeling and prevent myocardial hypertrophy and fibrosis [1,2]. As sST2 and ST2L compete with one another for interleukin-33 binding, the cardiovascular preventive benefits of the interleukin-33/ST2L interaction are probably mitigated [1,2].

Interest in sST2 has grown as a possible tool to help manage treatment for Chronic Heart Failure (CHF) and predict prognosis [3,4]. The interleukin-33/ST2L axis in CHF remains unresolved at this time, however sST2 levels in plasma have been observed to be typically higher in CHF patients compared to persons in good condition [4,5].

The role and significance of sST2 as an HF biomarker will be explored in this review, with particular emphasis given to the analytical issues surrounding sST2 measurement as well as the clinical implications of sST2 measurement for the diagnosis, prognosis, and monitoring of chronic HF.

Aims and Objectives

Soluble Suppression of Tumorigenicity 2 (sST2) belongs to the interleukin-1 receptor family and has been found to be elevated in different cardiovascular conditions [6,7]. However, its utility in predicting the severity of diseases or mortality outcomes has been a topic of debate [8-10]. Therefore, we conducted the study to assess the prognostic and diagnostic values of the novel biological marker sST2 in the patients with a heart failure with reduced ejection fraction.

METHODS

Study Population

A prospective cohort study was implemented in the design of this research. Following that, 111 CHF patients who were enrolled between May 2020 and January 2022 were split into two subgroups based on their sST2 concentration. N=65 for T1 (<35 ng/ml) and N=46 or T2 (>35 ng/ml). The patients were monitored for the emergence of the primary endpoints 1 month and 1 year later. The prognostic value of sST2 for the clinical outcome was determined employing the Cox proportional hazards model. The purpose of this cohort study was to analyze established biomarkers of heart failure in greater detail. Patients with reduced ejection fraction (EF<40%), who were diagnosed with heart failure within the last year during either stationary (inpatient) or ambulatory (outpatient) visits, Heart failure treatments were optimized 4 weeks prior to enrollment. Those with heart failure who were referred to Vivamedi Clinic were chosen at random and placed into groups using a convenient sampling technique. Patients over the age of eighteen who were admitted with a CHF diagnosis were included in our sample. The current study has received approval from Vivamedi's local ethics committee. After enrollment, each patient was Optimal Medication Therapy (OMT) with prescribed drugs and doses for at least the previous month, and adequate treatment of comorbidities. The criteria for exclusion were: Age<18 years, pregnancy, a systolic blood pressure of less than 100 mm Hg, glomerular filtration rate<30 ml/min/1.73 m^2, acute hospitalization owing to ADHF in prior 4 weeks, congenital valve defects, severe valvular stenosis any significant cardiovascular events within the previous four weeks, such as resuscitation, acute myocardial infarction, stroke, peripartum cardiomyopathies, Takotsubo cardiomyopathy, end-stage and active cancer.

Basic demographic and clinical information was collected, including age, sex, body mass index, as well as vital signs (BP, HR, RR, SPO2, t), abnormalities on the 12-lead electrocardiogram, an echocardiogram and the following parameters were measured: EF, LA dimension, IVS, LV end-diastolic dimensions, comorbidities (CKD, CAD, Arterial Hypertension, Diabetes Mellitus, atrial fibrillation, metabolic syndrome, Medication (ACEi/ARB, ARNI, MRA, Beta-blockers, SGLT2 inhibitors, Diuretics, Ivabradine, Digoxin,) Device therapy, KCCQ-12 Questionery. In the end, 111 patients with blood samples available for ST2 and NT-proBNP were recruited to the study. Cardiovascular mortality, number of rehospitalizations with diagnosis of Acute Decompensated Heart Failure (ADHF), and composite rate of death from cardiovascular disease and rehospitalizations with ADHF diagnoses were the primary outcomes. In under an hour adhering to admission, blood samples were drawn. Using an Enzyme-Linked Immuno Sorbent Assay, serum sST2 levels were consistently determined (ELISA).

Collection of Clinical and Echocardiographic Parameters

For the purpose of collecting clinical and echocardiographic data, hospital records were investigated. Patients received phone calls or in-person visits as a follow-up. The follow-up period was measured from the time of enrollment and continued 1 year (**Table 1**).

Table 1: Population baseline characteristics

Gender	N; %	P
Female	23 (20.7%)	p<0.001
Male	88 (79.3%)	p<0.001
Age	64.0 ± 9.5	p<0.001
Diabetes	38 (34.2%)	p<0.001
Metabolic Syndrome	4 (3.6%)	p<0.001
Prior MI and PCI		-
MI/PCI	14 (12.6%)	p<0.001
MI	24 (21.6%)	p<0.001
PCI	8 (7.2%)	p<0.001
ACEI/ARNI/ARB	109 (98.2%)	p<0.001
ARNI	28 (25.2%)	p<0.001
ACEI	71 (64.0%)	p<0.001
ARB	10 (9.0%)	p<0.001
SGIT2 inh	62 (55.9%)	p<0.001
Beta-Blockers	103 (92.8%)	p<0.001

Diuretics	103 (92.8%)	p<0.001
Anticoagulation/ Antiaggregating therapy	36 (32.4%)	p<0.001
Lipid-lowering drug	97(87.4%)	p<0.001
Diagnosis type		-
1-Ischemic Cardiomyopathy	36 (32.4%)	p<0.001
2-Dilated Cardiomyopathy	27 (24.3%)	p<0.001
NYHA		-
I	1 (0.9%)	p<0.001
II	49(44.1%)	p<0.001
III	41(36.9%)	p<0.001
HF Stages		-
B	1 (0.9%)	p<0.001
C	96 (86.5%)	p<0.001
D	14 (12.6%)	p<0.001
ECG		-
Sinus	62 (55.9%)	p<0.001
AFIB	44 (39.6%)	p<0.001
AFIBp	3 (2.7%)	p<0.001
PAC	1 (0.9%)	p<0.001
Life threating arrhythmias: VT and VF		p<0.001
VT	1 (0.9%)	p<0.001
VF	0	p<0.001
LBBB	3 (2.7%)	p<0.001
CRTD	3 (2.7%)	p<0.001
LVAD	0	p<0.001

Note: MI-Myocardial Infarction, PCI-Percutaneous Coronary Intervention, ARNI-Angiotensin Receptor/neprilysin Inhibitor, ACEi-Angiotensin Converting Enzyme Inhibitors ARB-Angiotensin Receptor Blocker SGLT2 Inhibitors-Sodium-Glucose Cotransporter-2 Inhibitors Afib-Atrial Fibrillation, Afibp-Paroxysmal form of Atrial Fibrillation, VT-Ventricular Tachycardia, VF-Ventricular Fibrillation, LBBB-Left Bundle Branch Block, CRTD-Implantable Cardiac Resynchronization Therapy Defibrillator, LVAD-Left Ventricular Assist Device, PAC-Premature Atrial Contractions, PVC-Premature Ventricular Contractions.

The study population had an average Left Ventricular Ejection Fraction (LVEF) of 30.4% with a standard deviation of 11.1%. The Left Atrium (LA) dimensions averaged 50.9 mm, with a standard deviation of 6.7 mm. The Interventricular Septum (IVS) thickness was measured at an average of 11.7 mm, with a standard deviation of 1.2 mm. The Left Ventricular (LV) end-diastolic volume was found to be 182.0 ml on average, with a standard deviation of 35.1 ml. The estimated Glomerular Filtration Rate (eGFR) was 63.6 ml/min/m², with a standard deviation of 18.8 ml/min/m². The entire cohort's sST2 levels were as follows: At baseline sST2-33.5 ± 19.4, at 1-month follow-up-31.3 ± 19.3. The delta sST2 at 1-month follow-up: 2.2 ± 8.5. At 1-year follow up: 27.5 ± 19.9. The delta sST2 at 1-year: 6.0 ± 11.8.

Statistical Analysis

Continuous variables were presented as mean ± Standard Deviation (SD) or median with Interquartile Range (IQR). Categorical variables, represented as percentages, were compared using the chi-square test. Correlations were analyzed using either the Pearson test or Spearman rank correlation coefficients. The Kaplan-Meier method was employed to estimate and plot survival curves, and the log-rank test was used to compare groups. The Hazard Ratio (HR) and 95% Confidence Interval (CI) were used to demonstrate the relationship between the primary endpoint and the variables. Due to the skewed distribution of sST2 and NT-proBNP, these data were log-transformed for the Cox regression analyses. A significance threshold of P<0.05 was applied to the data.

RESULTS

79% of the patients in this study were male, and their mean age was 64 years. The population average sST2 level was 33.5 ng/ml. The difference in baseline BNP values was highly significant (P<0.001). In the initial cohort with sST2 levels below 35 ng/ml, the average BNP was 844.17 ng/ml, whereas in the second cohort, it was markedly higher at 2396.03 ng/ml, indicating a substantial difference in BNP levels between these groups. Furthermore, the difference in BNP values after a one-month follow-up remained highly significant (P<0.001).

DISCUSSION

In the subgroup with higher baseline sST2 levels (>35 ng/ml), two distinct groups emerged: Those who survived and those who did not. Among those who survived, at one month follow up there was a more pronounced reduction in NT-proBNP levels compared to those who did not P<0.001. We can attribute this observation to the initial high baseline BNP concentration in severely affected patients, which subsequently decreased significantly. Conversely, in survived patients, the baseline BNP concentration was already below the mean, thus hindering the discernment of reduction dynamics.

Similarly, the baseline sST2 values demonstrated a significant difference between groups (P<0.001), and this significance persisted in the sST2 values observed after a one-year follow-up (P<0.001). At the one-month follow-up, there was no significant difference noted in the reduction of sST2 levels between surviving and deceased patients. However, a markedly greater decline was observed in surviving patients at the one-year follow up. Consequently, we can infer that sST2 may be more indicative of long-term prognostication rather than short-term prognosis.

Comparisons of Clinical Characteristics and Echocardiographic Parameters

There was no group difference in Left Ventricular Ejection Fraction (LVEF) or left atrium size. When sST2 was compared to NT-proBNP and NYHA class across all patients, Spearmen correlation analysis showed positive correlations (r=0.392 and 0.443, respectively; P and lt; 0.01), but no positive correlations (r=-0.119; P=0.031) were observed with LVEF values.

Relationship between sST2 and NYHA Functional Class in CHF Patients

The NYHA classification was applied to split the participants

into three subgroups. We learned that there were significant differences in sST2 and NT-proBNP concentrations between the groups, and that patients with a higher NYHA classes had higher sST2 levels (P<0.001) and higher NT-proBNP (p<0.001).

The NYHA class of impairment demonstrates an association with occurrences of rehospitalization. A univariate non-conditional logistic regression model was used to analyze the association between NYHA and primary outcome rehospitalizations. The individual predictors were examined further and indicated that baseline SST2 and NYHA_class were significant predictors in the model (P<0.05) (**Figure 1**).

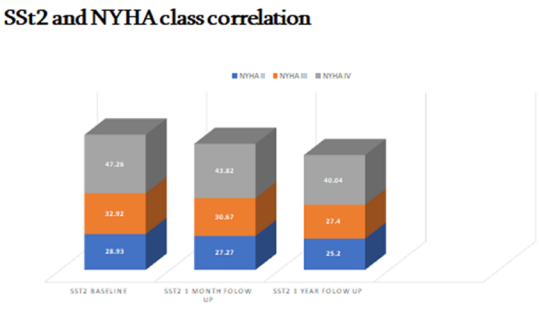


Figure 1: SSt2 and NYHA class correlation

The Correlation and Prognostic Value of sST2 for Outcome in CHF Patients

We evaluated the link between sST2 levels and the course of treatment. 8 cardiovascular deaths occurred over the course of a median follow-up of 12 months. In comparison to patients in the low and high sST2 group, patients in the upper half of sST2 had a lower survival rate (P<0.001) and high rehospitalization (P<0.001). In group 2 (sST2>35 ng/ml), individuals exhibiting elevated levels of both BNP and sST2 experienced increased rates of rehospitalizations and cardiovascular mortality (**Figure 2**). **Table 2** displayed Kaplan-Meier curves that estimate cardiovascular mortality based on sST2 groups (**Table 3**) (**Figure 3**).

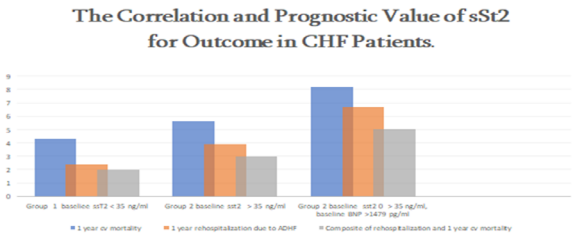


Figure 2: The correlation and prognostic value of sSt2 for outcome in CHF patients

Table 2: The correlation and prognostic value of sST2 for outcome in CHF patients

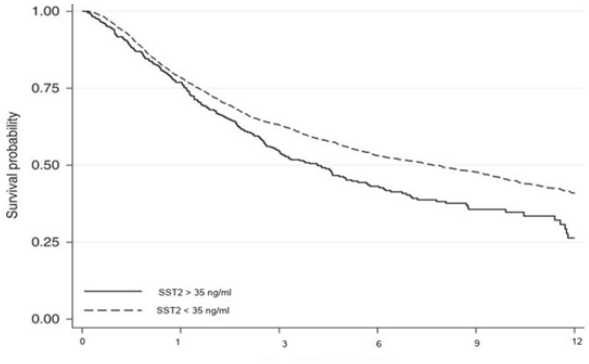
BNP screening					
Group	**n=**	**Mean**	**Standard Deviation**	**Standard Error**	**P**
1	65	844.17	918.83	113.97	<0.001
2	45	2396.03	2939.95	438.26	
BNP 1 month follow-up					
Group	**n=**	**Mean**	**Standard Deviation**	**Standard Error**	**P**
1	65	581.73	588.74	73.02	<0.001
2	46	1339.19	1115.94	164.54	
sST2 screening					
Group	**n=**	**Mean**	**Standard Deviation**	**Standard Error**	**P**
1	65	20.64	8.68	1.08	<0.001
2	46	51.75	15.43	2.28	
sST2 1 month follow-up					
Group	**n=**	**Mean**	**Standard Deviation**	**Standard Error**	**P**
1	65	20.35	9.86	1.22	<0.001
2	46	46.88	18.75	2.76	
SSt2 1 year follow-up					
Group	**n=**	**Mean**	**Standard Deviation**	**Standard Error**	**P**
1	65	20.23	10.41	1.29	<0.001
2	45	45.28	21.14	3.15	
LVEF, %					
Group	**n**	**Mean**	**Standard Deviation**	**Standard Error**	**P**
1	65	33.23	5.64	0.7	<0.002
2	46	29.61	6.35	0.94	
LA Dimensions, mm					

Group	n=	Mean	Standard Deviation	Standard Error	P
1	65	49.63	6.71	0.83	0.019
2	46	52.63	6.24	0.92	

Table 3: Kaplan-Meier curves that estimate cardiovascular mortality based on sST2 groups

1 year Cardiovascular mortality	Group 1 sST2<35 ng/ml	Group 2 sST2>35 ng/ml	Total
Yes	2 (2.2%)	6 (27.3%)	8 (7.2%)
No	87 (97.8%)	16 (72.7%)	103 (92.8%)
Total	89 (100.0%)	22 (100.0%)	111 (100.0%)
Rehospitalization 1 year ADHF	Group 1	Group 2	Total
0	59 (90.8%)	33 (71.7%)	92 (82.8%)
1	5 (7.7%)	6 (13.0%)	11 (9.9%)
2	1 (1.5%)	7 (15.2%)	8 (7.2%)
Total	65 (100.0%)	46 (100.0%)	111 (100.0%)

Note: ADHF: Acute Decompensated Heart Failure



Research was funded by Shota Rustaveli National Science Foundation of Georgia (Project ID PHDF-22-2513)

Figure 3: Kaplan-Meier curves

Outcome Measurement

This study employed univariate non-conditional logistic regression models to analyze the association between various baseline characteristics and two primary outcomes: 1-year mortality and 1-year hospitalization. The models were adjusted for sex and age at onset to test for confounding factors, and a p-value-based backward variable selection method was used to retain only variables with significant explicative value ($p<0.05$) in the final models.

1-Year Cardiovascular Mortality

The results of the multiple linear regression analysis indicated a strong collective significant effect of several predictors on 1-year cardiovascular mortality ($F(6,100)=7.96$, $p<0.001$, $R^2=0.63$, adjusted $R^2=0.60$). The significant individual predictors were: Baseline NT-pro BNP, 1-month NT-pro BNP, 1-month SST2, LVEF, ARNI, TAPSE.

These findings suggest that higher baseline NT-proBNP levels, no significant reductionof 1 month Nt-proBNP levels, higher SST2_1 levels, lower LVEF, no use of ARNI, and lower TAPSE are significant predictors of 1-year cardiovascular (CV) mortality. This model explains a substantial portion of the variance in 1-year CV mortality, as indicated by the high R^2 value.

1-Year Hospitalization

For the outcome of 1-year hospitalization, the multiple linear regression model also showed a significant collective effect ($F(3,107)=11.78$, $p<0.001$, $R^2=0.25$, adjusted $R^2=0.23$). The significant individual predictors were: Baseline SST2 concentration, NYHA class, Heartfailure stages.

These results indicate that higher baseline SST2 levels, lower NYHA class, and lower stage are significant predictors of 1-year hospitalization due to ADHF. However, this model explains a smaller portion of the variance in 1-year hospitalization compared to the mortality model (**Table 3**).

CONCLUSION

In summary, the findings suggest that sST2 levels are associated with heart failure severity as assessed by NYHA functional class and NT-proBNP levels. Moreover, both NYHA class and baseline sST2 levels are predictive of rehospitalizations, highlighting their potential clinical utility in risk stratification and management of heart failure patients. Further research is warranted to validate these findings and explore the mechanisms underlying the association between sST2 levels, NYHA class, and adverse outcomes in heart failure.

Baseline sST2 levels and NYHA class were identified as significant predictors of rehospitalizations, further supporting the utility of sST2 as a prognostic marker in heart failure patients. Based on the findings presented, several conclusions can be drawn:

- There was a positive correlation observed between sST2 levels and both NT-proBNP and NYHA class, indicating a potential relationship between sST2 and heart failure severity.
- However, no significant correlation was found between sST2 levels and left ventricular ejection fraction (LVEF), suggesting that sST2 may not directly reflect systolic function.

- Patients with higher NYHA functional classes exhibited significantly elevated sST2 levels and NT-proBNP concentrations, suggesting a potential role of sST2 as a biomarker for heart failure severity. This underscores the importance of NYHA classification in identifying patients at higher risk of adverse outcomes and highlights sST2 as a potential adjunctive biomarker for risk stratification in heart failure patients.

The study demonstrates a significant association between NYHA class and occurrences of rehospitalization, emphasizing the clinical relevance of NYHA classification in predicting adverse outcomes.

Elevated concentrations of the new biomarker sST2 (>35 bg/ml) should be taken into consideration as prognostic predictors of cardiovascular mortality and rehospitalizations due to heat failure in patients with chronic heart failure and reduced ejection fraction (<40%). In these patients, SST2 was not correlated with age, sex, multiple medical conditions, or left ventricular ejection fraction, but rather with NT-proBNP and NYHA functional class. When compared to either marker alone, elevated sST2 concentrations and high NT-proBNP levels together are stronger indications of a severe prognosis in chronic heart failure. Therefore, the combination of these two biomarkers ought to be taken into account when creating a multimarker prognostic panel. The study highlights that certain biomarkers (baseline BNP, 1 month BNP, 1 month SST2_1, baseline SST2), clinical measures (LVEF, TAPSE), medication use (ARNI), and disease classifications (NYHA class, stage) are significant predictors for both 1-year CV mortality and hospitalization in patients. These findings underscore the importance of these factors in managing patient outcomes and could inform clinical decision-making and risk stratification strategies. The stronger predictive power for mortality than for hospitalization suggests that different factors might influence these outcomes, emphasizing the need for tailored approaches in patient management.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The author's declared that they have no conflict of interest.

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