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High Soluble Suppression of Tumorigenicity-2 (sST2) is A Risk Factor for Rehospitalization and Mortality in Chronic Heart Failure Patients with Reduced Ejection Fraction

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ABSTRACT

Background: Chronic heart failure (CHF) impairs the heart's pumping ability due to structural or functional abnormalities. It is a leading cause of death worldwide, with mortality rates of 10-50% based on severity. Risk stratification methods help predict CHF prognosis. ST2, an interleukin-1 receptor, is valuable for forecasting rehospitalization and cardiovascular events. In progressive heart failure, increased sST2 receptor expression inhibits the protective effects of IL-33, worsening the condition. ***Methods:*** Chronic heart failure patients with LVEF <40% were studied in a cohort design. After sST2 blood samples were taken, patients were followed for 1 year and 10 months to monitor Major Cardiovascular Events (MACEs) like rehospitalization and mortality. Baseline characteristics included demographic, clinical, comorbidity, laboratory, and echocardiographic data. The best sST2 cut-off was determined using ROC curves. Kaplan-Meier and Cox Regression analyses assessed outcomes using SPSS 26.0. ***Results:*** All 80 samples completed the study with no drop-outs. The optimal sST2 cut-off for predicting Major Cardiovascular Events (MACEs) was >19.38 ng/mL (AUC 0.668, CI 95% 0.542-0.794; p=0.023), with 66.7% sensitivity and 66.1% specificity. Survival analysis showed patients with sST2 ≥19.4 ng/mL had lower long-term survival (58.8% vs. 84.8%; p=0.007). Adjusted for age and comorbidities, high sST2 levels significantly predicted MACEs, with a 3.581 times higher risk (95% CI 1.343-9.551; p=0.011) of rehospitalization and mortality. ***Conclusion:*** High sST2 levels (≥19.4 ng/mL) were associated as a risk factor of rehospitalization and mortality in chronic heart failure patients with reduced ejection fraction.

Keywords: sST2; chronic heart failure; major cardiovascular events; rehospitalization; mortality due to cardiovascular causes.

INTRODUCTION

Chronic heart failure (CHF) is a complex condition characterized by structural abnormalities or functional impairments that hinder the heart's ability to pump blood effectively [1]. The prevalence of CHF is expected to rise significantly in the next two decades, posing a worse prognosis compared to other non-communicable diseases like breast and prostate cancer. Cardiovascular disease remains the leading cause of mortality globally, with CHF death rates varying between 10% and 50%, depending on disease severity [2].

The ASIAN-HF study, a multinational prospective study on heart failure mortality in Asia, found a one-year all-cause mortality rate of 9.6% among CHF patients. Southeast Asian countries, particularly Indonesia and the Philippines, showed the highest mortality rates, with Indonesia reporting a 21.4% mortality rate. The study highlights the significant health and economic burden of CHF, with Indonesia allocating at least US$ 27 million annually for its management [3].

Risk stratification methods through clinical examination, imaging, and laboratory tests provide prognostic insights for CHF patients. Exercise intolerance and the New York Heart Association (NYHA) classification are key indicators of prognosis. Biomarkers such as soluble suppression of tumorigenicity-2 (sST2) have emerged as significant predictors of CHF progression and mortality. Elevated sST2 levels are associated with higher rehospitalization and mortality rates, and sST2 is considered a robust prognostic marker unaffected by obesity, age, atrial fibrillation, etiology, or previous heart failure diagnosis [4].

Despite its proven prognostic value, sST2 is not widely used in Indonesia, and data on its utilization remains limited. Current studies focus on acute myocardial infarction populations, with no direct examination of the relationship between sST2 and rehospitalization or mortality rates in CHF patients. This study aims to analyze the association between sST2 levels and rehospitalization and mortality in outpatient CHF patients in Indonesia.

METHOD

This study is an observational analytic study with a cohort design, starting from the measurement of sST2 in the past (control patients) based on blood specimens taken during previous outpatient visits. Follow-up is conducted based on medical records, the occurrence of rehospitalization and death, and continued follow-up for patients who have not experienced these outcomes for up to 22 months of the study period. This allows a comparison of the incidence rates of rehospitalization and mortality in chronic heart failure outpatients with reduced left ventricular ejection fraction, based on sST2 categories.

The inclusion criteria for this study are chronic heart failure patients with LVEF (left ventricle ejection fraction) <40%. The exclusion criteria are: 1) Pregnant patients; 2) Patients with acute coronary syndrome, acute myocarditis, and cardiogenic shock; 3) Severe systemic inflammatory diseases, tumors and/or cancer, sepsis, and autoimmune diseases; 4) Patients undergoing glucocorticoid therapy.

The study sample includes all participants aged at least 18 years with chronic heart failure who are undergoing routine outpatient care at the Heart Clinic in the Integrated Heart Center Building of RSUP Prof. I.G.N.G. Ngoerah and meet the inclusion and exclusion criteria based on anamnesis, physical examination, and other clinically indicated laboratory examinations. Anamnesis includes identity, current complaints, history of heart disease, treatment history, other medical history, and social history. Physical examination includes vital signs, general status, and local status. Additional laboratory examinations are only performed if clinically indicated.

Eligible participants who meet the inclusion criteria and do not meet the exclusion criteria will be given an explanation of the study and asked to sign an informed consent form as a form of agreement to participate in the study.

The sST2 examination is conducted using the enzyme-linked immunosorbent assay (ELISA) method with the human sST2 (soluble ST2) ELISA E-EL-H6082 assay kit (USA). The serum used is serum from stored biological materials that have been centrifuged at 3000 rpm for 5 minutes to obtain the serum, which is then stored in a refrigerator at 80°C until examination.

The diluted serum is placed into wells coated with anti-ST2 antibodies and incubated for a specified period. Following a series of steps where reagents are washed from the plate, additional reagents are added to the plate and then washed, and the analyte is finally detected by adding a colorimetric reagent. The generated signal is measured spectroscopically using a microtiter well reader at 450 nm within 15 minutes. Reagent preparation and the complete assay procedure can be found in the human sST2 (soluble ST2) ELISA E-EL-H6082 Assay Instruction for Use (USA).

Participants who have completed the initial phase of the study will be followed up through regular outpatient visits to determine the occurrence of rehospitalization due to their chronic heart failure. If participants do not attend scheduled routine visits, follow-up can be conducted by phone to confirm their status. Follow-up is conducted every 4 weeks to evaluate outcomes of rehospitalization and all-cause mortality.

Data were presented with mean and median for numerical variables, and frequency and percentage for categorical variables. The best cut-off point of sST2 levels was determined with ROC curves. Kaplan-Meier curves were used to assess rehospitalization and mortality trajectories based on sST2 levels, and multivariate analysis using Cox Regression was performed using SPSS version 26.0.

RESULT

This study, with a cohort design, was carried out over 22 months. Samples that met the inclusion and exclusion criteria underwent echocardiography, and blood samples were taken to examine sST2 plasma levels. During the research period, a total of 80 chronic heart failure patients with reduced ejection fraction were included. All samples were then divided into two groups based on exposure to risk factors (high sST2 levels) and those without (normal sST2 levels), and they were followed until rehospitalization and mortality were recorded. During the follow-up period, no samples were categorized as experiencing drop-out. Characteristic data in Table 1.

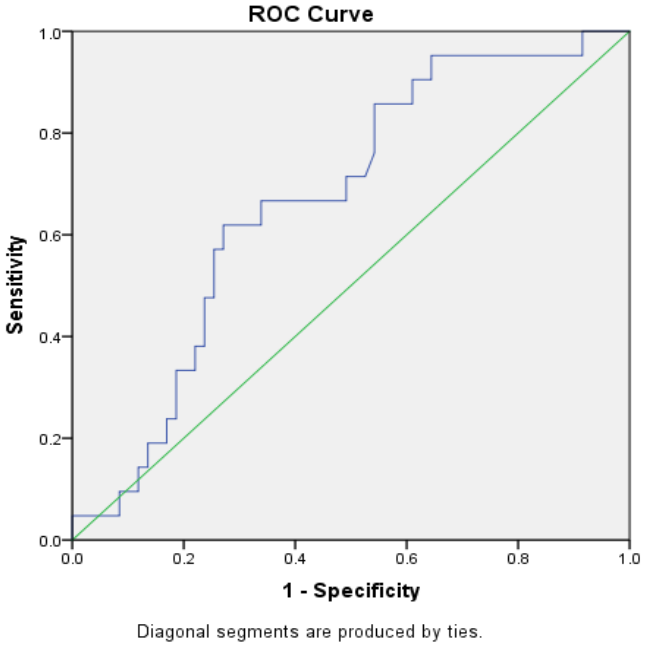
TABLE 1: Basic characteristics of the sample.

Basic Characteristics	Total (N=80)
Male, n (%)	62 (77.5)
Age, years, mean±SB	58.61±9.72
BMI, kg/m2, mean±SB	24.06 ± 4.16
Underweight (BMI <18.9 kg/m2), n (%)	7 (8.8)
Normal (BMI ≥18.9-22.9 kg/m2), n (%)	23 (28.8)
Overweight (BMI ≥23-24.9 kg/m2), n (%)	20 (25)
Obesity (BMI ≥25 kg/m2), n (%)	30 (37.5)
Comorbidities	
Hypertension, n (%)	33 (41.3)
Dyslipidemia, n (%)	65 (81.3)
Smoking, n (%)	55 (68.8)
Diabetes mellitus, n (%)	43 (53.8)
Coronary heart disease, n (%)	73 (91.3)
Echocardiography	
ejection fraction,%, mean±SB	30.42±6.53
TAPSE, cm, mean±SB	19.36±4.46
Estimated GFR, (ml/min/1.73 m2, mean±SB	69.05 ± 20.86
sST2, ng/mL, mean±SB	15.16±7.57
Outcome	21 (26.3)
Rehospitalization, n (%)	6 (7.5)
Mortality, n (%)	15 (18.8)
Follow-up duration, days, mean±SB	460.8 ± 143.7

Numerical data is displayed as mean ± standard deviation (SB), while categorical data is displayed as frequency (%).

In this study, most of the samples were male (62 samples or 77.5%) and the remaining small portion were female (18 samples or 22.5%). The sample involved in this study had a mean age of 58.61 ± 9.72 years. In terms of body weight, the majority of samples were classified as obese (37.5%) and normal (28.8%). Based on sample comorbidities, a history of coronary heart disease was the most common comorbidity (91.3%), followed by dyslipidemia (81.3%), smoking (68.8%), diabetes mellitus (53.8%) and hypertension (41.3%).

Over time follow-up with an average of 460 days, it was found that 21 samples (26.3%) experienced rehospitalization and mortality, of which 6 samples experienced rehospitalization and mortality in 15 samples. sST2 levels were evaluated through plasma blood examination which was analyzed with the human sST2 (soluble ST2) ELISA E-EL-H6082 assay kit (USA) which was carried out at the integrated biomedical laboratory of the Faculty of Medicine, Udayana University. The cut-off point for sST2 levels as a risk factor for rehospitalization and mortality was determined using ROC curve analysis. Based on this analysis, it was found that the best cut-off point for sST2 value as a risk factor for rehospitalization and mortality was >19.38 ng/mL with an area under the curve (AUC) value of 0.668 (95% CI 0.542-0.794; p=0.023), sensitivity 66.7% and specificity 66.1%.



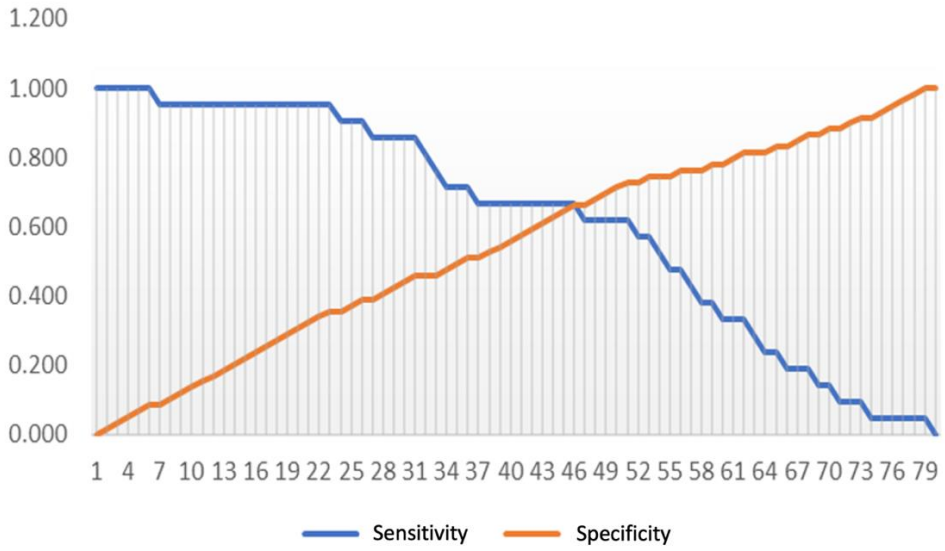


FIGURE 1: ROC curve and line diagram of sensitivity and specificity of sST2 levels as a risk factor for rehospitalization and mortality in patients with chronic heart failure with reduced ejection fraction.

Furthermore, samples with sST2 levels ≥19.38 ng/mL (rounded to 19.4 ng/mL) were categorized as risk factors, while samples with sST2 levels <19.38 ng/mL were categorized as comparison.

Through the normality test with Kolmogorov-Smirnov, all numerical variables such as age, BMI, HbA1C levels, eGFR and echocardiography parameters (LVEF and TAPSE) were found to be normally distributed with homogeneous variance ($p>0.05$). Table 2 presents a bivariate analysis of basic characteristics, comorbidities, laboratory parameters, and echocardiographic parameters based on the cut-off sST2 value that has been determined based on the previous ROC curve.

Based on bivariate analysis, patients with high sST2 levels were found to have significantly higher HbA1C levels (7.37 ± 2.09% versus 6.48 ± 1.15%, $p = 0.013$). In addition, the incidence of outcomes of rehospitalization and death, is significantly higher in patients with sST2 levels ≥19.4 ng/mL ($p=0.009$). No significant differences were found in age, BMI, comorbidities or echocardiographic parameters in patients with normal or high sST2 levels.

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TABLE 2: Sample characteristics based on sST2 levels.

Variable	sST2 levels (ng/mL)		P value
	<19.4 (N=46)	≥19.4 (N=34)	
Age, years, mean±SB	57.49±8.58	60.18±10.86	0.255
BMI, kg/m2, mean±SB	24.92±4.4	22.91 ± 3.57	0.268
Underweight	2 (28.6)	5 (71.4)	
Normal	14 (60.9)	9 (39.1)	0.396
Overweight	11 (55)	9 (45)	
Obesity	19 (63.9)	11 (36.7)	
Gender			
Male, n (%)	34 (54.8)	28 (45.2)	0.372
Female, n (%)	12 (66.7)	6 (33.3)	
Comorbid			
Hypertension			
Yes, n (%)	20 (60.6)	13 (39.4)	0.638
No, n (%)	26 (55.3)	21 (44.7	
Diabetes mellitus, n (%)			
Yes, n (%)	24 (55.8)	19 (44.2)	0.742
No, n (%)	22 (59.5)	15 (40.5)	
Smoking, n (%)			
Yes, n (%)	30 (54.5)	25 (45.5)	0.428
No, n (%)	16 (64)	9 (36)	
Dyslipidemia, n (%)			
Yes, n (%)	36 (55.4)	29 (44.6)	0.426
No, n (%)	10 (66.7)	5 (33.3)	
CHD history, n (%)			
Yes, n (%)	41 (56.2)	32 (43.8)	0.432
No, n (%)	5 (71.4)	2 (28.6)	

Variable	sST2 levels (ng/mL)		P value
	<19.4 (N=46)	<19.4 (N=46)	
AF, n (%)			
Yes, n (%)	1 (50)	1 (50)	0.828
No, n (%)	45 (57.7)	33 (42.3)	
Laboratory Parameters			
HbA1C, %, mean±SB	6.48 ± 1.15	7.37 ± 2.09	0.013*
eGFR, ml/min/m2, mean±SB	69.68±21.66	68.54 ± 20.81	0.981
Echocardiographic Parameters			
EF, %, mean±SB	32.70±5.68	28.82±5.74	0.929
TAPSE, mm, mean±SB	20.35±4.23	18.57±4.04	0.447
Outcome			
Rehospitalization and mortality, n (%)			
Yes, n (%)	7 (33.3)	14 (66.7)	0.009*
No, n (%)	39 (66.1)	20 (33.9)	

Note: Numerical data is displayed in mean ± standard deviation (SB). Numerical data analysis was carried out using the independent Student t-test. Categorical data were displayed in frequency (n) and percentage (%), and analyzed using the Chi-square test. BMI= body mass index; AF= atrial fibrillation; HbA1C= hemoglobin A1C; eGFR= estimated glomerular filtration rate; EF= ejection fraction; TAPSE= tricuspid annular plane systolic excursion.
*: There is a statistical difference between the two groups ($p<0.05$).

The bivariate analysis shown in Table 3 shows differences in characteristics between the groups that experienced it rehospitalization and mortality with the group that did not. The results of the bivariate analysis showed that the group that experienced rehospitalization and mortality had significantly higher sST2 levels than the group that did not (20.22 ± 6.1 ng/mL versus 15.56 ± 7.85 ng/mL, p = 0.022). There were no significant differences in the basic characteristics of the research subjects, comorbidities, laboratory parameters or echocardiography parameters in the two groups.

TABLE 3: Sample characteristics based on rehospitalization and mortality.

Variable	Rehospitalization and Mortality		P value
	No (N=59)	Yes (N=21)	
Age, years, mean±SB	58.04 ± 10.02	60.35±8.54	0.143
BMI, kg/m2, mean±SB	23.9±4.73	24.78±3.54	0.474
Underweight	6 (85.7)	1 (14.3)	0.499
Normal	19 (82.6)	4 (17.4)	
Overweight	14 (70)	6 (30)	
Obesity	20 (66.7)	10 (33.3)	
Gender			
Male, n (%)	44 (71)	18 (29)	0.294
Female, n (%)	15 (83.3)	3 (16.7)	
Comorbid			
Hypertension			
Yes, n (%)	25 (75.8)	8 (24.2)	0.732
No, n (%)	34 (72.3)	13 (27.7)	
Diabetes mellitus, n (%)			
Yes, n (%)	32 (74.4)	11 (25.6)	0.884
No, n (%)	27 (73)	10 (27)	
Smoking, n (%)			
Yes, n (%)	40 (72.7)	15 (27.3)	0.758
No, n (%)	19 (76)	6 (24)	
Dyslipidemia, n (%)			
Yes, n (%)	47 (72.3)	18 (27.7)	0.542
No, n (%)	12 (80)	3 (20)	
CHD history, n (%)			
Yes, n (%)	52 (71.2)	21 (28.8)	0.098
No, n (%)	7 (100)	0 (0)	
AF, n (%)			
Yes, n (%)	1 (50)	1 (50)	0.439
No, n (%)	58 (74.4)	20 (25.6)	

Variable	Rehospitalization and Mortality		P value
	No (N=59)	Yes (N=21)	
Laboratory Parameters			
HbA1C, %, mean±SB	6.89±1.8	6.78 ± 1.27	0.468
eGFR, ml/min/m2, mean±SB	68.82 ± 20.75	70.23±22.8	0.987
Echocardiographic Parameters			
EF, %, mean±SB	31.22 ± 6.08	30.5±5.86	0.929
TAPSE, mm, mean±SB	19.29 ± 4.07	20.41 ± 4.62	0.447
sST2 levels, ng/mL, mean±SB	15.56±7.85	20.22±6.1	0.022*

Note: Numerical data is displayed in mean ± SB. Categorical data are presented as frequencies (n) and percentages (%). BMI= body mass index; AF= atrial fibrillation; HbA1C= hemoglobin A1C; eGFR= estimated glomerular filtration rate; EF= ejection fraction; TAPSE= tricuspid annular plane systolic excursion, sST2= soluble suppression of tumorigenicity 2.
*: There is a statistical difference between the two groups (p<0.05).

Bivariate analysis in Table 4 shows that high sST2 (≥19.4 ng/dL) is a risk factor for primary endpoints (rehospitalization and mortality) that is 6.8 times higher in chronic heart failure patients with reduced ejection fraction (RR = 6, 8, p value=0.009).

TABLE 4: Sample characteristics based on rehospitalization and mortality.

Rehospitalization and mortality, n (%)	sST2 levels (ng/dL)		RR	P value
	sST2 ≥19.4	sST2 <19.4		
Yes	14 (66.7 %)	7 (33.3%)	6,8	0.009*
No	20 (33.9%)	39 (66.1%)		

Information: sST2= soluble suppression of tumorigenicity 2.
*: There is a statistical difference between the two groups (p<0.05).

The interaction of sST2 levels as a predictor of outcomes in the form of rehospitalization and death was carried out using survival analysis. Survival analysis is first carried out by checking assumptions proportional hazards (PH) using the Kaplan-Meier curve for the independent variable (sST2 levels) and dependent variables (rehospitalization and mortality) (Figure 2).

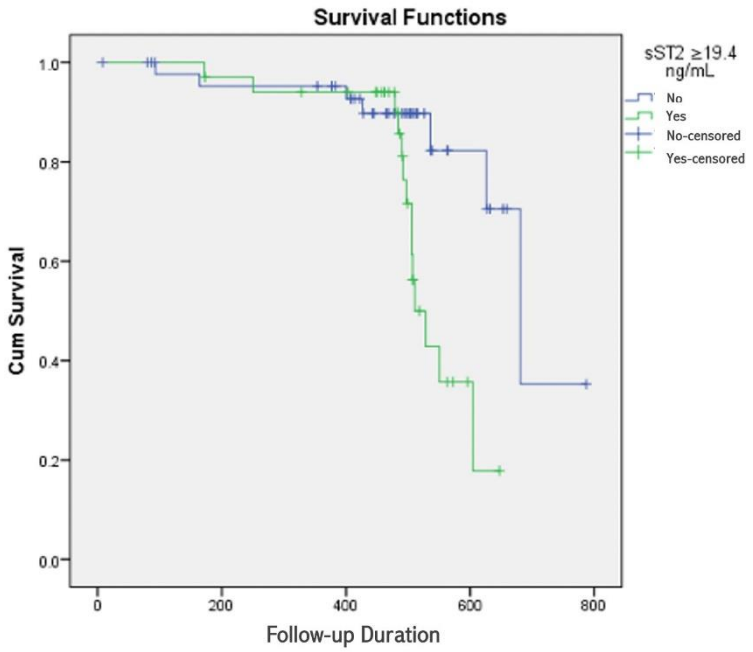

FIGURE 2: Kaplan-Meier survival curve based on sST2 levels (cut-off points <19.4 ng/mL and ≥19.4 ng/mL) on study outcomes.

Based on survival analysis, samples with sST2 levels ≥19.4 ng/mL at outpatient had a significantly lower long-term survival rate than patients with lower sST2 levels (58.8% versus 84.8%; p= 0.007), with a mean survival time of 532 days versus 660 days.

To identify risk factors that are independently associated as predictors of rehospitalization and death in chronic heart failure patients with low left ventricular systolic function, all variables that have p<0.25 in the test, namely demographic variables (age),

comorbid factors, laboratory parameters (HbA1C and eGFR levels), echocardiographic parameters (EF and TAPSE values) and sST2 levels were included in the multivariate analysis. Multivariate analysis was carried out using the Cox regression test with the backward method.

TABLE 5: Multivariate analysis results using the Cox regression test with the backward method.

Variable	HR	IK 95%		P value
		Lower limit	Upper limit	
Step 1				
Age	0.992	0.942	1,046	0.773
History of CHD	540728.1	0,000	.	0.982
sST2	3,622	1,332	9,844	0.012*
Step 3				
sST2	3,581	1,343	9,551	0.011*

Information: BMI= body mass index; AF= atrial fibrillation; HbA1C= hemoglobin A1C; eGFR= estimated glomerular filtration rate; EF= ejection fraction; TAPSE= tricuspid annular plane systolic excursion; sST2= soluble suppression of tumorigenicity 2.

Through backward analysis, after adjusting for confounding factors (hypertension and BMI), it was found that sST2 levels had a significant independent relationship as a predictor of rehospitalization and mortality in chronic heart failure patients with reduced ejection fraction. Samples with high sST2 levels had a 3.581 times higher risk (95% CI 1.343-9.551; p=0.011) of experiencing rehospitalization and long-term death compared to samples with lower sST2 levels.

DISCUSSION

Based on the bivariate analysis of patients with high sST2 levels, it was found that the mean sST2 levels were statistically significantly different between patients with sST2 levels ≥ 19.4 ng/mL and < 19.4 ng/mL. It was observed that patients with high sST2 levels had a significantly higher proportion of rehospitalization and mortality compared to those with low sST2 levels. Another study showed significantly different sST2 characteristics in patients with MACE and without MACE, with higher mean sST2 levels in the MACE group (38.29 ± 13.96 vs. 33.55 ± 11.97, p < 0.001). Multivariate Cox regression analysis found sST2 to be an independent predictor of MACE events (HR 1.01, p=0.025) [5]. Chen D. et al. divided sST2 levels into quartiles (Q1 - Q4) and found significant differences in patient characteristics. Increased sST2 levels correlated with higher proportions of atrial fibrillation, heart failure, older age, decreased HB, decreased eGFR, and increased hs-CRP. These results were most pronounced in quartile 4 (Q4) with sST2 levels >28.4 ng/mL. Multivariate analysis to determine risk factors for high sST2 levels in quartile 4 identified significant variables such as heart failure (OR 1.77, p=0.087), age (OR 1.03, p=0.022), beta-blocker usage (OR 2.05, p=0.033), and number of MACE events (OR 1.35, p=0.007) [6]. Another study on sST2 levels in patients with carotid artery stenosis found significantly higher sST2 levels in male patients, those with diabetes mellitus, and those with a history of coronary artery disease [7].

A study by Van den Berg VJ, related post-acute coronary syndrome (ACS) to sST2 levels, found higher sST2 levels in post-ACS patients compared to non-ACS patients (29.6 ng/mL vs. 33.7 ng/mL, p=0.052) with an adjusted HR of 1.64 (CI 95% 1.09-2.34; p=0.019) [8]. Two studies connected sST2 with myocardial infarction, both conducted by Dhillon et al., with comparable study designs. The first study involved 677 STEMI patients [9], and the second involved 577 NSTEMI patients [10]. In both studies, sST2 concentrations were measured between the 3rd and 5th days before hospital discharge, with patient follow-up for about one year. The authors performed a log10 transformation on sST2 concentrations, referring to a tenfold change in concentration. They found no association between sST2 and re-infarction in STEMI patients, but a tenfold increase in sST2 levels was associated with a 2.5 times higher risk of re-infarction in NSTEMI patients [9,10].

Soluble ST2 increases significantly when cardiomyocytes are stimulated by mechanical stress [11]. ST2 interacts with its functional ligand IL-33 in the cardiovascular system [12,13]. After tissue damage, IL-33 is expressed by stromal cells and signals local immune cells [14]. Generally, inflammation induction leads to the activation of the IL-33/ST2 axis, resulting in positive feedback that increases the production of proinflammatory cytokines/chemokines [15]. However, in cardiovascular pathophysiology, the intact IL-33/ST2 pathway is cardioprotective: treatment with exogenous IL-33 reduces hypertrophy, while genetic deletion of the membrane ST2 receptor eliminates IL-33's anti-fibrotic and anti-hypertrophic benefits. Soluble ST2 (sST2), a truncated form secreted from ST2L, acts as a decoy receptor, binding and inhibiting IL-33 [12]. Therefore, elevated circulating sST2 levels reduce systemic IL-33 effects. In an animal study, ApoE (-/-) mice treated with soluble sST2 developed significantly larger atherosclerotic plaques in the aortic sinus compared to control mice [16].

Additionally, sST2 was specifically expressed in arterial endothelial cells and played a role in atherosclerosis progression [17]. These findings suggest potential mechanisms by which sST2 functions as a marker for plaque burden and predicts future cardiovascular events.

This study found that the cut-off for sST2 as a predictor of rehospitalization and mortality was ≥19.4 ng/mL with an area under the curve (AUC) value of 0.668 (CI 95% 0.542-0.794; p=0.023), sensitivity of 66.7%, and specificity of 66.1%. Bivariate analysis showed that patients with high sST2 levels had significantly higher HbA1C levels (7.37±2.09% vs. 6.48±1.15%, p=0.013). Additionally, rehospitalization and death outcomes were significantly higher in patients with sST2 levels ≥19.4 ng/mL (p=0.009). There were no significant differences in age, BMI, comorbidities, or echocardiographic parameters between patients with normal and high sST2 levels. Cox regression analysis in this study found that samples with high sST2 levels had a 3.581 times higher risk (95% CI 1.343-9.551; p=0.011) of long-term rehospitalization and death compared to samples with lower sST2 levels.

These results align with the study by Gong et al., which reported that high sST2 levels increase the risk of rehospitalization and mortality in heart failure patients. This study emphasized that sST2 concentration values can be used as a prognostic biomarker for outpatient heart failure with reduced ejection fraction (HFrEF) patients at high risk for morbidity and mortality [18].

Dudek et al. also found results consistent with this study. Their study stated that sST2 protein is an independent risk factor for mortality in HFrEF patients. This study found the sST2 cut-off to be 45.818 ng/mL with an AUC of 0.676, p = 0.0009. The Kaplan-Meier graph showed that the probability of survival was significantly higher in the low sST2 concentration group (p = 0.0027). Multivariate regression analysis showed that sST2 concentration was an independent predictor of mortality in HFrEF patients with an HR of 1.00, p = 0.0206 [19].

Emdin et al.'s study also showed findings consistent with this study. They found that the best cut-off for sST2 as a predictor of all-cause death, cardiovascular death, and HF hospitalization was 28 ng/mL with good risk stratification in Kaplan-Meier analysis. In an analysis model that included age, gender, body mass index, ischemic etiology, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, glomerular filtration rate, HF medical therapy, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity troponin T (hs-TnT), the risk of all-cause death, cardiovascular death, and HF hospitalization increased by 26%, 25%, and 30% for every twofold increase in sST2. This study also stated that sST2 levels were independently associated with all-cause death, cardiovascular death, and HF hospitalization [20].

Aleksova et al.'s study explained that sST2 is part of the interleukin-1 receptor. Its levels increase in various cardiovascular diseases. sST2 mediates the inflammatory response. sST2 expression is influenced by cardiomyocyte stretch. Previous studies using mouse samples showed that sST2 is released by cultured myocytes after mechanical stress and increases in blood concentration after myocardial infarction. sST2 is expressed in macrovascular and microvascular endothelial cells and is secreted by cardiomyocytes and fibroblasts under mechanical [21]. Sciatti et al.'s study also stated that sST2 is a marker of myocardial fibrosis and ventricular remodeling. Galectin-3 (Gal-3) is also a marker reflecting myocardial fibrosis and remodeling [22]. A cohort study with 876 patients showed that sST2 is superior to Gal-3 in risk stratification. sST2 and Gal-3 were associated with an increased risk of all-cause mortality, but only sST2 was associated with cardiovascular mortality [23]. This may be due to Gal-3's primary role in the early stages of fibrosis and ventricular remodeling, while sST2 provides strong biohumoral insights into cumulative myocardial fibrosis processes [22].

Lin et al.'s study found that serum sST2 levels significantly increased in patients with abdominal obesity, prediabetes, and diabetes [24]. However, the relationship between sST2 levels and beneficial metabolic and cardiovascular effects in T2DM is not fully understood. Some researchers have reported a significant correlation between serum sST2 levels and glycemic control in individuals with T2DM [25]. In this study, poor glycemic control indirectly causes rehospitalization and mortality in the high sST2 group.

In this study, the average age of HFrEF patients who experienced rehospitalization and mortality was 52 to 69 years. Most patients were male (18/80; 29%) and had a history of CAD (21/80; 28.8%). Carnicelli et al.'s study in 2021 showed similar findings, with HFrEF patients predominantly male (68.1%) and aged between 55-73 years. Significant differences in sST2 levels were shown between the two groups (p<0.05), with higher mean sST2 levels in patients with rehospitalization and mortality (20.22±6.1) [26]. As in acute heart failure patients, prognostic information in chronic heart failure can be obtained from initial sST2 levels and sST2 patterns over time [27]. Several studies affirm the predictive value of sST2 in HFrEF patients, with sST2 predicting short-term mortality (2 weeks) or long-term death (>2.5 years), rehospitalization, and worsening heart failure [27,28]. In addition to prognosis, sST2 measurements identify heart failure patients who may benefit from specific management, such as patients with high sST2 (>35 ng/mL) and low beta-blocker doses (<50 mg doses) having an OR of 6.77 for cardiovascular events within 10 months compared to patients with low sST2 (<35 ng/mL) and higher beta-blocker doses [29]. In the recent PARADIGM-HF clinical trial, a decrease in sST2 within 1 month was an independent predictor of future cardiovascular events, and valsartan/sacubitril reduced sST2 more than enalapril [30].

Similar to natriuretic peptides and troponin, and unlike almost all other biomarkers listed by Dr. Braunwald in 2008, sST2 meets 2 fundamental criteria for clinically useful biomarkers: 1) accurate and repeatable measurements available at reasonable costs, with future automation tests likely providing further impetus for diffusion; and 2) providing additional information for careful clinical assessment, particularly for risk stratification [28,31,32]. However, knowledge about sST2 and its testing methodology remains incomplete, from the regulatory mechanisms of sST2 production in healthy and sick subjects to the binding sites of sST2 tests. More importantly, from a clinical perspective, researchers are still trying to understand when and how to measure sST2 levels and how to translate this information into better patient care.

In 2016, a meta-analysis of 7 studies involving 6372 patients reported that unadjusted sST2 levels can predict all-cause cardiovascular mortality in heart failure [33]. High sST2 concentrations significantly increased mortality risk in the first year, even after adjusting for several confounding factors [33]. Analysis of 4268 individuals from 11 cohorts found that the risk of all-cause mortality, cardiovascular death, and heart failure hospitalization increased exponentially with sST2 levels, with 28 ng/mL identified as the best cut-off point on the ROC curve for these outcomes [20]. The prognostic value of sST2 is independent of NT-proBNP, hs-TnT, and other variables with prognostic significance [20]. In this study, age, gender, BMI, and comorbidities did not differ significantly between heart failure patients with and without rehospitalization and mortality.

In acute heart failure, sST2 measurements can be used to assess discharge plans for hospitalized patients. Patients with non-decreasing sST2 levels can be considered high-risk and may indicate the need for longer hospital stays, increased heart failure medication titration, and regular follow-up after discharge to monitor for pulmonary congestion. In chronic conditions, sST2 values can predict remodeling in heart failure patients and recommend appropriate management. sST2 measurement is an important tool for risk stratification, either alone or accompanied by natriuretic peptides and troponin [34].

This study showed that rehospitalization and mortality significantly occurred in patients with sST2 levels ≥19.4 ng/dL after 22 months of observation. Chen et al.'s study (2023) also reported similar results, with Kaplan Meier analysis showing that at sST2 levels >16.8 ng/dL, a significantly higher MACE occurred after 1 year of observation. MACE included mortality, myocardial infarction, stroke, heart failure readmission, and revascularization readmission. Hou et al.'s study (2020) also reported higher mortality in heart failure patients with implantable cardioverter defibrillators (ICD) after 720 days of observation. These findings support the role of sST2 as a risk factor for rehospitalization and mortality in various cardiovascular disease spectrums, including heart failure [35].

ST2 is part of the IL-1 receptor consisting of two isoform forms: membrane-bound (ST2L) and soluble isoform (sST2). ST2 increases significantly due to cardiomyocyte stimulation by mechanical stretch. ST2 activity in the cardiovascular system is facilitated by the ligand function of IL-33 [12,13]. IL-33 is expressed under tissue damage conditions by stromal cells, which then signal local immune cells [14]. This inflammatory response occurs through a heterodimer receptor complex consisting of ST2L and IL-1. Inflammation results in the activation of the IL-33/ST2 axis. This activity creates positive feedback that then increases the production of pro-inflammatory cytokines [15]. However, in cardiovascular conditions, the IL-33/ST2 pathway is cardioprotective. Treatment with exogenous IL-33 reduces hypertrophy. Meanwhile, deletion of the ST2 gene eliminates IL-33's anti-fibrotic and anti-hypertrophic effects [13]. sST2 is a soluble form of the ST2L fragment, acting as a receptor that binds and inhibits IL-33 effects. sST2 has long been known as a marker of inflammatory response activation and hemodynamic overload. Therefore, increased circulating sST2 levels disrupt the effects of IL-33 [12]. This underlies the potential of sST2 as a marker for predicting rehospitalization and mortality.

This study further evaluated the prognostic role of sST2 for rehospitalization and mortality within 22 months in a cohort of heart failure patients with low left ventricular systolic function through multivariate analysis. Our study results showed that high sST2 is an independent factor for rehospitalization and mortality within 22 months. Li et al.'s study (2021) reported that high sST2 levels are independent factors for MACE and mortality in CAD patients with or without T2DM after controlling for age, gender, and other confounding variables [36]. Other studies have also confirmed these findings in various heart diseases other than heart failure. In the TIMI-ENTIRE study, increased sST2 levels in 810 STEMI patients correlated with mortality and onset or worsening of heart failure within 30 days post-STEMI [37]. The prognostic value of sST2 has also been evaluated over more extended periods. Kim et al.'s study (2021) showed that increased sST2 was associated with increased MACE in stable CAD patients after 2 years of observation [38]. Dudek et al. (2021) also reported that increased sST2 alone or combined with other markers, such as cardiac troponin and natriuretic peptides, could predict heart failure incidence, mortality, and heart failure hospitalization [39].

The underlying mechanism of sST2's association with MACE in cardiovascular disease patients is further linked to the hypothesis of inflammatory processes in atherosclerosis formation. IL-33 was initially reported as an inflammatory modulator balancing the role of CD4+ T helper type-2 immunity [12]. IL-33's effect on foam cells shows protective functions [40]. The presence of sST2, particularly in arterial endothelial cells, is involved in atherosclerosis progression [41]. These findings suggest that sST2 can serve as a marker of massive plaque and MACE predictor. IL-33 and sST2 are

abundantly expressed in adipose tissue, where IL-33 levels correlate with high BMI, indicating a relationship between IL-33 and obesity and diabetes. However, IL-33's functional role spans infection, inflammation, and metabolic diseases, which can indirectly explain sST2's significant role as a MACE predictor in patients with or without T2DM [36].

This study was a cohort of 80 heart failure patients at a single health center, namely RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar. This study was conducted at only one center. Additionally, this study did not include the gold standard biomarkers for heart failure patients, such as NT-proBNP, to compare with sST2, a new biomarker for heart failure patients.

CONCLUSSION

High sST2 levels (>19.4 ng/mL) are a risk factor for rehospitalization and mortality in chronic heart failure patients with reduced ejection fraction.

Ethical Clearance

Research Ethics Committee Unit, Faculty of Medicine, Udayana University No. 1142/UN14.2.2VII.14/LT/2023

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Declarations

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