Original Article

Establishing the Optimal sST2 Cut-off for Predicting 5-Year All-Cause Mortality in Hospitalized Patients with Heart Failure with Reduced Ejection Fraction

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Highlights

- Higher baseline sST2 was independently associated with 5-year all-cause mortality in the reported multivariable model.
- A cohort-derived admission sST2 cutoff of 27.1 ng/mL showed high discrimination for 5-year mortality.
- The proposed cutoff requires independent validation before routine clinical application.

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ABSTRACT

Background: Hospitalized patients with chronic heart failure (HF) may experience adverse left ventricular remodeling, systemic and pulmonary congestion, and changes in sST2. Thus, they may require an sST2 cutoff for predicting long-term mortality different from that of patients with stable chronic HF. This study aimed to determine the optimal cutoff value of sST2 predictive of long-term mortality in patients with heart failure with reduced ejection fraction (HFrEF).

Methods: This prospective cohort study included 162 hospitalized patients with HFrEF. Plasma sST2 levels were analyzed. Statistical analyses were performed to evaluate the predictive utility of sST2 levels for all-cause mortality and the optimal cutoff value.

Results: During follow-up, 99 of 162 patients (61.1%) died. The median admission sST2 concentration was 35.3 [19.1-57.3] ng/mL. The cohort-derived cutoff was >27.1 ng/mL (sensitivity, 89.9%; specificity, 84.1%). Patients above this threshold had a higher hazard of 5-year mortality than those with sST2 <=27.1 ng/mL (HR, 6.27; 95% CI, 3.02-13.05; P<0.001). In the reported multivariable model, each 1-unit increase in ln(sST2) was also associated with mortality (adjusted HR, 7.52; 95% CI, 4.07-13.90; P<0.001).

Conclusion: In hospitalized patients with HFrEF, sST2 levels were an independent and associated with 5-year all-cause mortality, and the optimal sST2 cutoff for predicting long-term survival is 27.1 ng/mL.

Keywords: Heart Failure; Soluble Suppression of Tumorigenesis 2 (sST2); Prognosis; Heart Failure with Reduced Ejection Fraction (HFrEF)

Introduction

Heart failure (HF) remains one of the major contributors to cardiovascular morbidity and mortality worldwide. The global burden of HF continues to rise as populations age and survival after cardiovascular diseases improves. In Southeast Asia, including Vietnam, the prevalence of HF has increased steadily, resulting in substantial health care utilization and repeated hospital admissions despite continuous advances in medical therapy. Consequently, identifying patients at high risk for adverse outcomes has become an important component of contemporary HF management.[1] The International Congestive Heart Failure study reported significantly distinct 1-year mortality outcomes for HF, with intermediate outcomes in Southeast Asia.[2] In Vietnam, HF is becoming increasingly prevalent in the population owing to the increase in life expectancy and high frequency of risk factors for HF. Based on a global prevalence of 2% to 3%, approximately 1.9 to 2.9 million people in Vietnam have HF.[3] Admissions for HF account for 15% of hospitalizations at the Hanoi Heart Hospital.[4] Although robust advances in the management of HF have significantly improved its outcomes, the mortality and hospitalization rates remain high.[5] The 1-, 5-, and 10-year mortality rates of patients with chronic HF are still high, up to 20% to 30%, over 50%, and 70% to 80%, respectively.[6] Accordingly, risk stratification of patients with HF is critical because it may help identify patients who require careful monitoring and intensive treatment.

Soluble suppression of tumorigenesis 2 (sST2) has emerged as an important biomarker reflecting myocardial stress, inflammation, and adverse cardiac remodeling in patients with HF.[7] Experimental and clinical evidence indicates that elevated circulating sST2 concentrations are associated with progressive myocardial fibrosis and worse clinical outcomes.[8]

Since the initial report by Weinberg et al,[10] numerous investigations have demonstrated that increased sST2 levels independently predict mortality and heart transplantation,[9] even after adjustment for natriuretic peptides. Compared with conventional biomarkers, sST2 exhibits relatively low biological variability and is minimally influenced by demographic characteristics or renal function, supporting its value for long-term prognostic assessment.[11]

Accurate risk stratification is essential for optimizing therapeutic decisions and follow-up strategies in patients with HF. Although N-terminal pro–B-type natriuretic peptide (NT-proBNP) remains an established prognostic biomarker, its interpretation may be affected by factors such as age, sex, body mass index (BMI), and renal function.[12] Because both NT-proBNP and sST2 are released in response to myocardial stress, the incremental prognostic contribution of sST2 has been extensively investigated.[13] Most available evidence, however, has been derived from ambulatory patients with stable chronic HF. Hospitalized patients with HFrEF represent a distinct clinical population characterized by active congestion, heightened inflammatory activity, and ongoing ventricular remodeling, all of which may alter circulating sST2 concentrations and the threshold associated with adverse outcomes. Although previous studies have suggested prognostic cutoff values ranging from approximately 28 to 35 ng/mL, whether these thresholds are applicable to hospitalized patients with HFrEF remains uncertain. Therefore, the present study aimed to determine the optimal sST2 cutoff for predicting long-term mortality in hospitalized patients with HFrEF.[11]

Methods

Study Design and Population

This single-center prospective cohort study enrolled consecutive patients hospitalized with HFrEF at the Cho Ray Hospital between May and December 2016. Clinical characteristics, laboratory findings, echocardiographic parameters, and biomarker measurements were obtained during the index hospitalization. Blood samples for sST2 and NT-proBNP assays were collected at admission before outcome assessment. Participants were subsequently for up to 60 months, and all-cause mortality was recorded as the primary endpoint. Inclusion criteria were HF with New York Heart Association (NYHA) functional class II–IV and left ventricular ejection fraction (LVEF) of equal to or less than 40%. The diagnosis of HF was based on typical symptoms

and clinical findings supported by appropriate investigations, such as NT-proBNP measurement and Doppler echocardiography, as recommended by the current guidelines of the American College of Cardiology/American Heart Association and the European Society of Cardiology. Eligible patients had symptoms and signs of HF, NYHA functional class II-IV, and an LVEF <=40%, supported by appropriate investigations including NT-proBNP measurement and Doppler echocardiography. Diagnosis and treatment were determined by the clinical team and were not influenced by study participation. Patients were excluded if they had acute infectious or inflammatory diseases, active malignancy, severe hepatic dysfunction, end-stage renal disease requiring dialysis, pregnancy, inability to provide informed consent, or insufficient follow-up information for ascertainment of the primary outcome.

The study was approved by the Ethics Committee of the University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam (454/DHYD-HD, December 30, 2015). Written informed consent was obtained from all participants prior to enrollment in the study, and the study adhered to the ethical standards of the Declaration of Helsinki. For patients unable to provide consent at the time of inclusion, written informed consent was obtained from each participant or, when the participant lacked decision-making capacity, from a legally authorized representative before enrollment.

Data Collection

Baseline evaluation included demographic information, medical history, physical examination findings, routine laboratory tests, electrocardiography, echocardiography, and biomarker assessment. Venous blood samples were processed immediately after collection according to standardized laboratory procedures before measurement of plasma sST2 levels. Standard transthoracic echocardiography was performed by an experienced cardiologist using routine clinical equipment. LV systolic function and chamber dimensions were assessed according to recommendations of the American Society of Echocardiography, with LVEF calculated using the modified Simpson biplane method.

NT-proBNP and sST2 Quantification

NT-proBNP and sST2 levels were measured in blood samples collected for routine biochemical parameters at admission. Levels of sST2 were measured using enzyme-linked immunosorbent assay with Presage ST2 sample set (Critical Diagnostics, CA, USA). NT-proBNP levels were measured using an immunofluorescence assay with Roche reagents on a Cobas 6000 analyzer at the biochemistry laboratory of Cho Ray Hospital, Southeast Vietnam.

Echocardiographic Measurements

All patients underwent a standard transthoracic echocardiographic examination performed by a single experienced cardiologist. This examination was performed using the available ultrasound equipment. LVEF was calculated using the Simpson rule from apical 4-chamber measurements.

Statistical Analysis

Categorical variables were expressed as counts (percentages), whereas continuous variables were expressed as mean (SD) or median (IQR). Data were compared using the t test, Kruskal–Wallis test, Fisher exact test, and $\chi 2$ test, as appropriate. The optimal cutoff value was determined using receiver operating characteristic (ROC) curve analysis and the Youden index (sensitivity + specificity − 1), which identifies the threshold providing the best balance between sensitivity and specificity. Two-group comparisons were performed using the Mann–Whitney U test. Linear regression was applied to evaluate the association between sST2 levels and other variables. Logistic regression was drawn upon to test the associations between laboratory parameters and clinical diagnoses in each sST2 group, while adjusting for covariates. ROC curves were generated to quantify the ability of sST2 levels to predict outcomes. Cox regression was used to identify predictors of mortality. Multivariable analysis that included all significant candidate variables (ie, those with P≤.1) in the univariable analysis was carried out to identify independent predictors of survival. NT-proBNP and sST2 values were log-transformed before

inclusion in regression models because of their skewed distribution. The study cohort was divided into 2 groups according to survival status, and trends in sST2 levels were compared between survivors and nonsurvivors using repeated-measures analysis of variance. The 5-year mortality rate was estimated using Kaplan–Meier survival analysis. All statistical analyses were performed using Stata/IC version 15.0 (StataCorp LLC; College Station, TX) for Windows and MedCalc 20.166 (MedCalc Software Ltd). Statistical significance was set at a P value less than .05.

Results

Baseline Patient Characteristics

The present study included 162 patients with HFrEF. The median follow-up duration was 60 months. A total of 99 deaths occurred, and the 12- and 60-month mortality rates were 33.3% and 61.1%, respectively. Patient characteristics are reported in (Table 1). There were no significant between-group differences in basic characteristics. Among the comorbidities, only diabetes and hypertension were associated with increased mortality. NYHA functional class (P<.001), number of comorbidities (P=.032), heart rate (P<.001), systolic blood pressure (P=.024), echocardiographic measures (P<.001 for all), and estimated glomerular filtration rate (eGFR) (P=.013) were significantly different between the 2 groups. Moreover, sST2 and NT-proBNP levels were also significantly higher in the nonsurvivor group. Regarding medical therapy, the proportion of patients taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, or loop diuretics was comparable between the 2 groups. There were also no differences in the median baseline doses of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, or loop diuretics (data not shown).

The nonsurvivor group tended to have more severe HF, as evidenced by a higher proportion of patients with T3 sounds, NYHA functional classes III and IV, lower LVEF, and greater left atrial diameter, LV end-systolic volume, and LV end-diastolic volume. The nonsurvivor group was also more likely to have a history of systemic arterial hypertension or diabetes mellitus. Consistent with more advanced HF, patients in the nonsurvivor group had higher median NT-proBNP and sST2 levels.

Levels of sST2 were not significantly correlated with age, BMI, systolic or diastolic blood pressure, hemoglobin levels, or eGFR, whereas they showed a weak positive correlation with the number of comorbidities (r=0.26; P=.0008). Nonetheless, sST2 levels were significantly correlated with heart rate (r=0.46; P<.0001) and NT-proBNP levels (r=0.37; P<.0001) (Table 2). The logarithm of sST2 was moderately correlated with heart rate and the logarithm of NT-proBNP. There was a weak correlation between sST2 levels and clinical factors, except for heart rate and NT-proBNP levels. In addition, sST2 levels did not significantly differ between men and women (33.2 ng/mL vs 37.6 ng/mL; P = .40), whereas they significantly differed according to NYHA functional class (NYHA II: 16.8 ng/mL vs NYHA III: 37.1 ng/mL and NYHA IV: 146.3 ng/mL; P = .0001) (Figure 1).

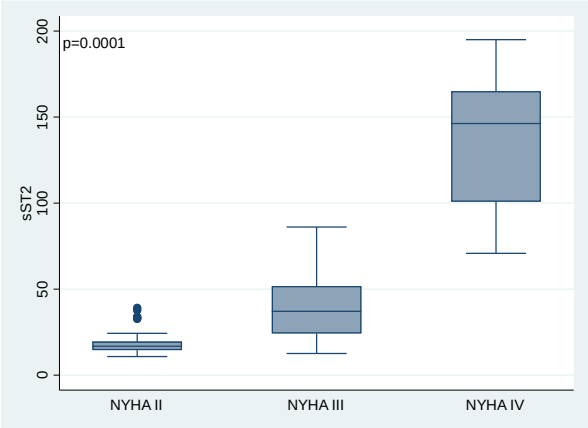

Figure 1. Distribution of sST2 concentrations across New York Heart Association (NYHA) functional classes

Log-transformed sST2 was positively correlated with left atrial volume index (r=0.34), left ventricular end-systolic volume index (r=0.63), and left ventricular end-diastolic volume index (r=0.61), and inversely correlated with LVEF (r=-0.58; all P<0.0001). There was a good correlation between sST2 levels and echocardiographic measures (Table 3).

Univariable and multivariable Cox regression results are shown in Table 4. ln(sST2) remained associated with 5-year all-cause mortality in the

reported multivariable model (adjusted HR, 7.52; 95% CI, 4.07-13.90; P<0.001). Heart rate and ln(NT-proBNP) also remained significant, while the estimate for left atrial volume index was reported at the conventional significance boundary. These findings demonstrate an adjusted association but do not, by themselves, establish incremental discrimination or calibration beyond a clinical model. Additionally, NT-proBNP levels also remained a significant predictor of all-cause mortality after adjusting for heart rate and left atrial diameter in the multivariable analysis (Table 4).

The optimal cutoff value of sST2 for predicting all-cause mortality was 27.1 ng/mL. This threshold yielded a sensitivity of 89.9% and a specificity of 84.1% for predicting 5-year mortality. Patients with baseline sST2 levels above this threshold had a significantly greater risk of death during the 5-year follow-up than those with lower levels (hazard ratio, 6.27; 95% confidence interval, 3.02 to 13.05; P<.001). Kaplan-Meier analysis further demonstrated clear separation of survival curves between the 2 groups (Figure 2 and Table 5).

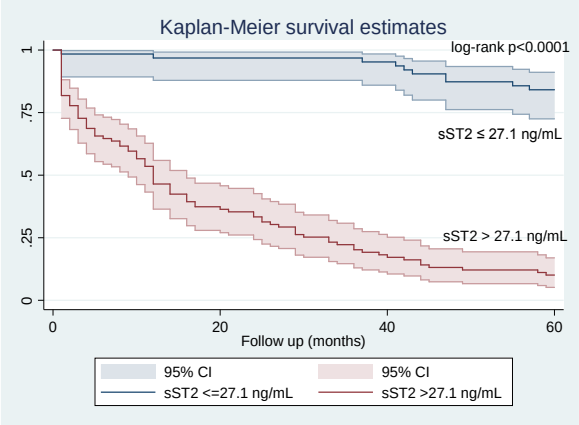

Figure 2. Kaplan-Meier survival curves for 5-year all-cause mortality according to admission sST2 <=27.1 versus >27.1 ng/mL

Table 1. Baseline clinicodemographic patient characteristics

Variables	All (n=162)	Survivors (n=63)	Non-survivors (n=99)	p
Age, y	66.1 +/- 14.7	65.4 ± 15.9	66.6 ± 14	0.60
Sex (male)	93 (57.4)	38 (60.3)	55 (55.6)	0.55
NYHA				<0.001
Class II	41 (25.3)	31 (49.2)	10 (10.1)	
Class III	91 (56.2)	31 (49.2)	60 (60.6)	
Class IV	30 (18.5)	1 (1.6)	29 (29.3)	
Ischemic heart failure	119 (73.5)	45 (71.4)	74 (74.8)	0.64
Medical history				
Diabetes	68 (42.0)	18 (28.6)	50 (50.5)	0.006
Hypertension	87 (53.7)	27 (42.9)	60 (60.6)	0.027
Hypercholesterolemia	37 (22.8)	13 (20.6)	24 (24.2)	0.59
Atrial fibrillation	26 (16.1)	12 (19.1)	14 (14.1)	0.41
Previous MI	23 (14.2)	8 (12.7)	15 (15.2)	0.66
Anemia	96 (59.3)	36 (57.1)	60 (60.6)	0.66
CKD	112 (69.1)	38 (60.3)	74 (74.8)	0.053
Smoking	12 (7.41)	5 (7.9)	7 (7.07)	0.84
Physical examination findings				
BMI, kg/m^2	21.5 +/- 3.5	22.0 ± 3.5	21.2 ± 3.4	0.15
Heart rate bpm	85.8 +/- 15.8	79.1 ± 14.7	90.0 ± 15.0	<0.001
Systolic BP, mmHg	118.0 ± 20.8	122.6 ± 23.6	115.1 ± 18.3	0.024
Diastolic BP, mmHg	72.3 +/- 10.7	73.3 ± 11.1	71.6 ± 10.4	0.32
Rales	38 (23.5)	11 (17.5)	27 (27.3)	0.15
Edema	53 (32.7)	16 (25.4)	37 (37.4)	0.11
T3	40 (24.7)	8 (12.7)	32 (32.3)	0.005
Echocardiography				
LVEF, %	32.1 +/- 6.6	36.1 ± 3.7	29.6 ± 6.8	<0.001
LAVi, ml/m²	28.3 +/- 5.1	26.0 ± 4.0	29.7 ± 5.2	<0.001
LVEDVi, mL/m2	126.5 +/- 46.4	99.0 ± 24.0	144.0 ± 48.7	<0.001
LVESVi, mL/m2	88.6 +/- 41.6	63.9 ± 19.9	104.3 ± 44.2	<0.001
Laboratory results				
Hgb, g/L	120.6 +/- 23.2	122.1 ± 19.7	119.7 ± 25.2	0.52
eGFR, mL/min/1.73 m^2	54.0 +/- 18.0	58.4 ± 17.8	51.2 ± 17.6	0.013
NT-proBNP, pg/mL	2518 [1140-5300]	1324 (1079-3557)	4084 (1288-8746)	0.0001
sST2, ng/mL	35.3 (19.1-57.3)	18.1 (15.2-23.1)	51.8 (35.3-96.4)	<0.001
Baseline medications				
ACEi	90 (55.6)	34 (54.0)	56 (56.6)	0.67
ARB	54 (33.3)	26 (41.3)	28 (28.3)	0.19

MRA	112 (69.1)	43 (68.3)	69 (69.7)	0.85
BBs	38 (23.5)	18 (28.6)	20 (20.2)	0.09
Loop diuretics	105 (64.8)	38 (60.3)	67 (67.7)	0.34

Values are n (%), mean +/- SD, or median [interquartile range]. Corrected overall continuous values were reconciled from the two vital-status groups and require confirmation against the source dataset. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LAVi, left atrial volume index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; sST2, soluble suppression of tumorigenicity-2.

Table 2. Correlation of ln(sST2) with baseline clinical factors

		Age	BMI	HR	Sys BP	Dia BP	Hgb	eGFR	NT-proBNP
sST2	r	-0.02	-0.07	0.46	-0.14	-0.05	-0.11	-0.05	0.37
	p	0.84	0.38	<0.0001	0.07	0.56	0.16	0.56	<0.0001

*Using Log(sST2) for analysis; Abbreviations: BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; HR, heart rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association

Table 3. Correlation of ln(sST2) with echocardiographic measures

	LVEF		LAVi		LVESVi		LVEDVi	
sST2	r	p	r	p	r	p	r	p
	-0.58	<0.0001	0.34	<0.0001	0.63	<0.0001	0.61	<0.0001

Abbreviations: LAVi, left atrial volume; LVEDVi, left ventricular end-diastolic volume; LVESVi, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; sST2, soluble suppression of tumorigenesis-2

Table 4. Cox regression analysis of predictors of 5-year all-cause mortality

Variable	All-cause mortality				
	Univariate analysis, HR [95% CI]	p	AUC [95% CI]	Multivariate analysis, HR [95% CI]	p
Age, per 1 year	1.00 [0.99-1.02]	0.56	0.51 [0.42-0.61]	-	-
Sex	1.22 [0.82-1.81]	0.33	0.52 [0.45-0.60]	-	-
Diabetes	2.10 [1.41-3.13]	<0.001	0.61 [0.53-0.68]	1.42 [0.72-2.79]	0.31
HTN	1.70 [1.14-2.55]	0.01	0.59 [0.51-0.67]	1.30 [0.75-2.25]	0.36
Anemia	1.17 [0.78-1.75]	0.45	0.52 [0.44-0.60]	-	
Comorbidity	1.41 [1.17-1.70]	<0.001	0.63 [0.54-0.71]	0.95 [0.67-1.35]	0.77
NYHA class, per 1-class increase	5.04 [3.45-7.36]	<0.001	0.76 [0.70-0.83]	0.70 [0.37-1.32]	0.27
Heart rate, per 1 beat/min	1.04 [1.03-1.05]	<0.001	0.72 [0.64-0.80]	1.02 [1.01-1.04]	0.005
Hemoglobin, per 1 g/L	0.99 [0.98-1.00]	0.10	0.46 [0.37-0.54]	-	-
eGFR, per 1 mL/min/1.73 m2	0.98 [0.97-1.00]	0.01	0.39 [0.30-0.48]	-	-
LVEF, per 1% increase	0.91 [0.88-0.93]	<0.001	0.21 [0.14-0.27]	1.00 [0.94-1.06]	0.99
LAVi, per 1 mL/m2	1.09 [1.06-1.12]	<0.001	0.71 [0.63-0.80]	1.08 [1.02-1.13]	0.05
LVEDVi, per 1 mL/m2	1.01 [1.01-1.02]	<0.001	0.81 [0.75-0.88]	1.00 [0.99-1.01]	0.73
ln(NT-proBNP), per 1-unit increase	1.59 [1.32-1.91]	<0.001	0.68 [0.60-0.76]	1.23 [1.01-1.50]	0.038
ln(sST2), per 1-unit increase	6.00 [4.45-8.10]	<0.001	0.93 [0.89-0.97]	7.52 [4.07-13.9]	<0.001

Abbreviations: eGFR, estimated glomerular filtration rate; Hgb, hemoglobin; HTN, hypertension; LAVi, left atrial volume; LVEDVi, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; AUC, area under the curve; HR, hazard ratio; CI, confidence interval

Table 5. The cutoff value of NT-proBNP for predicting all-cause mortality

	AUC [95% CI]	p	Cutoff	Youden index J	Sensitivity (%), [95% CI]	Specificity (%), [95% CI]	LR+	LR-
sST2	0.93 [0.89-0.97]	<0.0001	>27.1 ng/mL	0.74	89.9 [82.2-95.0]	84.1 [72.7-92.1]	5.66	0.12

Abbreviations: **NT-proBNP**, N-terminal pro-B-type natriuretic peptide; **AUC**, area under the curve; **CI**, confidence interval**; LR+**, positive likelihood ratio; **LR-**, negative likelihood ratio; **sST2**, soluble suppression of tumorigenesis-2

Discussion

The principal findings of the present study are 3-fold. First, circulating sST2 levels showed no significant association with age, BMI, hemoglobin concentration, or renal function, whereas significant correlations were observed with heart rate, NT-proBNP levels, and indices of cardiac remodeling derived from echocardiography. Second, baseline sST2 levels independently predicted 5-year all-cause mortality after adjustment for conventional prognostic variables. Finally, >27.1 ng/mL was the cohort-derived cutoff that maximized the Youden index. This threshold should be interpreted as an exploratory derivation result rather than a universally applicable clinical cutoff. Because both NT-proBNP and sST2 levels displayed skewed distributions, logarithmic transformation was performed before regression analyses.

Release of natriuretic peptides is stimulated by increased ventricular wall stress, making NT-proBNP a cornerstone biomarker for the diagnosis and prognostic evaluation of HF.[14] Nevertheless, circulating NT-proBNP concentrations are influenced by multiple patient characteristics, including age, adiposity, renal function, and ongoing medical therapy, which may complicate risk interpretation in routine clinical practice. In contrast, sST2 levels appear to be less susceptible to these confounding factors and more directly reflect myocardial fibrosis, inflammatory activation, and adverse ventricular remodeling, thereby providing complementary prognostic information.[15] Hence, sST2 levels provide essential prognostic information; an increase in sST2 levels predicts all-cause mortality independent of age, sex, BMI, or eGFR, and may offer higher accuracy in predicting mortality in patients with HF.

The correlations between sST2 and left atrial volume, left ventricular volumes, and LVEF support an association with structural remodeling.[16,17] Patients with larger ventricular volumes and lower EF tended to have higher circulating sST2 levels, suggesting that progressive ventricular dilation and systolic dysfunction are accompanied by enhanced inflammatory and fibrotic activity.[18,19] The positive correlation with NT-proBNP further suggests that the two biomarkers reflect overlapping but not identical aspects of HF severity.[20,21] Structural changes include enlargement of the ventricular chambers, especially the LV, which can be easily identified using echocardiography or other imaging modalities.[16] As a result, sST2 levels are correlated with NT-proBNP levels and echocardiographic measures. The biological relevance of sST2 extends beyond its role as a circulating biomarker. By functioning as a soluble decoy receptor for interleukin-33, sST2 attenuates the protective IL-33/ST2L signaling pathway that normally limits myocardial hypertrophy and fibrosis. Consequently, elevated sST2 levels reflect persistent myocardial injury and maladaptive remodeling, providing a plausible mechanistic explanation for the strong association between increased sST2 levels and adverse long-term outcomes observed in the present study.

In addition to sST2 levels, increasing evidence highlights the prognostic importance of systemic inflammation in HF progression. Inflammatory biomarkers combined with nutritional indices have been shown to provide incremental prognostic value. For instance, the C-reactive protein–to–albumin ratio, prognostic nutritional index, and systemic immune-inflammation index have all been associated with long-term mortality in HFrEF populations, particularly in patients with implantable cardiac devices. These findings suggest that integrating inflammatory and nutritional markers may improve risk stratification beyond single biomarkers.[16,17]

Although several prognostic NT-proBNP thresholds have been proposed, no universally accepted cutoff applicable across different HF populations and clinical settings has been established.[22,23] In the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial, an NT-proBNP cutoff of greater than 1000 pg/mL was also found to be disadvantageous because patients needed repeat NT-proBNP quantification. Further, variations in NT-proBNP based on age, BMI, and renal function limit its prognostic role.[24] Previous investigations have proposed different prognostic thresholds for sST2 depending on the study population and clinical setting. A value near 35 ng/mL has often been used in chronic ambulatory HF, while the meta-analysis by Aimo et al. reported substantial heterogeneity across studies,[11] whereas Felker et al.evaluated sST2 in

an ambulatory HF cohort; that study was not a meta-analysis.[25] In our cohort of hospitalized patients with HFrEF, the optimal cutoff was 27.1 ng/mL, closely approximating the pooled estimate while remaining slightly below the commonly used clinical threshold. This difference may be related to differences in patient characteristics, disease severity, and biomarker profiles between hospitalized patients with HFrEF and stable ambulatory HF populations. These findings suggest that population-specific sST2 thresholds may improve risk stratification in clinical practice, requiring refinement according to patient characteristics and disease acuity rather than applying a single universal threshold. Our findings further indicate that progressively higher sST2 levels were associated with an increasing risk of long-term mortality, suggesting a dose-response relationship between biomarker elevation and adverse clinical outcomes. From a therapeutic perspective, anti-inflammatory strategies may play an important role in modifying disease progression. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated significant clinical benefits in HF, partly through anti-inflammatory and antifibrotic mechanisms. Recent meta-analyses have also shown improvements in right ventricular function with SGLT2 inhibitor therapy, further supporting the interplay between inflammation and cardiac remodeling.

Despite the fact that NT-proBNP remains the recommended biomarker for the initial evaluation of suspected HF, its prognostic utility is often strengthened through serial measurements during follow-up. Likewise, accumulating evidence suggests that repeated assessment of sST2 levels may better capture changes in disease activity and therapeutic response than a single baseline measurement. Future prospective studies should determine whether serial sST2-guided management can further improve clinical outcomes in patients with HFrEF. Given the complexity of HF pathophysiology, future risk stratification models may benefit from integrating multiple biomarkers, clinical variables, and inflammatory indices. Artificial intelligence and machine learning approaches offer the potential to identify complex nonlinear relationships and interactions among predictors, thereby improving prognostic accuracy. Such approaches have already shown promise in other cardiovascular settings and may be adapted to optimize risk prediction in HFrEF populations.

Limitations

Several limitations should be acknowledged. First, this was a relatively small single-center cohort, limiting precision and external validity. Second, the 27.1 ng/mL cutoff was derived and evaluated in the same sample, creating optimism in the estimated AUC, sensitivity, specificity, and hazard ratio; no internal resampling or external validation was reported. Third, the published report does not fully document missing data, loss to follow-up, censoring, covariate-selection procedures, functional-form assessment, or proportional-hazards testing. Fourth, the multivariable model included several correlated markers of HF severity and remodeling, so residual confounding and model instability are possible. Fifth, treatment reflected practice during the enrollment period and differs from contemporary guideline-directed therapy. Sixth, data on implantable devices, right ventricular function, valvular regurgitation, and several established risk-score predictors were unavailable. Finally, the study assessed a single admission sST2 measurement; serial measurements and changes during hospitalization were not evaluated in this analysis.

Conclusions

In this single-center cohort of hospitalized Vietnamese patients with HFrEF, higher admission sST2 was independently associated with 5-year all-cause mortality in the reported multivariable model. A cohort-derived threshold of 27.1 ng/mL showed high apparent discrimination, but it should be considered exploratory and requires independent validation before routine clinical application.

Data Availability Statement

The authors should ensure that the deposited dataset, data dictionary, and analysis code correspond to the corrected tables and model results. Research data supporting this publication are available from the Mendeley Data repository at https://data.mendeley.com/datasets/b2stjtk6f2/1.

Author Contributions

KDN, SVH, and DTB contributed to conceptualization, data curation, formal analysis, investigation, methodology, resources, supervision, validation, and visualization. KDN contributed to project administration and software. KDN, SVH, DTB, TML, and LMBT contributed to writing–original draft and writing–review and editing.

Use of Artificial Intelligence

No artificial intelligence (AI) tools or AI-assisted technologies were used in the preparation, writing, analysis, or revision of this manuscript.

Declarations:

Ethical Approval

The study was approved by the Ethics Committee of the University of Medicine and Pharmacy in Ho Chi Minh City, Vietnam (No. 454/DHYD-HD; December 30, 2015). Written informed consent was obtained from each participant or, when appropriate, from a legally authorized representative after explanation of the study procedures.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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