Increased Ratio of sST2/LVMI Predicted Cardiovascular Mortality and Heart Failure Rehospitalization in Heart Failure with Reduced Ejection Fraction Patients: A Prospective Cohort Study

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Abstract

Background: Inflammation is considered to be one of the principal triggering mechanisms for Left ventricular (LV) fibroblast and remodeling in heart failure(HF), which are related to adverse events in HF failure patients. Soluble ST2 (sST2), a member of the interleukin-1 receptor family, is assumed to play a significant role in the inflammatory response of fibroblasts. The present study aimed to investigate the prognostic value of sST2/ left ventricular mass index (LVMI), a parameter of the pre-fibrotic inflammatory phase of heart failure in comparative to remodeling, in the heart failure with reduced ejection fraction (HFrEF).

Methods: The present study was a cohort study. A total of 45 consecutive patients with suspected HFrEF from 1/9/2015 to 31/12/2016 were prospectively enrolled. The target-independent variable was the ratio of sST2/LVMI measured at baseline. The primary endpoint was the composite endpoint of cardiovascular-cause mortality or heart failure readmission. The prognostic impact of the ratio of sST2/LVMI was evaluated by multivariable Cox proportional-hazards regression model.

Results: 45 patients were enrolled, the average age was 48±14 years old, and about 20% of them were male. Patients were followed for 9 months, during which the primary outcome occurred in 15 patients. By Kaplan–Meier analysis, patients with high ratio of the ratio of sST2/LVMI ≥ 0.39 had shorter event-free survival than the middle (ratio of sST2/LVMI between 0.39 and 0.24) and low ratio of sST2/LVMI (ratio of sST2/LVMI < 0.24) patients (log-rank, P = 0.022). Results of fully-adjusted multivariable Cox regression analysis showed the ratio of sST2/LVMI was positively associated with the composite outcome of HFrEF patients after adjusting confounders hazard ratio (HR) 1.64, 95% CI (1.06, 2.54). By subgroup analysis, a stronger association was found in patients whose ages between 40 and 55 years old, systolic blood pressure 115 or≥129mmHg, diastolic blood pressure< 74 mmHg, hematocrit < 44.5%, and interventricular septum ≥8.5mm.

Conclusion: In HFrEF patients, the relationship between the ratio of sST2/LVMI and the composite outcome is linear. A higher baseline ratio of sST2/LVMI levels is associated with increased risk of cardiovascular-cause mortality and HF rehospitalization in patients with HFrEF in the short term follow up.

Background

As a fatal and malignant disease, heart failure(HF) is becoming a growing epidemic that poses significant clinical and economic challenges[1]. Cardiac fibrosis characterized by excessive deposition of extracellular matrix (ECM) proteins and fibroblast accumulation is a fundamental component of the adverse myocardium structural remodeling in the failing heart, which also accelerates the progression to heart failure[2]. Inflammation provoked by biomechanical forces or increasing the deposition of collagen in the myocardial interstitium[3], which awaken cardiac fibroblasts, is considered the fundamental driving factor of cardiac fibrosis [4].

Soluble ST2 (sST2), a powerful independent predictor of mortality in HF patients[5], was reported to possess two different functions: inhibit inflammation[6] and promote pathological cardiac remodeling[4, 7] by acting as a nonfunctional decoy IL-33 receptor, rendering it unavailable to membrane-bound ST2 receptors limiting IL-33/ST2L signaling[8]. However, in the Framingham Heart Study, sST2 was not associated with either echocardiographic finding[9]. No correlation between sST2 levels and cardiac fibrosis was detected by LGE in CMRI in myocarditis patients[10]. The sST2 levels in the circulation were also reported to not correlate with cardiac fibrosis in HF patients[11].

We hypothesized that the primary cause of increased sST2 in patients with heart failure is the anti-inflammatory response induced by factors such as biomechanical forces, and the promoting pro-cardiac fibrotic effect of elevated sST2 is just an additional effect secondary to the inflammatory response. This study was designed to test the hypothesis that sST2/ left ventricular mass index (LVMI), a novel parameter of the pre-fibrotic inflammatory phase of heart failure, which eliminates of cardiac remodeling factors from the circulation sST2, is associated with the prognosis of HFrEF patients, in which the standard cardiac magnetic resonance imaging (CMRI) technique was used to assess LVMI.

Methods

Study population

We conducted a prospective cohort study at the Department of Cardiology, Zhongshan Hospital of Fudan University, Shanghai city, China, from September 1, 2015, to December 31, 2016. HFrEF patients were prospectively evaluated for inclusion in the study. In this study, HFrEF were prospectively evaluated for inclusion. HFrEF was diagnosed according to the current consensus statements of the American Heart Association[1] and Guidelines for the diagnosis and treatment of Heart failure in China 2018 [12]. All subjects were screened according to the inclusion and exclusion standards at baseline, detailed as follows.The inclusion criteria: (1) symptoms or signs of heart failure, (2) N-terminal prohormone of brain natriuretic peptide (NT-proBNP) > 125 ng/L,(3) left ventricular ejection fraction (LVEF) < 40%,and (4) New York Heart Association functional (NYHA) class ≥ II. Exclusion criteria included (1) congenital heart disease, (2)acute coronary syndrome in the last 30 days, (3) pericardial disease, (4) pacemaker or other conditions precluding patients from CMR, (5)severe anemia (hemoglobin < 7 g/dL), (6) chronic obstructive pulmonary disease GOLD 3 or 4, and (7)estimated glomerular filtration rate < 30 mL/min/1.73 m2. The study protocol conformed to the Declaration of Helsinki, and its subsequent amendments were approved by the local ethics committee of Zhongshan Hospital, Fudan University; all subjects signed informed consent.

Collection of clinical, echocardiographic, CMR imaging and biochemical variables

Covariates in the present study included general information, demographic, variables that can affect the ratio of sST2/LVMI or cardiac mortality, and HF hospitalization based on our clinical experiences and reported by previous literature.

Demographic data, clinical and biochemical variables including age, gender, BMI, diastolic blood pressure, systolic blood pressure, heart rate, NYHA functional class, medical history, and cardiovascular risk factors(smoking, hypertension, diabetes mellitus). Serum biomarkers of myocardial fibrosis (sST2, PICP, PINP, PIIINP), hemoglobin, white blood cells, NT-proBNP, sodium, creatinine, blood urea nitrogen, serum uric acid, albumin, total bilirubin, total cholesterol, high-density lipoprotein cholesterol, hypersensitive C-reactive protein, and hematocrit were collected. Same as our previous work, Enzyme-linked immunosorbent assay (ELISA) was performed to measure the concentration of sST2 using the Presage ST2 assay kit (CriticalDiagnostics, California, USA) [13].

Echocardiography was performed according to the recommendations of ASE guidelines[14]. All participants underwent transthoracic echocardiography using a Philips iE33 ultrasound machine (Philips Medical Systems, Eindhoven, The Netherlands) equipped with an S5–1 and X3–1 probe by board-certified physicians. Left atrial diameter (LAD), LVEF, left ventricular end-diastolic diameter (LVEDD), interventricular septal thickness (IVST) were analyzed.

As our previous work demonstrating[15], all subjects received clinical CMR scans by 2 dedicated CMR technologists with a 1.5-T CMR system (MAG-NETOM Area, Siemens Healthcare, Erlangen, Germany) with an 18-channel phased-array cardiovascular coil.CMR data analysis was performed using dedicated software Argus(Siemens Medical Solution, Erlangen, Germany) by an observer blinded to all clinical data. LVM was determined by tracing the epicardial and endocardial border of each slice at end-diastole, summing the myocardial volume of all slices, and multiplying by myocardial density (1.05 g/mL) [16].LVM was indexed to body surface area (LVMI). Other CMR imaging variables were measured using the methods described in our previous published paper[15].

Follow-up and outcomes

Patients were followed by telephone calls and ambulatory visits at 9-month intervals. The primary outcome was a combined end-point consisting of HF rehospitalization or cardiovascular-cause death. The follow-up time was calculated from discharge to the primary outcome or 9 months after discharge.Endpoints were adjudicated by all coauthor together.

Statistical analysis

Data are expressed as mean (standard deviation) (Gaussian distribution) or median (min, max)(Skewed distribution) for continuous variables and as numbers and percentages for categorical variables. $\chi 2$ (categorical variables), One-Way ANOVA test (normal distribution), or Kruskal-Whallis H test (skewed distribution) were used to detect the differences among different the ratio of sST2/LVMI (tertile). We used

univariate and multivariate Cox proportional-hazards regression models to test the link between the ratio of sST2/LVMI and primary outcome with three distinct models. Model 1 is the non-adjusted model with no covariates adjusted. Model 2 is the minimally-adjusted model with only sociodemographic variables adjusted. Model 3 is the fully-adjusted model. Because Cox proportional-hazards regression model-based methods are often suspected for their inability to deal with non-linear models, nonlinearity between the ratio of sST2/LVMI and primary outcome were addressed using Cox proportional hazards regression model with cubic spline functions and the smooth curve fitting (penalized spline method). If nonlinearity was detected, we first calculated the inflection point using the recursive algorithm and then constructed a two-piecewise Cox proportional-hazards regression model on both sides of the inflection point. The subgroup analyses were performed using a stratified Cox proportional-hazards regression model. For a continuous variable, we first converted it to a categorical variable according to the clinical cut point or tertile and then performed an interaction test. Tests for effect modification for those of subgroup indicators were followed by the likelihood of ration test.Log-rank tests for Kaplan–Meier survival curves were performed for testing different prognostic values in various levels of the ratio of sST2/LVMI.

Data were analyzed using the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www. empowerstats.com, X&Y Solutions, Inc, Boston, MA). All statistical tests were 2-sided, and a P-value < 0.05 was considered statistically significant.

Results

Baseline characteristics and outcomes of HFrEF patients

After baseline evaluation, a total of 45 patients were enrolled. After followed for 9 months, 15 patients reached the primary end-point(33.3%), of which 2 patients died, and 13 patients were rehospitalized due to worsening HF. No patient was lost to follow up. We showed baseline characteristics of these selected participants in Table 1, according to Tertile of the ratio of sST2/LVMI. In general, the average age of the 45 selected participants was 48 ± 14 years old, and about 20% of them were male. Participants with the highest group of the ratio of sST2/LVMI(Q3) had significantly higher blood sST2. They consisted of more patients with a medical history of ACEI or ARB than those of the other groups. The opposite patterns were observed in myocardium post-contrast T1 time, LVMI. There were no differences in other serum biomarkers, echocardiographic, and CMR measurements among different the ratio of sST2/LVMI groups (all p values > 0.05).

Table 1
Baseline characteristics of HFrEF patients

	sST2/LVMI			
	Q1 ＜0.24	**Q2 0.24–0.39**	**Q3 ≥ 0.39**	**P-value**
Age, mean (SD), years	49.20 (16.72)	44.33 (14.87)	50.20 (15.05)	0.548
Body mass index, mean (SD) (kg/m2)	25.12 (4.41)	26.17 (4.23)	25.89 (3.58)	0.791
Heart rate, mean (SD) (bpm)	90.67 (27.12)	86.47 (20.11)	82.47 (13.74)	0.570
Systolic blood pressure, mean (SD) (mmHg)	128.73 (15.90)	117.07 (14.07)	124.60 (23.59)	0.221
Diastolic blood pressure, mean(SD) (mmHg)	81.53 (10.37)	79.53 (12.87)	82.73 (15.89)	0.800
Gender				1.000
Female (n, %)	3 (20.00%)	3 (20.00%)	3 (20.00%)	
Male (n, %)	12 (80.00%)	12 (80.00%)	12 (80.00%)	
NYHA functional class				0.153
II (n, %)	9 (60.00%)	8 (53.33%)	4 (26.67%)	
III–IV (n, %)	6 (40.00%)	7 (46.67%)	11 (73.33%)	
Laboratory characteristics				
Sodium, mean (SD) (mmol/L)	141.27 (2.40)	140.93 (2.60)	140.67 (3.85)	0.862
Hemoglobin, mean (SD) (g/L)	145.13 (18.30)	140.53 (17.73)	143.60 (17.99)	0.777
White blood cells, mean (SD) (109/L)	6.89 (2.27)	6.00 (2.18)	6.82 (1.75)	0.436
Total cholesterol, mean (SD) (μmol/L)	4.01 (0.74)	3.79 (1.18)	3.93 (1.56)	0.887
High density lipoprotein cholesterol, mean (SD) (mmol/L)	0.93 (0.22)	0.84 (0.27)	1.01 (0.34)	0.252
Albumin, mean (SD) (g/L)	38.43 (3.06)	38.33 (5.19)	39.93 (3.08)	0.466
Creatinine, mean (SD) (μmol/L)	87.40 (16.86)	95.13 (22.96)	103.00 (30.70)	0.222
Blood urea nitrogen, mean (SD) (mmol/L)	6.45 (1.72)	6.54 (2.23)	7.17 (2.67)	0.635
Serum uric acid, mean (SD) (μmol/L)	482.47 (155.16)	534.87 (241.30)	521.20 (128.77)	0.716

	sST2/LVMI			
Total bilirubin, mean (SD) (μmol/L)	13.40 (4.86)	16.17 (7.24)	17.21 (10.70)	0.408
Hypersensitive C-reactive protein, median (Q1–Q3) (mg/L)	1.85 (0.40–64.80)	3.30 (0.00-51.50)	1.70 (0.40–37.80)	0.527
Hematocrit, mean (SD) (%)	43.90 (5.12)	43.19 (4.81)	43.52 (5.66)	0.932
NT-proBNP, median (Q1–Q3) (pg/mL)	2547.00 (798.10-10743.00)	1182.00 (389.40–5919.00)	2172.00 (132.90-11029.00)	0.320
Serum biomarkers of myocardial fibrosis				
PINP, median (Q1–Q3) (ng/mL)	45.20 (17.30-136.60)	39.70 (13.00-77.70)	33.20 (15.30–100.00)	0.342
PIIINP, mean (SD) (ng/mL)	7.24 (1.82)	7.18 (1.59)	7.13 (2.28)	0.989
PICP, mean (SD) (ng/mL)	293.79 (112.34)	308.21 (82.07)	310.64 (106.56)	0.886
sST2, mean (SD) (ng/mL)	21.61 (6.08)	30.62 (5.89)	50.28 (13.46)	< 0.001
Echocardiography				
LV ejection fraction, mean (SD) (%)	31.13 (5.40)	29.07 (6.91)	32.27 (6.80)	0.390
Left atrial diameter, mean (SD) (mm)	51.93 (5.38)	51.73 (9.74)	49.80 (6.46)	0.688
Left ventricular end-diastolic diameter, mean (SD) (mm)	65.93 (7.88)	71.67 (13.15)	67.80 (9.89)	0.324
Interventricular septum, mean (SD) (mm)	10.07 (2.34)	9.40 (1.68)	9.20 (2.04)	0.482
Cardiac MR				
Myocardium native T1 time, mean (SD) (ms)	1076.64 (33.76)	1083.01 (21.81)	1085.89 (35.39)	0.706
Myocardium post contrast T1 time, mean (SD) (ms)	419.19 (10.40)	416.41 (14.43)	399.64 (16.77)	< 0.001
Extracellular volume, mean (SD) (%)	28.99 (0.81)	29.53 (1.53)	30.11 (1.73)	0.108
LV EDV index, median (Q1–Q3), (mL/m2)	175.70 (128.80-352.10)	153.95 (101.40-218.50)	155.90 (96.40-1342.50)	0.405

	sST2/LVMI			
LV ESV index, mean (SD), (mL/m2)	151.91 (50.06)	123.35 (39.76)	141.83 (63.07) 127.80	0.338
LVEF, mean (SD) (%)	20.07 (6.11)	22.27 (9.06)	22.07 (7.84)	0.694
RV EDV index, mean (SD) (mL/m2)	93.95 (18.60)	83.51 (21.11)	89.03 (30.65)	0.498
RV ESV index, mean (SD) (ml/m2)	66.72 (22.02)	56.09 (19.77)	65.78 (30.54)	0.430
RVEF, median (Q1–Q3) (%)	29.70 (8.10–55.10)	29.80 (18.30–49.80)	31.10 (4.00-56.60)	0.520
CI, median (Q1–Q3) (L/min/m2)	2.25 (1.70–10.80)	2.37 (1.54–4.97)	2.47 (1.36–6.36)	0.983
LVM index, mean (SD) (g/m2)	117.15 (26.36)	100.38 (24.34)	87.35 (26.12)	0.010
Lambda coefficient, mean (SD)	0.52 (0.06)	0.53 (0.07)	0.53 (0.04)	0.588
Medical history				
ACE-I or ARB				0.034
No (n, %)	12 (80.00%)	9 (60.00%)	5 (33.33%)	
Yes (n, %)	3 (20.00%)	6 (40.00%)	10 (66.67%)	
Diuretics other than MRA				0.448
No (n, %)	9 (60.00%)	6 (40.00%)	6 (40.00%)	
Yes (n, %)	6 (40.00%)	9 (60.00%)	9 (60.00%)	
MRA				0.310
No (n, %)	6 (40.00%)	9 (60.00%)	10 (66.67%)	
Yes (n, %)	9 (60.00%)	6 (40.00%)	5 (33.33%)	
Digoxin				0.099
No (n, %)	15 (100.00%)	11 (73.33%)	13 (86.67%)	
Yes (n, %)	0 (0.00%)	4 (26.67%)	2 (13.33%)	
Cardiovascular risk factors				
smoking				0.516
No (n, %)	9 (60.00%)	11 (73.33%)	8 (53.33%)	
Yes (n, %)	6 (40.00%)	4 (26.67%)	7 (46.67%)	
Hypertension				0.695

	sST2/LVMI			
No (n, %)	8 (53.33%)	10 (66.67%)	8 (53.33%)	
Yes (n, %)	7 (46.67%)	5 (33.33%)	7 (46.67%)	
Diabetes mellitus				0.146
No (n, %)	14 (93.33%)	12 (80.00%)	15 (100.00%)	
Yes (n, %)	1 (6.67%)	3 (20.00%)	0 (0.00%)	
Etiology				0.276
Cardiomyopathy (n, %)	15 (100.00%)	11 (73.33%)	13 (86.67%)	
Ischemic heart failure (n, %)	0 (0.00%)	3 (20.00%)	1 (6.67%)	
Valvular heart disease (n, %)	0 (0.00%)	1 (6.67%)	1 (6.67%)	

The results of the relationship between the ratio of sST2/LVMI and the composite outcome

In this study, we constructed three models to analyze the independent effects of the ratio of sST2/LVMI on the composite outcome using multivariate Cox regression analysis. The effect sizes (Hazard ratio (HR)) and 95% confidence intervals were listed in Table 2. In the crude model, the ratio of sST2/LVMI showed positive correlation with the composite outcome (HR = 1.24, 95% confidence interval (CI) 1.03 to 1.51, P = 0.00258). In the minimally adjusted model (adjusted gender, age, body mass index, diastolic blood pressure, systolic blood pressure, and heart rate), the result did not have obvious changes (HR = 1.31, 95% confidence interval (CI) 1.03 to 1.51, P = 0.0288). In a fully adjusted model, a stronger association can be found (HR = 1.64, 95% confidence interval (CI) 1.06 to 2.54, P = 0.027), which means for each additional per 0.1 change of the ratio of sST2/LVMI, risk of heart failure readmission increased by 64%.

Table 2
Relationship between sST2/LVMI and the composite outcome in different models

Variable	Crude model (HR, 95% CI, P)	Minimally adjusted model(HR, 95% CI, P)	Fully adjusted model (HR, 95% CI, P)
sST2/LVMI(per 0.1 change)	1.24 (1.03, 1.51) 0.0258	1.31 (1.03, 1.67) 0.0288	1.64 (1.06, 2.54) 0.0270
Crude model we did not adjust other covariants,			
minimally adjusted model we adjusted age, gender, body mass index, heart rate, systolic blood pressure and diastolic blood pressure,			
fully adjusted model we adjusted age, gender, body mass index, heart rate, systolic blood pressure,diastolic blood pressure, NYHA functional class,smoking, hypertension, diabetes mellitus, etiology, blood urea nitrogen, serum uric acid, Albumin,LV ejection fraction, PINP, median (Q1–Q3) (ng/mL),PIIINP, mean (SD) (ng/mL),PICP, mean (SD) (ng/mL)			

The results of the nonlinearity of the ratio of sST2/LVMI and primary endpoint

In the present study, we analyzed the non-linear relationship between the ratio of sST2/LVMI and composite outcome (Fig. 1). Smooth curve and the result of the Cox proportional hazards regression model with cubic spline functions showed that the relationship between the ratio of sST2/LVMI and the composite outcome was positive, linear after adjusting for gender, age, body mass index, diastolic blood pressure, systolic blood pressure, and heart rate. No non-linear relationship was observed. We used the Cox proportional hazard model and the two-piecewise Cox balanced hazard model to fit the association based on *P* for the log likelyhood ratio test(Table 3).

Table 3
the non-linear relationship of sST2/LVMI and primary endpoint

Model 1: Fitting model by standard linear regression	
One line slope	35.06 (1.05, 1176.39) 0.0472
Model 2: Fitting model by two-piecewise linear regression	
Inflection point	0.68
< 0.68	1862.72 (0.68, 5130355.03) 0.0624
> 0.68	0.00 (0.00, 68659.53) 0.4028
P for log likelyhood ratio test	0.199

The results of subgroup analyses

As shown in Table 4, Only a small number of interactions were observed including: age, systolic blood pressure, diastolic blood pressure, hematocrit, interventricular septum and RV EDV index (all P values for interaction < 0.05). In the present study, the stronger association were found in patients whose age between 40 and 55 years old(HR = 2.10 [1.29, 3.42], P = 0.0030), systolic blood pressure <115 mmHg (HR = 1.90 [1.19, 3.05], P = 0.0072)or ≥ 129 mmHg(HR = 4.87 [1.82, 13.08], P = 0.0017), diastolic blood pressure < 74 mmHg(HR = 2.58 [1.34, 4.99], P = 0.0047), hematocrit < 39.8%(HR = 1.73 [1.01, 2.96], P = 0.0476) or between 39.8% and 44.5%(HR = 2.59 [1.25, 5.37], P = 0.0105), interventricular septum ≥ 9.5 mm (HR = 1.53 [1.07, 2.18], P = 0.0187) or between 8.5 and 9.5 mm(HR = 7.70 [1.71, 34.71], P = 0.0079), RV EDV index <74.3 mL/m^2 (HR = 1.75 [1.07, 2.87], P = 0.0256) or ≥ 94.3 mL/m^2(HR = 2.43 [1.38, 4.29], P = 0.0022).

Table 4
Effect size of sST2/LVMI on the composite outcome in prespecified and exploratory subgroups

Characteristic	No of participants	Effect size (95% CI)	P value	P for interaction
Age (years)				
< 40	16	0.88 (0.49, 1.60)	0.6792	0.0243
40–55	13	2.10 (1.29, 3.42)	0.0030	
≥ 55	16	1.51 (0.99, 2.30)	0.0560	
Gender				
Female	9	6.42 (1.52, 27.17)	0.0115	0.0058
Male	36	1.17 (0.95, 1.45)	0.1323	
Body mass index, (kg/m^2)				
< 24	14	1.74 (0.98, 3.07)	0.0570	0.3916
24–26.1	14	1.30 (0.91, 1.87)	0.1540	
≥ 26.1	13	1.10 (0.82, 1.48)	0.5308	
Heart rate (bpm)				
< 71	12	0.99 (0.38, 2.60)	0.9906	0.1291
71–83	14	1.60 (1.11, 2.31)	0.0126	
≥ 83	19	0.97 (0.62, 1.52)	0.8781	
Systolic blood pressure (mmHg)				
< 115	17	1.90 (1.19, 3.05)	0.0072	0.0002
115–129	11	0.80 (0.45, 1.40)	0.4338	
≥ 129	17	4.87 (1.82, 13.08)	0.0017	
Diastolic blood pressure (mmHg)				
< 74	14	2.58 (1.34, 4.99)	0.0047	0.0447
74–83	14	1.11 (0.77, 1.61)	0.5814	
≥ 83	17	1.68 (0.86, 3.25)	0.1267	
NYHA functional class				
II	21	0.89 (0.46, 1.75)	0.7455	0.0961
III–IV	24	1.45 (1.09, 1.92)	0.0100	

Characteristic	No of participants	Effect size (95% CI)	P value	P for interaction
Hemoglobin (g/L)				
< 130	14	1.96 (1.18, 3.25)	0.0090	0.1263
130–146	14	1.27 (0.75, 2.16)	0.3721	
≥ 146	17	1.11 (0.86, 1.43)	0.4210	
White blood cells, 109/L				
< 5.47	15	1.32 (0.75, 2.33)	0.3418	0.9801
5.47–7.04	15	1.25 (0.94, 1.68)	0.1298	
≥ 7.04	15	1.30 (0.89, 1.90)	0.1668	
Hematocrit (%)				
< 39.8	14	1.73 (1.01, 2.96)	0.0476	0.0303
39.8–44.5	15	2.59 (1.25, 5.37)	0.0105	
≥ 44.5	16	1.06 (0.81, 1.40)	0.6621	
Sodium, mean (SD) (mmol/L)				
< 139.5	13	1.31 (0.92, 1.86)	0.1282	0.7023
139.5–142	12	1.46 (0.96, 2.20)	0.0735	
≥ 142	20	1.14 (0.74, 1.76)	0.5540	
Total cholesterol (μmol/L)				
< 3.53	16	1.40 (0.94, 2.07)	0.0956	0.4460
3.53–4.08	15	1.15 (0.87, 1.53)	0.3228	
≥ 4.08	12	2.04 (0.78, 5.35)	0.1483	
Creatinine (μmol/L)				
< 83	12	0.57 (0.14, 2.36)	0.4412	0.2448
83–95	13	1.23 (0.96, 1.57)	0.0951	
≥ 95	20	1.53 (0.98, 2.41)	0.0621	
Blood urea nitrogen (mmol/L)				
< 5.2	13	1.01 (0.64, 1.61)	0.9563	0.0725
5.2–6.8	16	2.01 (1.28, 3.15)	0.0023	

Characteristic	No of participants	Effect size (95% CI)	P value	P for interaction
≥ 6.8	16	1.28 (0.88, 1.85)	0.1896	
Serum uric acid (μmol/L)				
< 366	11	2.86 (1.16, 7.04)	0.0224	0.0990
366–520	15	1.34 (0.92, 1.95)	0.1268	
≥ 520	19	1.08 (0.82, 1.44)	0.5729	
Total bilirubin (μmol/L)				
< 10.6	12	2.80 (0.97, 8.07)	0.0567	0.1033
10.6–14	14	1.26 (0.80, 1.96)	0.3168	
≥ 14	19	1.12 (0.87, 1.45)	0.3642	
Albumin (g/L)				
< 37.5	13	1.37 (0.68, 2.77)	0.3834	0.4407
37.5–40.5	17	1.05 (0.73, 1.52)	0.7909	
> 40.5	14	1.41 (1.03, 1.93)	0.0333	
Hypersensitive C-reactive protein (mg/L)				
< 1	14	0.83 (0.38, 1.84)	0.6544	0.2197
1–5.5	12	1.91 (0.97, 3.76)	0.0608	
≥ 5.5	14	1.22 (0.92, 1.61)	0.1652	
NT-proBNP (pg/mL)				
< 722	8	inf. (0.00, Inf)	0.9990	0.0363
722–2333	18	1.14 (0.71, 1.81)	0.5874	
≥ 2333	19	1.20 (0.98, 1.47)	0.0703	
PINP (ng/mL)				
< 31.75	15	1.88 (1.05, 3.35)	0.0335	0.1494
31.75–44.3	15	1.15 (0.73, 1.82)	0.5338	
≥ 44.3	15	2.08 (1.37, 3.16)	0.0005	
PIIINP (ng/mL)				
< 6.24	15	2.00 (1.24, 3.24)	0.0048	0.1078

Characteristic	No of participants	Effect size (95% CI)	P value	P for interaction
6.24–7.84	15	1.10 (0.77, 1.57)	0.5981	
≥ 7.84	15	1.17 (0.80, 1.72)	0.4052	
PICP (ng/mL)				
< 248	15	0.98 (0.53, 1.80)	0.9469	0.5393
248–304	15	1.45 (0.96, 2.18)	0.0749	
≥ 304	15	1.35 (1.01, 1.82)	0.0461	
Growth stimulation–expressed gene 2 (ng/mL)				
< 25.5	17	1.91 (0.31, 11.72)	0.4847	0.5469
25.5–38.0	13	2.13 (0.60, 7.57)	0.2409	
≥ 38.0	15	1.10 (0.80, 1.52)	0.5621	
Left atrial diameter (mm)				
< 45.5	9	1.82 (0.97, 3.39)	0.0609	0.2040
45.5–53.5	12	1.02 (0.63, 1.63)	0.9397	
≥ 53.5	24	1.44 (0.96, 2.16)	0.0745	
Left ventricular end-diastolic diameter (mm)				
< 59.5	9	1.98 (1.22, 3.23)	0.0060	0.1316
59.5–68.5	17	1.29 (0.87, 1.93)	0.2070	
≥ 69	19	1.11 (0.79, 1.56)	0.5655	
Interventricular septum (mm)				
< 8.5	13	1.00 (0.74, 1.34)	0.9775	0.0052
8.5–9.5	9	7.70 (1.71, 34.71)	0.0079	
≥ 9.5	23	1.53 (1.07, 2.18)	0.0187	
LV ejection fraction, (%)				
< 28.5	16	1.23 (0.67, 2.24)	0.5046	0.9500
28.5–36.5	19	1.36 (0.95, 1.93)	0.0899	
≥ 36.5	10	1.28 (0.91, 1.79)	0.1528	

Characteristic	No of participants	Effect size (95% CI)	P value	P for interaction
Myocardium native T1 time (ms)				
< 1048	9	1.61 (0.95, 2.73)	0.0762	0.3102
1048–1097.8	18	1.94 (1.02, 3.69)	0.0426	
≥ 1079.8	18	1.20 (0.89, 1.61)	0.2253	
Myocardium post contrast T1 time (ms)				
< 407.9	15	1.06 (0.80, 1.42)	0.6711	0.1579
407.9–418.3	17	2.00 (1.10, 3.64)	0.0240	
≥ 418.3	13	1.38 (0.42, 4.61)	0.5957	
LV EDV index, (mL/m^2)				
< 137.3	15	1.92 (1.18, 3.11)	0.0081	0.0951
137.3–181.7	14	1.03 (0.73, 1.45)	0.8802	
≥ 181.7	15	1.44 (0.98, 2.11)	0.0598	
LV ESV index, (mL/m^2)				
< 108	15	1.90 (1.14, 3.19)	0.0146	0.0863
108–144	14	1.02 (0.74, 1.40)	0.9023	
≥ 144	15	1.44 (0.98, 2.11)	0.0623	
LVEF (%)				
< 18	15	1.11 (0.84, 1.46)	0.4846	0.0807
18–24	15	2.20 (1.21, 4.00)	0.0100	
≥ 24	15	1.63 (0.94, 2.83)	0.0789	
CI ($L/min/m^2$)				
< 2	14	1.18 (0.92, 1.51)	0.1861	0.1136
2–2.6	14	1.20 (0.67, 2.14)	0.5424	
≥ 2.6	15	2.46 (1.25, 4.85)	0.0093	
LVM index, mean (SD) (g/m^2)				
< 88.6	15	1.17 (0.90, 1.51)	0.2433	0.9866

Characteristic	No of participants	Effect size (95% CI)	P value	P for interaction
88.6–105	15	1.12 (0.72, 1.76)	0.6106	
≥ 105	15	1.08 (0.25, 4.60)	0.9144	
RVEF (%)				
< 24.4	14	1.11 (0.87, 1.41)	0.4152	0.1653
24.5–34.4	16	1.13 (0.63, 2.03)	0.6857	
≥ 34.4	15	1.83 (1.12, 3.00)	0.0162	
RV EDV index, (mL/m^2)				
< 74.3	15	1.75 (1.07, 2.87)	0.0256	0.0032
74.3–94.3	15	0.91 (0.62, 1.35)	0.6516	
≥ 94.3	15	2.43 (1.38, 4.29)	0.0022	
RV ESV index, (mL/m^2)				
< 46.7	15	1.84 (1.11, 3.07)	0.0187	0.0878
46.7–68.5	15	0.72 (0.34, 1.55)	0.4062	
≥ 68.5	15	1.22 (0.95, 1.56)	0.1183	
ACE-I or ARB				
No	26	1.87 (1.22, 2.84)	0.0038	0.1643
Yes	19	1.28 (0.95, 1.74)	0.1091	
Beta-blockers				
No	28	1.87 (1.17, 2.97)	0.0084	0.0628
Yes	17	1.11 (0.85, 1.45)	0.4529	
Diuretics other than MRA				
No	21	1.24 (1.00, 1.53)	0.0462	0.9446
Yes	24	1.22 (0.83, 1.80)	0.3163	
MRA				
No	25	1.32 (0.93, 1.88)	0.1196	0.6768
Yes	20	1.21 (0.96, 1.53)	0.1116	
Digoxin				

Characteristic	No of participants	Effect size (95% CI)	P value	P for interaction
No	39	1.49 (1.16, 1.91)	0.0018	0.1094
Yes	6	0.60 (0.04, 8.72)	0.7094	
SMOKING				
No	28	1.27 (1.02, 1.57)	0.0342	0.7623
Yes	17	1.18 (0.81, 1.74)	0.3921	
Hypertension				
No	26	1.22 (0.95, 1.58)	0.1260	0.7005
Yes	19	1.33 (0.95, 1.85)	0.0968	
Diabetes mellitus				
No	41	1.23 (1.02, 1.50) 0.0344		0.0845
Yes	4	inf. (0.00, Inf) 0.9981		
Etiology				
Cardiomyopathy	39	1.26 (1.02, 1.56) 0.0310		0.1225
Ischemic heart failure	4	8.70 (0.41, 186.13) 0.1664		
Valvular heart disease	2	24481.66 (0.00, Inf) 0.9979		

The predictive value of the ratio of sST2/LVMI for composite outcome in patients with HFrEF

Kaplan–Meier curves estimated the survival free from the composite outcome(Figure. 2). Patients with high the ratio of sST2/LVMI ≥ 0.39 had shorter event-free survival than the middle (the ratio of sST2/LVMI between 0.39 and 0.24) and low (the ratio of sST2/LVMI < 0.24) the ratio of sST2/LVMI patients (log-rank, $P = 0.022$).

Discussion

The present study demonstrated the ratio of sST2/LVMI, which eliminates cardiac remodeling factors from the circulation sST2, was positively associated with the composite endpoint of cardiovascular-

cause mortality or heart failure readmission in Chinese HFrEF patients. The relationship between the ratio of sST2/LVMI and the primary outcome was linear. Subgroup analysis showed the stronger association were detected in patients whose age between 40 and 55 years old, systolic blood pressure < 115 or ≥ 129 mmHg, diastolic blood pressure < 74 mmHg, hematocrit < 44.5%, interventricular septum ≥ 8.5 mm, RV EDV index < 74.3 or ≥ 94.3 mL/m2.

Transmembrane binding receptor (ST2L) and soluble ST2 (sST2) are the two primary functional forms of ST2[17]. After interleukin-33 recognition by ST2L, different intracellular signaling pathways are activated. IL-33/ST2L signaling leads to inflammatory gene transcription and the production of inflammatory cytokines/chemokines[18]. ST2L/IL-33 signaling also activates intracellular signaling to promote cell survival, .results in several cardioprotective effects, such as reduces myocardial fibrosis and cardiomyocyte hypertrophy[19].sST2, a powerful independent predictor of mortality in HF patients, acts as a decoy receptor for IL-33, rendering it unavailable to membrane-bound ST2 receptors[20]. The biology of the ST2 system is complex, and its role in cardiovascular disease is not entirely elucidated[21].

Cardiac fibrosis of heart failure patients are maladaptive and predispose to cardiovascular morbidity and mortality[22]. Inflammation activated by biomechanical strain and neurohormonal activation is an important trigger and maintenance factor for cardiac fibrosis[23]. In terms of molecular mechanism, sST2 was reported to possess two functions: inhibit inflammation[6] and promote cardiac fibrosis[4]. However, a number of clinical studies in the real world reported that sST2 was not associated with cardiac fibrosis[9][10][11]. We hypothesized that the promoting pro-cardiac fibrotic effect of elevated sST2 is an additional effect secondary to the inflammatory response. In the present study, we test our hypothesis using a novel parameter- sST2/ LVMI, which eliminates cardiac remodeling factors from the circulation sST2 in Chinese HFrEF patients. CMR measured LVMI at baseline. We found that after eliminating cardiac remodeling factors, circulation sST2 was positively associated with the composite endpoint of cardiovascular-cause mortality or heart failure readmission. However, our theory needs to be further explored in the following research.

The clinical value of the present study is as follows (1) To our best knowledge, we proposed the theory that promoting the pro-cardiac fibrotic effect of elevated sST2 is just an additional effect secondary to the inflammatory response for the first time. This indicates the direction for the clinical application of ST2 related drugs in the future. (2) To our best knowledge, it is the first time to report the independent association between the ratio of sST2/LVMI and cardiac death/ heart failure rehospitalization in HFrEF patients, which separates sST2's anti-inflammatory effect from its fibrogenic effect.(3)The findings of this study should help future research on the establishment of diagnostic or predictive models of heart failure readmission for HFrEF patients or cardiovascular-cause mortality.

Our study has some strengths. (1) this study is an observational study and, therefore, susceptible to potential confounding. We used strict statistical adjustment to minimize residual confounders; (2) we address the nonlinearity in the present study; (3) the effect modifier factor analysis uses data better and yield stable conclusions in different subgroups in this study.

Limitation

It should be pointed out that the present study has several limitations. (1) our research subjects are Chinese HFrEF patients. Therefore, there is a certain deficiency in the universality and extrapolation of research. (2) we reported a single-center, medium-sample data suffer from some bias. A multi-center, large-sample study is still needed to verify. (3)we only investigated the correlation between the ratio of sST2/LVMI baseline at admission level and prognosis and did not discuss the significance of dynamic changes of the ratio of sST2/LVMI.

Conclusions

In summary, The relationship between baseline the ratio of sST2/LVMI and the composite outcome is linear in HFrEF patients. High baseline, the ratio of sST2/LVMI was associated with a higher rate of cardiovascular-cause mortality or heart failure readmission during nine months follow up. The ratio of sST2/LVMI has an independent prognostic value in HFrEF patients.

List Of Abbreviations

sST2 soluble growth stimulation expressed gene 2

LVMI left ventricular mass index

HFrEF heart failure with reduced ejection fraction

LV left ventricular

HF heart failure

HR hazard ratio

CI confidence interval

ECM extracellular matrix

IL-33 interleukin-33

CMRI cardiac magnetic resonance imaging

LEG late gadolinium enhancement

NYHA New York Heart Association functional

BMI body mass index

PINP N-terminal propeptide of type I procollagen

PIIINP N-terminal propeptide of type III procollagen

PICP type I procollagen carboxyterminal propeptide

NT-proBNP N-terminal prohormone of brain natriuretic peptide

LAD left atrial diameter,

LVEF left ventricular ejection fraction

LVEDD left ventricular end-diastolic diameter

IVST interventricular septal thickness

ACEI angiotensin-converting enzyme inhibitor

ARB angiotensin II receptor blocker

RV EDV right ventricular end-diastolic volume

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committee of Zhongshan Hospital, Fudan University, all participants gave informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

Fuhai Li and Jingmin Zhou were equally responsible for the writing of the manuscript. Mengying Xu, Mingqiang Fu, Xiaotong Cui ,Kai Hu participated in the study design and conduct and assisted in the writing of the document. Junbo Ge provided expert guidance in the design and conduct of this study and assisted in the writing of the manuscript. Each author made substantial contributions to the conception or design of the work, the acquisition, analysis or interpretation of data, and drafting and final approval of the manuscript. All authors read and approved the final manuscript.

Jingmin Zhou conceived the study and had ultimate oversight for the design and conduct and writing of this manuscript.

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Figures

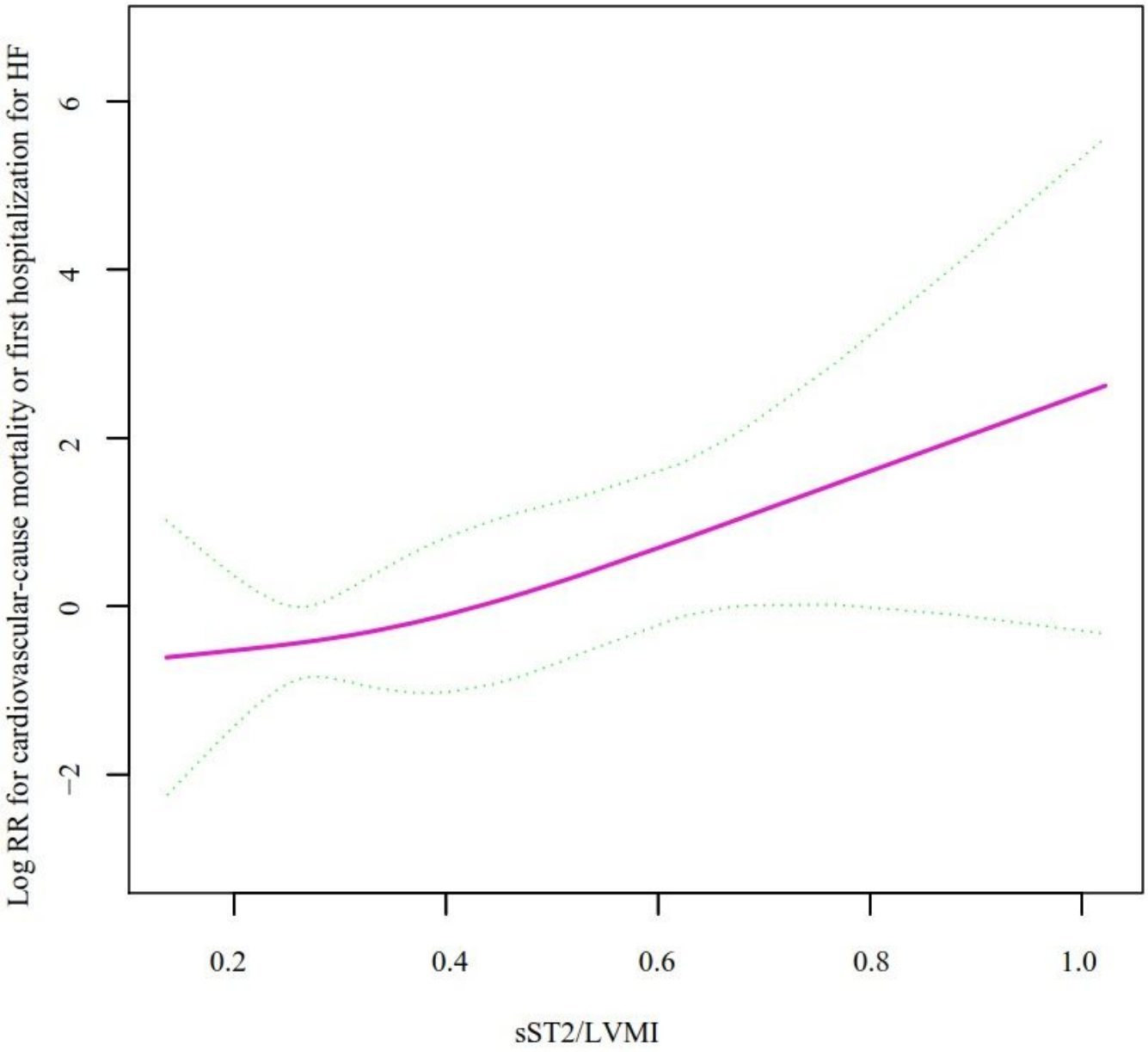

Figure 1

The relationship between the ratio of sST2/LVMI and the composite outcome (using the penalized spline method).

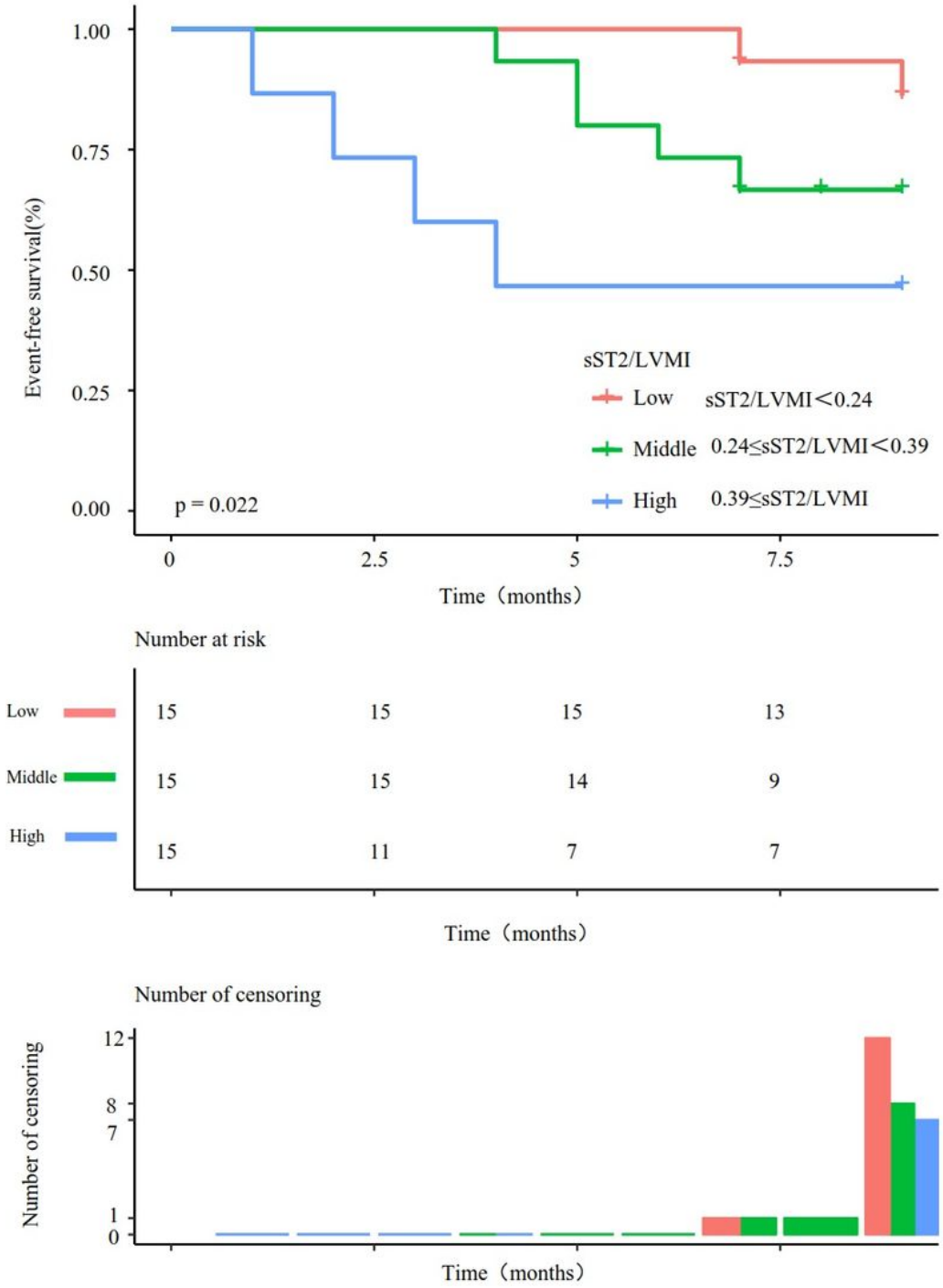

Figure 2

Kaplan–Meier curves showing the event-free survival in HFrEF patients according to the ratio of sST2/LVMI cut off.