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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Research article

Keywords: Soluble suppression of tumorigenicity 2 (sST2), left ventricular mass index (LVMI), Heart failure, Prognosis, HFrEF

DOI: https://doi.org/10.21203/rs.3.rs-91660/v1

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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. χ2 (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 HF Ref 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).
|                                | 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

| Metric                          | Value 1 | Value 2 | Value 3 | p-value |
|--------------------------------|---------|---------|---------|---------|
| LV ESV index, mean (SD), (mL/m²) | 151.91 (50.06) | 123.35 (39.76) | 141.83 (63.07) | 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**

| No (n, %) | Yes (n, %) |
|-----------|------------|
| 12 (80.00%) | 3 (20.00%) |
| 9 (60.00%) | 6 (40.00%) |
| 5 (33.33%) | 10 (66.67%) |

**Diuretics other than MRA**

| No (n, %) | Yes (n, %) |
|-----------|------------|
| 9 (60.00%) | 6 (40.00%) |
| 6 (40.00%) | 9 (60.00%) |
| 6 (40.00%) | 9 (60.00%) |

**MRA**

| No (n, %) | Yes (n, %) |
|-----------|------------|
| 6 (40.00%) | 9 (60.00%) |
| 9 (60.00%) | 6 (40.00%) |
| 10 (66.67%) | 5 (33.33%) |

**Digoxin**

| No (n, %) | Yes (n, %) |
|-----------|------------|
| 15 (100.00%) | 0 (0.00%) |
| 11 (73.33%) | 4 (26.67%) |
| 13 (86.67%) | 2 (13.33%) |

**Cardiovascular risk factors**

**smoking**

| No (n, %) | Yes (n, %) |
|-----------|------------|
| 9 (60.00%) | 6 (40.00%) |
| 11 (73.33%) | 4 (26.67%) |
| 8 (53.33%) | 7 (46.67%) |

**Hypertension**

| No (n, %) | Yes (n, %) |
|-----------|------------|
| 9 (60.00%) | 9 (60.00%) |
| 6 (40.00%) | 9 (60.00%) |
| 5 (33.33%) | 10 (66.67%) |
| 4 (26.67%) | 9 (60.00%) |
| 2 (13.33%) | 9 (60.00%) |

| No (n, %) | Yes (n, %) |
|-----------|------------|
| 15 (100.00%) | 0 (0.00%) |
| 11 (73.33%) | 4 (26.67%) |
| 13 (86.67%) | 2 (13.33%) |

#### p-values

- LV ESV index, mean (SD), (mL/m²): 0.338
- LVEF, mean (SD) (%): 0.694
- RV EDV index, mean (SD) (mL/m²): 0.498
- RV ESV index, mean (SD) (ml/m²): 0.430
- RVEF, median (Q1–Q3) (%): 0.520
- CI, median (Q1–Q3) (L/min/m²): 0.983
- LVM index, mean (SD) (g/m²): 0.010
- Lambda coefficient, mean (SD): 0.588
- ACE-I or ARB: 0.034
- Diuretics other than MRA: 0.448
- MRA: 0.310
- Digoxin: 0.099
- Cardiovascular risk factors: 0.516
- Hypertension: 0.695
### sST2/LVMI

|                  | No (n, %) | Yes (n, %) | Diabetes mellitus | Etiology |
|------------------|-----------|------------|-------------------|----------|
|                  | 8 (53.33%)| 10 (66.67%)|                   |          |
| No (n, %)        |           |            |                   |          |
| Yes (n, %)       | 7 (46.67%)| 5 (33.33%)  |                   |          |
| Diabetes mellitus|           |            |                   |          |
| No (n, %)        | 14 (93.33%)| 12 (80.00%)|                   |          |
| Yes (n, %)       | 1 (6.67%) | 3 (20.00%) |                   |          |
| Etiology         |           |            |                   |          |
| 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 covariates,
- **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/m² (HR = 1.75 [1.07, 2.87], P = 0.0256) or ≥ 94.3 mL/m² (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/m²)                    |                    |                       |          |                   |
| < 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/m²)                  |                    |                                     |         |                   |
| < 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/m²)                  |                    |                                     |         |                   |
| < 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/m²)                           |                    |                                     |         |                   |
| < 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/m²)            |                    |                                     |         |                   |
| < 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/m²) |                    |                      |         |                  |
| < 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/m²) |                    |                      |         |                  |
| < 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               |                    |                      |         |                  |
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 $sST2/LVMI \geq 0.39$ 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
PIIIINP 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.

Funding
This study was supported by a grant from the National Natural Science Foundation of China (No. 81873123) and Program for the Outstanding Academic Leaders supported by the Shanghai Municipal Science and Technology Commission (16XD1400700).

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.

Acknowledgment

We gratefully acknowledge all the people who participated in this study for their efforts in the conduction of the study.

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