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Original article

Soluble ST2 and brain natriuretic peptide predict different mode of death in patients with heart failure and preserved ejection fraction

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ABSTRACT

Background: Soluble ST2 (sST2) is a marker of inflammation and fibrosis, which is a significant predictor of prognosis of heart failure (HF), independent of brain natriuretic peptide (BNP). This study aimed to clarify how sST2 associates with clinical outcome through investigations of clinical correlates and mode of death in patients with heart failure with preserved ejection fraction (HFpEF).
Methods: A total 191 patients with acute decompensated HF and EF ≥50% were prospectively enrolled. Echocardiographic and laboratory data including sST2 were obtained in pre-discharge stable condition.
Results: Serum sST2 level showed significant positive correlations with C-reactive protein and pentraxin3 levels, and negative correlations with body mass index, albumin, and hemoglobin. Serum sST2 level was significantly higher in patients with all-cause death and non-cardiovascular (CV) death compared to those without events, whereas there was no significant difference in sST2 level between patients with and without CV death. On the other hand, BNP level was significantly higher in patients with all-cause death and CV death compared to those without events. Cox regression analyses adjusted for age and sex revealed that sST2 was a significant predictor of non-CV death, whereas BNP was a significant predictor of CV death.
Conclusions: Serum sST2 level was associated with non-CV death showing significant correlations with systemic factors including malnutrition and inflammation, while BNP was associated with CV death.

Introduction

ST2 is a member of the interleukin (IL) 1 receptor family. Soluble ST2 (sST2) is one of the isoforms of ST2, binding IL-33 which results in inhibition of cardioprotective antiremodeling effects of IL-33 [1,2]. Elevated sST2 level has been reported to be a marker of worse prognosis in patients with heart failure with reduced ejection fraction (HFrEF) [3–6]. Furthermore, several studies have shown that sST2 has a predictive value for mortality in patients with heart failure with preserved ejection fraction (HFpEF) [7,8]. In addition, the predictive value of sST2 is independent and additive to brain natriuretic peptide (BNP) levels. Studies have shown that patients with HFpEF have higher prevalence of non-cardiac comorbidities compared to those with HFrEF, and the prevalence of non-cardiovascular (CV) death was higher in HFpEF than in HFrEF [9–11]. Therefore, systemic proinflammatory state driven by comorbidities has been proposed as the additional cause of myocardial remodeling and dysfunction besides diastolic dysfunction due to hypertensive heart disease [12,13]. The findings suggest that it is important to understand HFpEF patient-specific pathophysiology and predict risk for non-CV events in management of HFpEF as well as for CV events. Therefore, the present study aimed to clarify how serum sST2 level associates with clinical outcome through investigations of clinical correlates and mode of death in patients with HFpEF.

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Methods

The Ibaraki Cardiac Assessment Study-Heart Failure (ICAS-HF) registry was a multicenter, prospective registry involving 11 hospitals in Ibaraki Prefecture, Japan. This registry consisted of 838 patients admitted for acute decompensated heart failure (ADHF) from June 2012 to March 2015. The diagnosis of HF was made according to the Framingham criteria. Patients were enrolled in this registry during initial hospitalization period and followed at each institution until March 2016. The exclusion criteria of the registry were as follows: patients aged <20 years, patients who did not provide informed consent to the attending physician, patients with limited life expectancy owing to malignant neoplasms, patients for whom two years of observation was predicted to be impossible, and patients who were medically judged as inappropriate by the attending physician. In this analysis, we included patients who had left ventricular ejection fraction (LVEF) calculated using the modified Simpson's method of greater than 50% and excluded patients with acute coronary syndrome, severe valvular heart disease, hypertrophic cardiomyopathy, and end-stage renal disease for the analysis of this study. Finally, our study population comprised 191 patients with HFpEF. Cardiologists of participating hospitals classified mode of death as CV death or non-CV death. CV death was defined as sudden death or death from heart failure, myocardial infarction, cerebrovascular disease, and other vascular diseases. Written informed consent was obtained from all patients and study protocol was approved by each institutional review board.

Soluble ST2 was measured using Human ST-2 ELISA kit (R&D Systems, Minneapolis, MN, USA). Blood sample was obtained in stable condition before discharge and stored in the frozen state at core laboratory. BNP and other laboratory data were measured from specimens collected at the same time.

Comprehensive Doppler echocardiography was performed at each institution before discharge. Echocardiographic measurements were obtained according to the American Society of Echocardiography guidelines [14,15]. LV end-diastolic volume (LVEDV), end-systolic volume (LVESV), and LVEF were calculated using the Simpson biplane methods of discs. Maximum left atrial (LA) volume was measured by the biplane Simpson's method and indexed to body surface area (LAVI). Peak early (E) and late diastolic (A) velocities of the LV inflow, and the average of peak early diastolic velocity on the septal and the lateral corner of mitral annulus (e') were measured in the apical 4-chamber view. The E/e' ratio was obtained by dividing E by e'. Tricuspid regurgitation pressure gradient (TRPG) was derived from peak TR jet velocity. The maximum diameter of the inferior vena cava (IVC) was measured in the subcostal view 1.0–2.0 cm from the junction with the right atrium with the patient in the supine position.

Results are expressed as number (%), mean ± SD, or median and interquartile range (IQR) if the variables were not normally distributed. Comparisons of data were performed using the Student t-test for unpaired continuous variables, the Mann-Whitney U test for continuous variables that were not normally distributed, and chi-square tests for categorical variables. The correlations between sST2 (log transformed) and other variables [including log-transformed C-reactive protein (CRP) and pentraxin 3 (PTX3)] were shown in scatter plots with 95% confidence ellipse and Pearson correlation coefficients. We tested whether sST2 and BNP were associated with all-cause death, CV death, and non-CV death by using Cox proportional hazard regression analysis. The univariate factors with a value of $p < 0.05$ were entered into the multivariable models to assess the effect of the parameters on the endpoints. To avoid over fitting of the multivariate models, a step-up procedure was used in the multivariable model analysis. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using commercially available software: JMP 13 (SAS Institute, Cary, NC, USA).

Results

At baseline, mean age was 76.4 ± 11.9 years and 92 of 191 (48.2%) were female. Median value of sST2 was 18.0 pg/ml with interquartile range of 11.9–26.2 pg/ml. We divided patients according to quartile of sST2. Table 1 shows characteristics compared by quartile of sST2. Higher sST2 groups showed higher percentage of male gender, lower levels of body mass index (BMI), albumin, and hemoglobin, and higher level of CRP, PTX3, noradrenaline, and BNP. There was no association between sST2 level and age, renal function. Among the echocardiographic indices, TRPG was associated with sST2 level, whereas LV function and structure showed no associations.

The log-sST2 showed significant positive correlation with log-CRP, log-PTX3, and TRPG, and negative correlation with BMI, albumin, and hemoglobin (Fig. 1).

Association between biomarkers and endpoints

During a median follow-up of 445 days, endpoint occurred in 34 of 191 patients (24 CV deaths and 10 non-CV deaths). Breakdown of mode of death is shown in Table 1. The rate of CV death was not significantly different between quartile groups. Among CV-death, HF death was the most frequent mode of death (55%) followed by sudden death or fatal myocardial infarction (33%). CV death other than sudden death or fatal myocardial infarction was not observed in the lowest quartile group, however, sudden death or fatal myocardial infarction occurred in all quartile groups. On the other hand, 7 out of 10 non-CV deaths occurred in the highest quartile group and the rate of non-CV death was significantly different between quartile groups ($p = 0.006$). Among non-CV death, infection/sepsis was the most frequent mode of death and 4 out of 5 deaths from infection/sepsis occurred in the highest quartile. Soluble ST2 level was significantly higher in patients with all-cause death and non-CV death compared to those without events (median of 23.1 pg/ml vs. 17.1 pg/ml for all-cause death, $p = 0.004$; 36.6 pg/ml vs. 17.9 pg/ml for non-CV death, $p = 0.02$, respectively), whereas there was no significant difference in sST2 level between patients with and without CV death (median of 20.0 pg/ml vs. 17.6 pg/ml, $p = 0.081$) (Fig. 2). On the other hand, BNP level was significantly higher in patients with all-cause death and CV death compared to those without event (median of 309 pg/ml vs. 142 pg/ml for all-cause death; $p < 0.001$, 325 pg/ml vs. 146 pg/ml for CV death, $p < 0.001$, respectively), whereas there was no significant difference in BNP level between patients with and without non-CV death (median of 228 pg/ml vs. 181 pg/ml, $p = 0.59$). Cox regression analyses adjusted for age and sex revealed that both sST2 and BNP were significant predictors of all-cause death (HR 1.01, 95% CI 1.00–1.03, $p = 0.03$, HR per 10 pg/ml increase in BNP 1.01, 95% CI 1.00–1.02, $p = 0.004$, respectively) (Table 2). With respect to the mode of death, only sST2 was a significant predictor of non-CV death (HR 1.03, 95% CI 1.00–1.04, $p = 0.01$) and BNP rather than sST2 was a significant predictor of CV death (HR per 10 pg/ml increase in BNP 1.02, 95% CI 1.01–1.03, $p < 0.001$).

Discussion

In the present study, circulating levels of sST2 were negatively correlated with albumin level, BMI, and hemoglobin level and positively correlated with levels of CRP and PTX3 and right ventricular pressure in patients with HFpEF. LV systolic function and geometry including LV volume and mass were not associated with sST2 level. Furthermore, we evaluated the relationship

Table 1
Characteristics of all patients and groups divided by quartile of soluble ST2.

	All patients N = 191	First Quarter N = 47	Second Quarter N = 48	Third Quarter N = 48	Fourth Quarter N = 48	p-Value*
Age (years)	76.4 ± 11.9	74.4 ± 12.0	75.3 ± 11.9	76.4 ± 12.8	79.3 ± 10.2	0.20
Male, no (%)	99 (52)	20 (43)	20 (42)	26 (54)	33 (68)	0.02
Body weight (kg)	54.7 ± 12.1	55.7 ± 11.9	57.7 ± 13.4	53.4 ± 11.6	52.1 ± 10.9	0.11
Body mass index (kg/m^2)	22.5 ± 3.9	22.8 ± 3.8	23.6 ± 3.7	22.1 ± 3.4	21.3 ± 4.1	0.02
Heart rate (bpm)	67.7 ± 14.4	66.8 ± 13.1	67.1 ± 16.4	71.0 ± 14.2	66.2 ± 13.4	0.35
Atrial fibrillation, no (%)	48 (25)	7 (14)	14 (29)	13 (27)	14 (29)	0.28
Coronary artery disease, no (%)	49 (26)	9 (19)	11 (22)	18 (37)	11 (22)	0.19
Hypertension, no (%)	133 (70)	28 (59)	37 (77)	32 (66)	36 (75)	0.22
COPD, no (%)	11 (6)	2 (4)	2 (4)	2 (4)	5 (10)	0.51
Diabetes mellitus, no (%)	68 (36)	18 (38)	20 (41)	18 (37)	12 (35)	0.32
Medications						
Beta-blocker, no (%)	125 (65)	31 (65)	33 (68)	29 (60)	32 (66)	0.84
ACE inhibitor or ARB, no (%)	123 (64)	30 (63)	32 (66)	33 (68)	28 (58)	0.73
Diuretics, no (%)	146 (76)	37 (78)	35 (72)	39 (81)	35 (72)	0.69
Aldosterone antagonist, no (%)	102 (53)	23 (48)	24 (50)	33 (68)	22 (45)	0.09
Statin, no (%)	64 (34)	16 (34)	22 (45)	12 (25)	14 (29)	0.15
Laboratory findings						
Albumin (g/dl)	3.5 ± 0.6	3.6 ± 0.5	3.8 ± 0.4	3.5 ± 0.5	3.2 ± 0.7	<0.001
Hemoglobin (g/dl)	11.5 ± 2.2	11.9 ± 1.8	12.0 ± 2.1	11.0 ± 2.2	10.9 ± 2.2	0.02
eGFR (ml/min)	47.9 ± 22.9	48.8 ± 21.3	50.7 ± 27.5	48.9 ± 19.6	42.8 ± 22.0	0.35
Sodium (mEq/l)	139.3 ± 3.4	139.5 ± 3.1	139.5 ± 2.9	138.7 ± 3.2	139.3 ± 4.1	0.56
Potassium (mEq/l)	4.4 ± 0.5	4.5 ± 0.4	4.4 ± 0.3	4.5 ± 0.4	4.2 ± 0.6	0.04
Total cholesterol (mg/dl)	169.4 ± 36.6	171 ± 34	170 ± 39	172 ± 38	163 ± 32	0.63
HbA1c (%)	6.3 ± 1.0	6.3 ± 0.8	6.4 ± 1.3	6.2 ± 0.9	5.9 ± 0.6	0.13
C-reactive protein (mg/l)	0.33 [0.16–0.82]	0.24 [0.11–0.78]	0.23 [0.13–0.58]	0.35 [0.16–1.20]	0.52 [0.19–1.33]	0.02
Pentraxin3 (ng/ml)	3.7 [2.7–5.7]	2.9 [2.6–3.9]	3.6 [2.0–4.7]	3.7 [2.7–5.9]	4.9 [3.1–8.8]	<0.001
Plasma renin activity (ng/ml/h)	3.4 ± 4.6	3.1 ± 3.5	3.8 ± 5.7	4.8 ± 5.5	1.8 ± 2.3	0.054
Plasma aldosterone concentration (pg/ml)	80.6 ± 69.7	96.7 ± 72.1	88.3 ± 76.1	76.3 ± 81.4	62.2 ± 42.6	0.12
Noradrenaline (pg/ml)	392 ± 267	326 ± 169	305 ± 166	441 ± 291	503 ± 354	0.005
Brain natriuretic peptide (pg/ml)	185 [86–324]	100 [60–157]	162 [78–319]	202 [86–315]	304 [185–516]	<0.001
Soluble ST2 (pg/ml)	18.0 [11.9–26.2]	9.4 [8.3–10.7]	14.8 [13.0–15.9]	21.9 [19.2–23.9]	34.5 [29.9–51.0]	<0.001
Echocardiography						
Ejection fraction (%)	60.0 ± 7.6	60.4 ± 8.3	61.2 ± 8.2	57.6 ± 5.5	60.6 ± 7.5	0.09
End-diastolic volume (ml)	85.7 ± 42.6	85.0 ± 35.2	87.2 ± 50.2	88.8 ± 40.6	81.9 ± 43.9	0.88
End-systolic volume (ml)	35.0 ± 20.8	34.7 ± 17.9	34.7 ± 25.4	38.0 ± 19.1	32.6 ± 19.9	0.67
Left atrial volume index (ml/m^2)	53.8 ± 36.7	52.2 ± 24.7	55.4 ± 55.6	52.4 ± 28.6	55.0 ± 31.6	0.96
Left ventricular mass index (g/m^2)	122 ± 42	119 ± 45	124 ± 51	124 ± 32	120 ± 38	0.93
Relative wall thickness	0.41 ± 0.09	0.39 ± 0.09	0.42 ± 0.09	0.40 ± 0.10	0.41 ± 0.08	0.68
E wave (cm/s)	88 ± 37	80 ± 29	85 ± 33	90 ± 31	97 ± 49	0.16
E/*e*′	15.5 ± 8.4	14.9 ± 7.0	14.2 ± 4.8	16.1 ± 9.1	16.4 ± 11.1	0.57
Tricuspid regurgitation pressure gradient (mmHg)	29 ± 13	25 ± 11	27 ± 10	34 ± 15	30 ± 11	0.01
Inferior vena cava diameter (mm)	15.1 ± 4.8	14.5 ± 4.7	14.9 ± 4.5	15.7 ± 5.3	15.1 ± 4.4	0.7
Mode of death						
CV death, no (%)	24 (13)	3 (6)	5 (10)	8 (17)	8 (17)	0.34

Table1 (*Continued*)

	All patients $N = 191$	First Quarter $N = 47$	Second Quarter $N = 48$	Third Quarter $N = 48$	Fourth Quarter $N = 48$	*p*-Value*
Sudden death or MI death, no (% of CV death)	8 (33)	3 (100)	1 (20)	3 (38)	1 (12.5)	
HF death, no (% of CV death)	13 (55)	0	3 (60)	4 (50)	6 (75)	
Cerebrovascular death, no (% of CV death)	1 (4)	0	1 (20)	0	0	
Other vascular death, no (% of CV death)	2 (8)	0	0	1 (12)	1 (12.5)	
Non-CV death, no (%)	10 (5)	1 (2)	2 (4)	0	7 (15)	0.006
Infection/sepsis, no (% of non-CV death)	5 (50)	0	1 (50)	0	4 (57)	
Renal failure, no (% of non-CV death)	1 (10)	0	0	0	1 (14)	
Traumatic hemorrhage, no (% of non-CV death)	1 (10)	0	0	0	1 (14)	
Suicide, no (% of non-CV death)	1 (10)	1 (100)	0	0	0	
Others, no (% of non-CV death)	2 (20)	0	1 (50)	0	1 (14)	

Values are expressed as mean ± SD or median [interquartile range].
COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; CV, cardiovascular; MI, myocardial infarction; HF, heart failure.
* ANOVA between quartile groups.

between sST2 and BNP and mode of death. Soluble ST2 was a significant predictor of all-cause death and non-CV death, whereas BNP was significantly associated with all-cause death and CV death.

There have been several reports that studied clinical correlates of sST2 level [4,16–18]. As with the previous reports [4,17], female patients showed lower level of sST2 than male patients. Explanation for the gender difference of sST2 level is still unclear. However, the analysis from the Valsartan Heart Failure Trial showed that the relationship between sST2 and outcomes were similar between men and women [4]. AbouEzzeddine et al. described the clinical correlates of sST2 in 174 patients with HFpEF from the Phosphodiesterase-5 Inhibition to Improve Clinical Status And Exercise Capacity in Diastolic Heart Failure (RELAX) trial. They reported that elevated sST2 levels in HFpEF were associated with proinflammatory comorbidities including diabetes mellitus, renal dysfunction, and atrial fibrillation; systemic congestion, and RV pressure overload and dysfunction; as well as biomarkers reflecting systemic inflammation and fibrosis [16]. These findings were similar to the present study in that systemic inflammation and RV pressure overload were associated with sST2 level. On the other hand, BMI was not correlated with sST2 level and levels of albumin and hemoglobin were not presented in the previous study. These differences may be due to patients' characteristics. The present study is an analysis from the registry data based on clinical practice resulting in enrolling more elderly patients compared with the RELAX trial, which is a randomized controlled trial. Low BMI, hypoalbuminemia, and anemia may be associated with malnutrition [19–21]. Malnutrition is a common problem leading to poor prognosis in patients with both HFrEF and HFpEF [20,22,23]. Moreover, low BMI, hypoalbuminemia, and anemia may be age-related changes and caused by comorbidities such as chronic kidney disease and chronic obstructive pulmonary disease. Furthermore, serum levels of albumin and hemoglobin are influenced by systemic congestion known as a cause of inflammation and neurohormonal activation [24].

Soluble ST2 has been considered as a marker related with LV remodeling and dysfunction through blocking the IL-33/ST2L signaling that reduces myocardial fibrosis and prevents cardiomyocyte hypertrophy. Zile et al. measured sST2 in 70 patients who underwent coronary artery bypass graft and reported that sST2 was increased in patients with hypertension and further elevated in those with HFpEF [25]. Moreover, sST2 was significantly correlated with pulmonary capillary wedge pressure and increased collagen-dependent stiffness. These findings indicate that sST2 is involved in development of HFpEF. However, we did not observe an association between the degree of LV remodeling and sST2 level in our study population of hospitalized HFpEF patients. Furthermore, among Doppler echocardiographic indices, only TRPG was correlated with sST2 level in the present study. Pulmonary hypertension (PH) secondary to HFpEF is caused by not only LV diastolic dysfunction and volume overload but also intrinsic pulmonary vascular disease (precapillary PH) [26]. Since sST2 was not correlated with LA volume and E/e', the association between sST2 and PH may be related to systemic volume overload and precapillary component caused by pulmonary disease and systemic inflammation. Given the results of the present study, sST2 may represent the recently proposed concept that systemic inflammation and microvascular endothelial dysfunction driven by coexisting conditions are the additional mechanisms of myocardial remodeling and dysfunction leading to HFpEF [11,12,27]. Systemic or cardiac inflammation in HF may be induced by a variety of factors such as myocardial stress, systemic congestion, and pro-inflammatory comorbidities. It is likely that modest correlations of sST2 in the present study were because of diverse mechanisms of inflammation in HF.

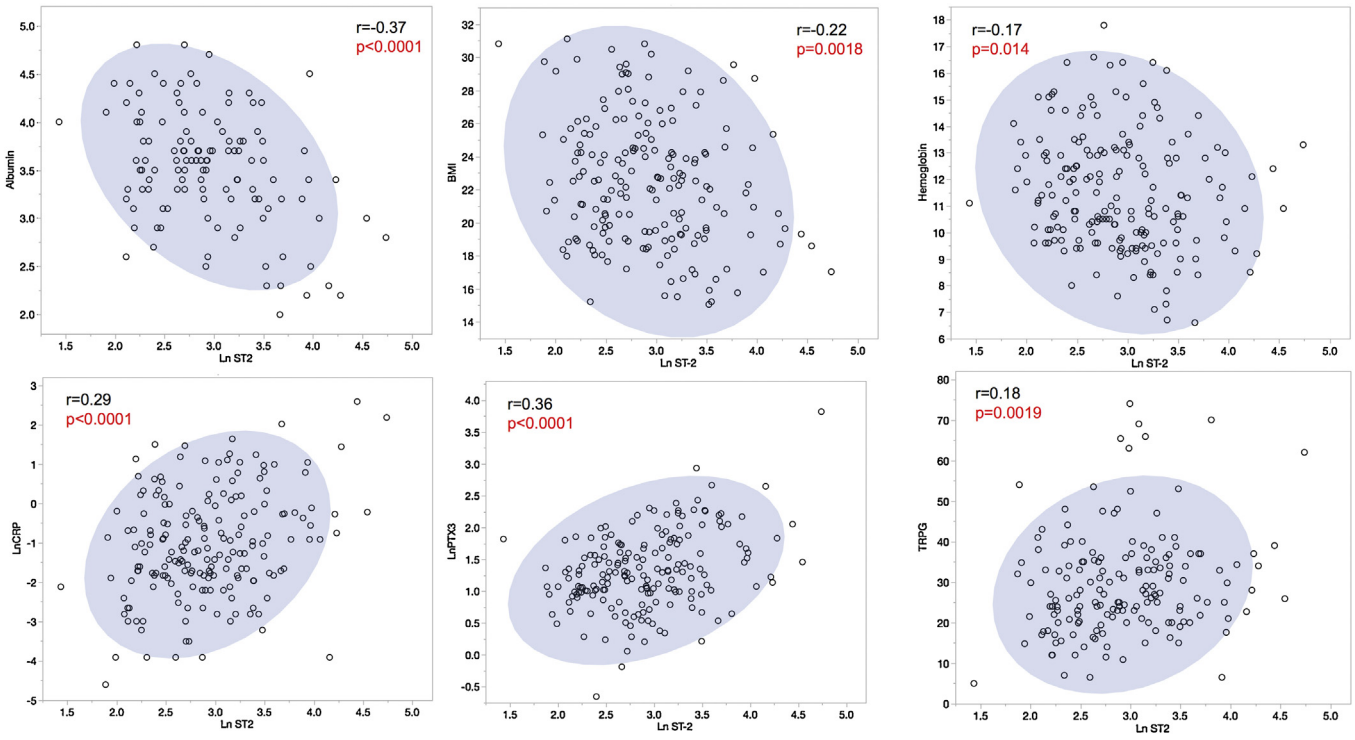

Fig. 1. The correlation between ln-transformed soluble ST2 (sST2) level and clinical variables. Levels of albumin, body mass index (BMI), and hemoglobin were negatively correlated with ln-transformed sST2. Levels of ln-transformed C-reactive protein (CRP), ln-transformed pentraxin3 (PTX3), and tricuspid regurgitation pressure gradient (TRPG) were positively correlated with ln-transformed sST2.

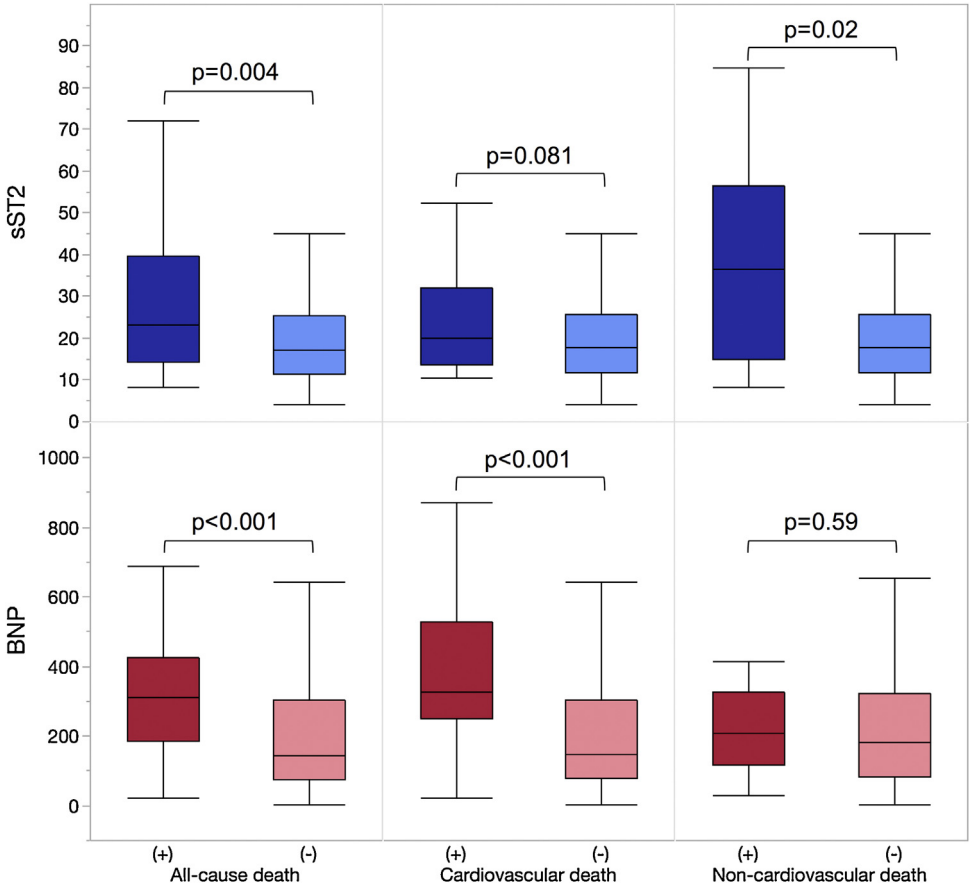

Fig. 2. Comparison of levels of soluble ST2 (sST2) and brain natriuretic peptide (BNP) in patients with or without endpoint. Level of sST2 was significantly higher in patients with all-cause death and non-cardiovascular (CV) death compared with those without. Level of BNP was significantly higher in patients with all-cause death and CV death compared with those without.

Table 2
Cox proportional hazard models for all-cause death, cardiovascular death, and non-cardiovascular death.

	All-cause death				Cardiovascular death				Non-cardiovascular death			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Age	1.07 (1.03–1.12)	<0.001	1.07 (1.003–1.11)	0.001	1.07 (1.03–1.13)	<0.001	1.08 (1.03–1.13)	0.001	1.06 (0.99–1.16)	0.05		
Male	1.11 (0.56–2.20)	0.75			0.98 (0.43–2.22)	0.97			1.48 (0.42–5.8)	0.53		
BMI	0.88 (0.80–0.97)	0.02			0.86 (0.76–0.97)	0.02			0.92 (0.77–1.09)	0.39		
GFR	0.97 (0.95–0.99)	0.005			0.97 (0.95–0.99)	0.02			0.97 (0.93–1.00)	0.09		
Hemoglobin	0.79 (0.67–0.94)	0.008			0.79 (0.64–0.97)	0.02			0.80 (0.58–1.08)	0.16		
sST2	1.02 (1.01–1.03)	<0.001	1.02 (1.009–1.04)	0.002	1.02 (1.00–1.03)	0.01			1.03 (1.01–1.05)	0.002	1.02 (1.01–1.04)	0.003
BNP per 100 pg/ml	1.12 (1.030–1.21)	0.003	1. 17 (1.07–1.29)	0.005	1.16 (1.07–1.25)	<0.001	1.24 (1.11–1.38)	<0.001	0.99 (0.99–1.00)	0.73		
CRP	1.22 (1.04–1.38)	0.02			1.05 (0.76–1.29)	0.68			1.43 (1.17–1.68)	0.002	1.41 (1.20–1.70)	0.004
PTX3	1.01 (0.94–1.06)	0.57			1.02 (0.93–1.07)	0.54			1.00 (0.81–1.08)	0.94		
Noradrenaline per 100 pg/ml	1.03 (1.01–1.006)	0.004			1.02 (1.01–1.04)	0.02			1.00 (0.91–1.01)	0.13		

HR, hazard ratio; CI, confidence interval; BMI, body mass index; GFR, glomerular filtration rate; sST2, soluble ST2; BNP, brain natriuretic peptide; CRP, C-reactive protein; PTX3, pentraxin3.

Previous studies have reported sST2 as a predictor of all-cause mortality or composite endpoint of all-cause mortality and HF re-admission in HFpEF patients [7,8,28]. However, there have been no studies that assess the association of sST2 with mode of death in HFpEF. The present study showed that sST2 was associated with all-cause and non-CV death and was not a predictor of CV death, whereas BNP was a predictor of all-cause and CV death. As mentioned above, in the present study, elevated level of sST2 was associated with systemic inflammation, low BMI, and hypoalbuminemia, independent of BNP released in response to a ventricular filling pressure [29]. This finding can explain the difference in those two biomarkers in the prediction of clinical outcome. Kinugasa et al. reported in the study of 152 hospitalized HFpEF patients that low geriatric nutritional risk index representing low BMI and hypoalbuminemia was associated with not only CV mortality risk but also non-CV mortality risk [20]. It has been reported that patients with HFpEF have higher comorbidity burden and higher non-HF hospitalization or non-CV death compared with those with HFrEF [9,11]. Therefore, it is important to assess not only CV mortality risk but also non-CV mortality risk in the management of HFpEF. Since BNP is a useful biomarker for the assessment of hemodynamic wall stress and CV risk, sST2 in conjunction can be useful in the management of HFpEF through assessing the non-CV mortality risk. Considering the correlation with low BMI and hypoalbuminemia, nutritional assessment seems one of the possible situations of practical use of sST2. Nutritional intervention may be one of the potential treatments in HF patients because malnutrition is a common problem and related to poor prognosis among patients with HF. We speculate that sST2 may help us to evaluate necessity for nutritional intervention. However, further studies are needed to confirm the association with nutritional status.

The present study has several limitations. First, the number of patients with events was small. Therefore, the number of variables that could enter multivariable Cox hazard regression models was limited. Second, we used a research-use-only assay for sST2 measurement. A considerable difference between the research-use-only assay and widely used one was reported [30]. Further study is needed to confirm whether our findings are replicated with the use of a commercially available method.

Conclusion

In conclusion, serum sST2 level was associated with systemic inflammation, malnutrition, and PH in patients with HFpEF. However, LV function and structure were not associated with sST2 level. Soluble ST2 was associated with non-CV death, while BNP was associated with CV death.

Conflict of interest

The authors have no conflict of interest.

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