Elevated Soluble ST2 and Depression Increased the Risk of All-Cause Mortality and Hospitalization in Patients With Heart Failure

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SUMMARY

This study aimed to assess the predictive effect of soluble ST2 (sST2) and depressive symptoms in patients with heart failure (HF) and to determine whether the prognosis of HF patients with preserved ejection fraction (HFpEF) differs from those with reduced ejection fraction (HFrEF). A cohort of 233 HF patients was followed for 1 year. Depressive symptoms were evaluated by the Hospital Anxiety and Depression Scale. The primary endpoint was all-cause mortality and HF-related hospitalization. For the analysis of survival, the left ventricular ejection fraction (LVEF) cut-offs for defining HFpEF were set at 50%, 45%, and 40%, respectively. With increasing LVEF, levels of sST2 were gradually decreased (45.2 ng/mL, 35.8 ng/mL, and 32.1 ng/mL in patients with LVEF $\leq$ 40%, 41% to 49%, and $\geq$ 50%, respectively, P for trend $<$ 0.001), as well as the prevalence of depressive symptoms (35.4%, 33.3%, and 20.4%, respectively, P for trend = 0.022). After 1-year follow-up, 128 patients (54.9%) achieved the primary endpoint and 47 patients (20.2%) died. Depressive symptoms were independent risk factors of all-cause mortality and HF-related hospitalization. The combined presence of elevated sST2 ($>$ 36.0 ng/mL) and depressive symptoms was associated with a 4.9-fold increased risk of the primary endpoint. Regardless of LVEF cut-offs, the associated risk of adverse outcomes in HFpEF was as high as in HFrEF after adjustment for significant risk factors including sST2 and N-terminal pro-brain natriuretic peptide. In conclusion, depressive symptoms provided additional prognostic information to that of sST2 in HF patients. The prognosis of HFpEF patients was similar to that of HFrEF patients. (Int Heart J 2014; 55: 445-450)

Key words: Depressive symptoms, N-terminal pro-brain natriuretic peptide

In China's rapidly aging population, heart failure (HF) has become a serious public health problem with an estimated 4.2 million patients experiencing HF in 2010.¹⁾ Approximately half of those affected patients present a preserved ejection fraction. Despite advances in pharmacological therapy and device therapy, no improvements in outcome have been achieved in patients with HF with preserved ejection fraction (HFpEF) in contrast to those with reduced ejection fraction (HFrEF), implying there are pathophysiological differences between the 2 groups.

ST2 (growth stimulation expressed gene 2) is a member of the interleukin (IL)-1 receptor family. It is expressed predominantly on T helper 2-related immune cells and exists in both a transmembrane (ST2L) form and a soluble form (sST2).²⁾ IL-33/ST2L signaling has been reported as a crucial cardioprotective mechanism, while sST2 acts as a decoy receptor of IL-33 and leads to cardiac fibrosis and ventricular dysfunction.^{2,3)} Recent studies revealed that elevated levels of sST2 were associated with adverse outcomes in patients with acute dyspnoea, acute coronary syndromes, and HF.⁴⁻⁶⁾ Depres-

sion, a common psychological disorder in HF patients with prevalence rates ranging from 17% to 77.5%,⁷⁾ is an independent risk factor for adverse outcomes in HF.^{8,9)} To date, the cause/effect relationship between depression and HF is still poorly understood. It is usually assumed that depression was caused by the severity of HF and may hasten the progression of HF via an excessive inflammatory response and neurohormonal dysregulation.¹⁰⁾ However, Gottlieb and colleagues,¹¹⁾ using HF-ACTION (Heart Failure And a Controlled Trial Investigating Outcomes of Exercise Training) data, found minimal or no association between depression and objective parameters of HF severity, such as brain natriuretic peptide and LVEF. It remains unknown if depression is associated with levels of sST2, a novel HF biomarker which reflected both immune response and cardiac fibrosis. In addition, most of these studies were focused on patients with HFrEF. The prognostic role of sST2 and depression in HFpEF remains to be fully elucidated.

Therefore, the purpose of this study was: (1) to assess the relationship between levels of sST2 and depressive symptoms;

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(2) to evaluate the effect of depressive symptoms or sST2 on prognosis in HF patients across a broad range of ejection fraction; (3) to investigate whether the prognosis of patients with HFpEF differs from those with HFrEF.

METHODS

Study population: A total of 233 consecutive HF patients, hospitalized in Union Hospital (Wuhan, China), were enrolled from October 2011 to November 2012. The inclusion criteria were: (1) aged over 18 years, (2) clinical diagnosis of HF with New York Heart Association (NYHA) functional class II-IV, and (3) treated with standard medications of HF for at least 3 months. The exclusion criteria included myocardial infarction within 1 month; moderate-to-severe valvular disease; congenital heart disease; chronic inflammatory disease; thyroid diseases; malignancy; obvious cognitive impairments; alanine transaminase ≥ 2 times the upper limit of normal or serum creatinine > 3 mg/dL.

For the analysis of epidemiological features, participants were divided into 3 groups: a group with reduced left ventricular ejection fraction (LVEF $\leq 40\%$), a group with borderline LVEF (LVEF 41%-49%), and a group with preserved LVEF (LVEF $\geq 50\%$), according to the 2013 ACCF/AHA guideline for the management of HF.¹²⁾ To compare the prognosis of HFpEF patients with HFrEF patients, the LVEF cut-offs for defining HFpEF were set at 50%, 45%, and 40%, respectively. LVEF was assessed by echocardiography using the modified biplane Simpson method.¹³⁾ Pulmonary flow, mitral inflow and annular tissue Doppler imaging were recorded for the assessment of diastolic function.¹⁴⁾ Body mass index (BMI) was calculated as weight/height² (kg/m²). All patients gave informed consent and the study protocol was approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology.

Assessment of psychological status: Patients enrolled in the present study were asked to complete the Hospital Anxiety and Depression Scale (HADS) independently. HADS, a widely used self-report scale with 7 items related to anxiety (HADS-A) and 7 items related to depression (HADS-D), is an assessment focused on psychological symptoms. Items are evaluated on a 4-point scale ranging from 0 to 3. According to the recommended classification of the test author,¹⁵⁾ a score of HADS-D ≥ 8 is considered as having depressive symptoms, and HADS-A ≥ 8 as having anxiety symptoms.

Biochemical analysis: Fasting blood samples were collected by venipuncture into tubes containing EDTA the next day after admission at 6-7 AM. Plasma was separated by centrifugation and then stored at -80°C . sST2 was determined using a quantitative sandwich monoclonal enzyme immunoassay technique (Critical Diagnostics, San Diego, CA, USA). The assay has a total coefficient of variation of 10% and the analytic measurement was 3.1 ng/mL to 200 ng/mL. N-terminal pro-brain natriuretic peptide (NT-pro BNP) measurement was performed by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) as described previously.³⁾

Follow-up: Follow-up was performed every 3 months by telephone calls or outpatient clinic service during a 1-year period. The primary endpoint was a composite of all-cause mortality and rehospitalization for HF due to worsening of the severity

of HF or directly related to HF. Information on mortality was obtained from the patients' medical records or their proxies. Patients were followed until they reached the endpoint or termination of the study.

Statistical analysis: Normally distributed data were expressed as means $\pm$ standard deviation, and for non-normally distributed data, frequency (percent) or median (interquartile range, IQR) were reported. Values of sST2 and NT-pro BNP were log-transformed before analysis. Group comparisons of baseline characteristics were performed by one-way ANOVA for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Spearman correlation analysis and multiple linear regression analysis were then carried out to determine the clinical correlates of log₂ (sST2) in the whole patient population. Receiver operating characteristic (ROC) curves were plotted for sST2, NT-pro BNP and scores of HADS-D, and the area under the curves was compared using Z-testing.

The combined predictive value of sST2 and depressive symptoms or NT-pro BNP was evaluated according to depressive status (HADS-D ≥ 8), the risk reference thresholds of sST2 (> 36.0 ng/mL)⁶⁾ and NT-pro BNP (> 1000 pg/mL).¹⁶⁾ Survival curves were acquired by the Kaplan-Meier method, using a log-rank test for the 3 group differences. Potential risk factors of outcomes, which were statistically significant in univariate Cox regression analysis, were included in multivariate Cox models. The HF group (HFpEF versus HFrEF), with different LVEF cut-offs, was forced into models to calculate the adjusted hazard ratio (HR) between the 2 groups. Statistical significance was set at a two-sided $P < 0.05$. Data analyses were performed using SPSS 19.0 (Inc., Chicago, IL, USA).

RESULTS

Baseline clinical and biochemical characteristics: The patients enrolled in this study included 82 with reduced LVEF, 103 with preserved LVEF, and 48 with borderline LVEF. Associations between LVEF and the baseline characteristics of the study population are shown in Table I. In comparison with patients with lower LVEF, those with higher LVEF were older, more frequently females, and had a lower rate of NYHA III or IV, but a higher rate of NYHA II. They were also more likely to have hypertension and coronary heart disease, and less commonly treated with digitalis, diuretics, and β -blockers.

Levels of sST2 and prevalence of depressive symptoms (HADS-D ≥ 8) were gradually decreased with increasing LVEF (Table I). Univariate and multivariate correlations between sST2 and clinical variables are shown in Table II. Levels of sST2 were independently associated with HADS-D scores, heart rates, troponin I, and NT-pro BNP. However, R^2 of the model was low (0.37).

ROC analysis for predicting mortality and HF-related hospitalization: After 1-year follow-up, there were 47 deaths (20.2%) and 128 patients (54.9%) achieved the primary endpoint. All patients completed the study and no one was lost to follow-up. The median levels of sST2 were significantly increased in patients who experienced the primary endpoint (42.0 ng/mL versus 31.9 ng/mL, $P < 0.001$), as well as in those experienced all-cause death (48.8 ng/mL versus 33.9 ng/mL, $P < 0.001$).

ROC curve analysis, for the occurrence of all-cause mor-

Table I. Baseline Characteristics

Variable	Overall (n = 233)	LVEF ≤ 40% (n = 82)	LVEF 41%-49% (n = 48)	LVEF ≥ 50% (n = 103)	P for trend
Depressive symptoms, n (%)	67 (28.8)	29 (35.4)	16 (33.3)	21 (20.4)	0.022
HADS-D scores	4.0 (3.0-8.0)	6.0 (4.0-9.0)	5.0 (3.0-8.0)	3.0 (2.0-5.0)	< 0.001
Anxiety symptoms, n (%)	64 (27.5)	24 (29.3)	15 (31.3)	25 (24.3)	0.43
Age (years)	62 ± 11	58 ± 11	64 ± 12	65 ± 10	< 0.001
Female, n (%)	102 (43.8)	23 (28.0)	9 (18.8)	70 (68.0)	< 0.001
Heart rate (beats/min)	77 ± 16	86 ± 18	76 ± 16	71 ± 11	< 0.001
Body mass index (kg/m ²)	24.1 ± 3.5	22.9 ± 2.8	23.3 ± 3.5	25.4 ± 3.5	< 0.001
Atrial fibrillation, n (%)	40 (17.2)	20 (24.4)	8 (16.7)	12 (11.7)	0.023
Hypertension, n (%)	150 (64.4)	44 (53.17)	26 (54.2)	80 (77.7)	0.001
Coronary heart disease, n (%)	110 (47.2)	29 (35.4)	22 (45.8)	59 (57.2)	0.012
NYHA class, n (%) I	94 (40.3)	14 (17.1)	17 (35.4)	63 (61.2)	< 0.001
III-IV	139 (59.7)	68 (82.9)	31 (64.6)	40 (38.8)	
β-Blockers, n (%)	177 (76.0)	69 (84.1)	38 (79.2)	70 (68.0)	0.010
Digitalis, n (%)	77 (33.0)	41 (50.0)	16 (33.3)	14 (13.6)	< 0.001
Diuretics, n (%)	130 (55.8)	70 (85.4)	34 (70.8)	26 (25.2)	< 0.001
Soluble ST2 (ng/mL)	35.6 (28.4-48.5)	45.2 (32.6-63.9)	35.8 (30.8-46.1)	32.1 (23.8-37.4)	< 0.001
NT-pro BNP (pg/mL)	951 (1721-4388)	4575 (2120-7515)	1978 (577-5639)	197 (127-300)	< 0.001

Values are expressed as mean ± standard deviation, frequency (percent), or median (interquartile range). HADS-D indicates depression subscale of hospital anxiety and depression scale; NYHA class, New York Heart Association functional class; and NT-pro BNP, N-terminal pro-brain natriuretic peptide.

Table II. Association between sST2 Levels and Clinical Covariates

	Univariate		Coefficient	Multivariate		P
	r	P		95% Confidence interval lower	upper	
LVEF (%)	-0.39	< 0.001	0.003	-0.004	0.009	0.43
HADS-D scores	0.29	< 0.001	0.022	0.003	0.056	0.044
NT-pro BNP (pg/mL)	0.47	< 0.001	0.22	0.062	0.39	0.007
Troponin I (ng/mL)	0.42	< 0.001	0.14	0.028	0.26	0.015
Heart rates (beats/min)	0.31	< 0.001	0.008	0.004	0.013	0.001
Creatinine (mg/dL)	-0.20	< 0.001	-0.001	-0.004	0.002	0.44
Body mass index (kg/m ²)	-0.23	< 0.001	-0.016	-0.041	0.006	0.15

Values of sST2, NT-pro BNP and troponin I were log transformed. HADS-D indicates depression subscale of hospital anxiety and depression scale.

Figure 1. Receiver operating characteristic analysis of soluble ST2 (sST2), NT-pro BNP, and HADS-D for the primary endpoint (A), and all-cause mortality (B). The primary endpoint includes all-cause mortality and heart failure-related hospitalization. HADS-D indicates depression subscale of hospital anxiety and depression scale; and AUC, area under curve.

Figure 2. Survival curves demonstrate the incidence of the primary endpoint (A) and all-cause mortality (B) according to the presence or absence of high sST2 (> 36 ng/mL) and depressive symptoms (HADS-D ≥ 8). Adverse outcomes comparisons are presented as hazard ratio (HR) and 95% confidence interval (CI), adjusted by age, heart rate, BMI, creatinine, NT-pro BNP, NYHA class (II versus III/IV) and history of hypertension. The primary endpoint includes all-cause mortality and heart failure-related hospitalization.

tality and HF-related hospitalization during a 1-year follow-up (Figure 1A), showed an area under the curve (AUC) of 0.75 for sST2 [95% confidence interval (CI) 0.69-0.82], which was similar to NT-pro BNP (AUC = 0.74, 95% CI 0.68-0.81, $P = 0.75$ versus sST2). Combining sST2 with NT-pro BNP (AUC = 0.78, 95% CI 0.73-0.87) significantly improved the prognostic value compared to sST2 or NT-pro BNP alone ($P = 0.014$ versus sST2; $P = 0.039$ versus NT-pro BNP). The combination of sST2 and HADS-D had an AUC of 0.77 (95% CI 0.71-0.83), which was greater than sST2 alone ($P = 0.041$) but similar to the combination of sST2 with NT-pro BNP ($P = 0.80$). The appropriate cut-off point of sST2 for predicting 1-year all-cause mortality and HF-related hospitalization was 37.0 ng/mL with the Youden index being 0.44 (sensitivity 0.64, specificity 0.80). For 1-year all-cause mortality, combining sST2 and NT-pro BNP substantially improved the AUC compared with either biomarker alone ($P = 0.012$ versus sST2; $P = 0.045$ versus NT-pro BNP, Figure 1B).

Predictive value of sST2 and depressive symptoms: Multivariate Cox regression analysis demonstrated that depressive symptoms (HR 2.54, 95% CI 1.68-3.84, $P < 0.001$) and elevation of sST2 (log₂ transformed, HR 2.19, 95% CI 1.55-3.10, $P < 0.001$) were both independent predictors of all-cause mortality and HF-related hospitalization even after adjustment for age, heart rate, BMI, creatinine, NT-pro BNP, NYHA class (II versus III/IV), and history of hypertension.

The combined risks of sST2 and depressive symptoms were assessed by dividing the cohort into 3 groups. Patients with both high sST2 (> 36.0 ng/mL) and depressive symptoms had an approximately 4.9-fold increased risk of all-cause mortality and HF-related hospitalization (HR 4.88, 95% CI 2.81-8.46, $P < 0.001$), and patients with either high sST2 or depressive symptoms had a 2.9-fold increased risk (HR 2.86, 95% CI 1.81-4.51, $P < 0.001$, Figure 2A), compared with those with neither high sST2 nor depressive symptoms, adjusting for age, heart rate, BMI, creatinine, NT-pro BNP, NYHA class (II versus III/IV), and history of hypertension. Similar trends were also observed for all-cause mortality (Figure 2B).

Combined predictive value of sST2 and NT-pro BNP: Compared with patients with low levels of sST2 and NT-pro BNP

(Figure 3A), either an elevated sST2 or NT-pro BNP was associated with a significant 2.2-fold risk of the primary endpoint when adjusted for age, heart rate, BMI, creatinine, NYHA class (II versus III/IV), history of hypertension, and depressive symptoms. Patients with both elevated biomarkers had a remarkably increased risk (HR 3.71, 95% CI 2.13-6.47, $P < 0.001$). Consistent trends were also found for all-cause mortality alone (Figure 3B).

Prognosis of HFpEF in comparison to HFpEF: Regardless of whether the cut-off value for LVEF was 50%, 45% or 40%, patients with HFpEF had a lower primary endpoint rate and a lower mortality rate than patients with HFpEF after adjustment for age, heart rate, BMI, creatinine, NYHA class (II versus III/IV), and history of hypertension, except for sST2 and NT-pro BNP. However, the risk of both mortality and the primary endpoint had no significant difference between patients with HFpEF and those with HFpEF when additionally adjusted for sST2 and NT-pro BNP (Table III).

DISCUSSION

In the present study, we found that elevated levels of sST2 and depressive symptoms were both independent risk factors of all-cause mortality and HF-related hospitalization at 1-year in patients with HF, and the survival rate was lowest in patients with both high levels of sST2 and depressive symptoms compared with those with either or neither high levels of sST2 or depressive symptoms. A wealth of clinical data have demonstrated that levels of sST2, as well as depressive symptoms, are strongly associated with severity of HF.^{3,7)} In addition, Han, *et al*¹⁷⁾ found large expressions of IL-33 and sST2 in astrocytes or microglia, whose activation or reduction are key features of depression.^{18,19)} In our study, sST2 was independently but not significantly related to the HADS-D scores, and this result was consistent with the HF-ACTION trial which showed that functional and subjective indexes of HF severity were much more closely associated with depressive symptoms than objective parameters.¹¹⁾ Thus, depression and sST2 might adversely affect HF progression by different pathophysiologic pathways,

Figure 3. Survival curves demonstrate the incidence of the primary endpoint (A) and all-cause mortality (B), according to the presence of none, either or both high sST2 (> 36 ng/mL) and high NT-pro BNP (> 1000 pg/mL). Adverse outcomes comparisons are presented as hazard ratio (HR) and 95% confidence interval (CI), adjusted by age, heart rate, BMI, creatinine, NYHA class (II versus III/IV), history of hypertension, and depressive symptoms (HADS-D ≥ 8 versus HADS-D < 8). The primary endpoint includes all-cause mortality and heart failure-related hospitalization.

Table III. Cox Regression Analysis for Comparing Prognosis of HFrEF and HFpEF Using Different LVEF Cut-offs

	Primary endpoint		All-cause mortality	
	HR (95% CI)	P	HR (95% CI)	P
HFrEF versus HFpEF (50% cut-off)				
unadjusted	2.54 (1.75-3.70)	< 0.001	2.59 (1.34-4.99)	0.004
adjusted with clinical covariates	1.93 (1.23-3.03)	0.004	1.70 (1.08-2.83)	0.027
adjusted with clinical covariates plus sST2 and NT-pro BNP	1.02 (0.53-1.95)	0.95	1.07 (0.49-2.36)	0.86
HFrEF versus HFpEF (45% cut-off)				
unadjusted	2.52 (1.76-3.63)	< 0.001	2.47 (1.32-4.61)	0.005
adjusted with clinical covariates	1.91 (1.22-2.99)	0.005	1.90 (1.04-3.58)	0.036
adjusted with clinical covariates plus sST2 and NT-pro BNP	1.01 (0.55-1.87)	0.96	0.53 (0.23-1.24)	0.14
HFrEF versus HFpEF (40% cut-off)				
unadjusted	2.59 (1.82-3.67)	< 0.001	3.58 (1.99-6.46)	< 0.001
adjusted with clinical covariates	2.34 (1.52-3.63)	< 0.001	2.47 (1.23-4.98)	0.011
adjusted with clinical covariates plus sST2 and NT-pro BNP	1.53 (0.95-2.56)	0.067	1.74 (0.83-3.65)	0.14

Clinical covariates including age, heart rate, body mass index, creatinine, NYHA class (II versus III/IV), history of hypertension and depressive symptoms (HADS-D ≥ 8 versus HADS-D < 8). Values of sST2 were $\log_2$ transformed and NT-pro BNP were $\log_{10}$ transformed. HR indicates hazard ratio; CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; and HFpEF, heart failure with preserved ejection fraction.

and adding depressive symptoms to sST2 may improve risk discrimination of HF patients.

Another finding of this investigation was that, regardless of the LVEF cut-offs, the prognosis was similar between HFpEF and HFrEF patients when adjusted for significant covariates including sST2 and NT-pro BNP. This result was inconsistent with previous studies which assumed that patients with HFpEF had a better prognosis than those with HFrEF.^{20,21} One possible explanation for this discrepancy is due to the limited value of LVEF in the prognostication of patients with HF, especially in those with HFpEF.^{22,23} As indicated by the CHARM program (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity), LVEF is so load-dependent, and this measurement is incomplete to estimate diastolic function or true myocardial function in a variety of pathological conditions.²³ In contrast, sST2, expressed increasingly by fibroblasts and cardiomyocytes in responding to mechanical stress and inflammation,² is positively associated with natriuretic peptides, LVEF and diastolic filling pressures.^{4,24} It could provide additional prognostic information to that of NT-pro BNP.^{5,6} Thus, elevated levels of sST2 and NT-pro BNP de-

crease the survival for both HF groups and specifically for HFpEF, presenting a comparable rate of mortality and readmission with that of HFrEF. The combination of sST2 with NT-pro BNP may have the important clinical implication that it is more effective for controlling the severity of heart failure than LVEF alone. The combined assessment of the 2 biomarkers may not only be beneficial for designing clinical trials but also valuable for assessing disease progression of HF.

Our study also showed that the prevalence of depressive symptoms in patients with HFpEF was lower than that in those with HFrEF, which is in disagreement with the result of Kato and colleagues (24% versus 25%, $P > 0.05$).²⁵ This can probably be attributed to the different exclusion criteria of Kato, *et al*, who excluded patients with NYHA functional class IV who were more likely to be depressed, while we did not. Furthermore, their sample size was smaller (61 HFpEF and 45 HFrEF). Additionally, we found that depressive symptoms and older age were both independent risk factors of all-cause mortality and/or HF-related hospitalization, consistent with the results from previous studies.^{8,9} The Cardiovascular Health Study also revealed that motivational depletion might play an

important role in the relation between depression and mortality in elderly adults (≥ 65 years) from the general population.²⁶⁾

Our study has several limitations. First, the sample size was relatively small, and thus larger and multicentre studies in diverse populations are needed. Second, we did not assess the changes in depressive symptoms and concentrations of sST2 and NT-pro BNP at the end of follow-up, which prevented us from exploring the prognostic association between biomarkers and depressive symptoms. Third, we did not analyze the correlation between sST2 and echocardiographic parameters although previous studies did.^{4,27)}

In conclusion, sST2 and depressive symptoms were independent and additive predictors of all-cause mortality and heart failure-related hospitalization in patients with HF. The prognosis of patients with HFpEF was as poor as that of patients with HFrEF when sST2 and NT-pro BNP were adjusted. Our findings may offer potential important implications for clinical management and therapeutic decisions.

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