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Original Article

The relationship between peripheral blood soluble ST2, BNP levels, cardiac function, and prognosis in patients with heart failure

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Abstract: Objective: To analyze the relationship between peripheral blood soluble growth-stimulated expression gene 2 protein (sST2) and B-type natriuretic peptide (BNP) levels and cardiac function and prognosis in patients with heart failure (HF). Methods: HF patients (n = 183) and 50 healthy volunteers were enrolled in this retrospective study. The relationships between peripheral blood sST2 and BNP levels and cardiac function in patients with HF were analyzed by Pearson's correlation analysis. HF patients were divided into a poor prognosis group (n = 25) and a good prognosis group (n = 158) during the 1-year follow-up period, and variables that might affect the prognosis of HF patients were screened by univariate analysis. Result: The peripheral blood sST2 and BNP levels of HF patients were higher than those of healthy controls. Compared to the good prognosis group, the poor prognosis group had higher LVDs, LVDd, but lower LVEF, D-dimer, hemoglobin (HB) levels, uric acid, sST2, BNP, troponin I (TnI), creatine kinase isozyme-MB, myoglobin, creatinine (Cr), and hypersensitive C-reactive protein. LVEF, sST2, BNP, TnI, and HB were independent risk factors affecting the prognosis of patients with HF. Higher levels of peripheral blood sST2 and BNP were associated with the worse prognosis in HF. Conclusion: Peripheral blood sST2 and BNP levels in HF patients were correlated with cardiac function. LVEF, sST2, BNP, TnI, and HB were independent risk factors affecting the prognosis of HF patients, among which sST2 and BNP were all negatively correlated with prognosis.

Keywords: Heart failure, cardiac function, soluble growth-stimulated expression gene 2 protein, B-type natriuretic peptide, prognosis

Introduction

Heart failure (HF) is characterized by ventricular dysfunction and altered neurohumoral regulation, often accompanied by dyspnea, fluid retention, reduced exercise tolerance, and significantly shorter survival time [1, 2]. The high morbidity and mortality rates of HF are associated with hospitalization and post-discharge clinical endpoints [3]. HF is not a single entity, but a clinical syndrome that may have different characteristics depending on age, sex, race, left ventricular ejection fraction (LVEF), and HF etiology [4]. Despite the ambiguities and overlap with other chronic conditions, the unquestionable multifold higher risk for cardiovascular death as well as subsequent repeat exacerbations of symptoms, require hospitalizations for HF patients with this clinically determined diagnosis [5]. Therefore, early assessment of the condition and prognosis of patients with HF is of great importance. In addition to clinical investigation, echocardiography is an important tool to diagnose HF, and it can be used to distinguish different kinds of HF and monitor disease progression [6]. However, it does not provide insight into the underlying molecular and cellular processes. Plasma biomarkers have the potential to provide information about specific processes that drive cardiac dysfunction and the transition from compensated to decompensated HF in patients, so they may add prognostic value and help guide therapy [7].

The source of tumorigenicity 2 (ST2) represents a member of the interleukin (IL)-1 cytokine receptor superfamily and exists in both mem-

brane-bound and soluble (sST2) forms [8]. After myocardial mechanical stretch stimulation, the peripheral blood sST2 was significantly elevated in patients with HF [9, 10]. sST2 competitively binds to IL-33 and is involved in myocardial fibrosis, ventricular remodeling, and myocardial hypertrophy [11, 12]. sST2 is mainly produced outside of the heart in response to hemodynamic overload, inflammation, and profibrotic stimuli, which are common in HF [13]. However, the relationship between sST2 and the prognosis in HF patients is unclear. B-type natriuretic peptide (BNP) is mainly synthesized and secreted by myocytes in the LV as a response to myocytes stretched by pressure overload or volume expansion of the ventricle [14]. An elevated level of BNP is closely related to the severity of disease in HF patients [15, 16]. Furthermore, BNP levels have been reported to be positively associated with all-cause and HF mortality [17]. In this study, we analyzed the relationship between peripheral blood sST2 and BNP levels and the cardiac function and prognosis in patients with HF.

Data and methods

General data

This retrospective study included a total of 183 patients with HF admitted to the Division of Cardiology, Department of Internal Medicine, the First Affiliated Hospital of Chongqing Medical University, from January 2020 to July 2021 (named the HF group). There were 91 males and 92 females, aged 24-89, with a mean age of (66.29 ± 10.30). Fifty volunteers for health checkups were enrolled as well (named the healthy control group). There were 25 males, aged 25-76, with a mean age of (65.81 ± 9.46). HF group and healthy control group had no significant differences in general information ($P > 0.05$).

Inclusion criteria for patients with HF were as follows: (1) met the HF diagnostic criteria proposed by the Chinese Heart Failure Diagnosis and Treatment Guidelines 2018 [18], including signs and symptoms of HF (e.g., elevated jugular venous pressure and altered apical beat position), altered LVEF (< 40%; 40%-49%; ≥ 50%), elevated natriuretic peptide combined with left ventricular hypertrophy and/or left atrial enlargement and/or abnormal cardiac diastolic function; (2) were aged > 18 years and had clinical symptoms of dyspnea, limited physical activity, cough, nausea, and vomiting; (3) lung imaging showed increased lung texture, enhanced hilar vascular shadow, with or without pleural effusion, and interlobular pleural thickening. Exclusion criteria were as follows: (1) those with hypertrophic obstructive cardiomyopathy, heart valve disease, and previous medical history; (2) those with malignancy, metabolic dysfunction, or congenital cognitive impairment; (3) those transferred or lost to the hospital during the study period. Peripheral blood was collected from patients after the diagnosis of HF and from volunteers during the same period. Clinical data from patients with HF at the time of admission were used for subsequent analysis. Approval was obtained from the in-house medical ethics committee before the implementation of the study.

Sample treatment

The supernatant was separated and divided into two aliquots and labeled. The level of sST2 (E-EL-H6082, Elabscience Biotechnology Co., Ltd., Wuhan, Hubei, China) was measured by enzyme-linked immunosorbent assay for specimen 1, and the level of BNP (KL-H0461c, KLSW, Shanghai, China) in peripheral blood for specimen 2 by chemiluminescence immunoassay.

Patients with HF were followed up for 1 year after discharge using outpatient follow-up and telephone, and clinical endpoint events (all-cause death, HF-related readmission) were used as the primary outcome measure. Patients with HF who had clinical endpoint events were included in the poor prognosis group, while the rest of the patients with HF were the good prognosis group.

Clinical data were collected from HF patients, including gender, age, body mass index (BMI), New York heart association (NYHA) cardiac function class, systolic blood pressure, diastolic blood pressure, and cardiac ultrasound parameters: left atrial diameter (LAD), left ventricular end-systolic diameter (LVDs), left ventricular end-diastolic diameter (LVDd), LVEF, laboratory parameters: sodium, uric acid, troponin I (TnI), creatine kinase isoenzyme-MB (CK-MB), myoglobin (MYO), D-dimer (D-D), hemoglobin (HB), creatinine (Cr), high-density lipoprotein (HDL), triglycerides (TG), high-sensitivity C reactive protein (hs-CRP).

Table 1. Comparison of peripheral blood sST2 and BNP levels, and cardiac function index levels in the HF group and healthy control group (means ± SD)

Group	Number	sST2 (ng/mL)	BNP (ng/mL)	LAD (mm)	LVDs (mm)	LVDd (mm)	LVEF (%)
HF	183	43.25 ± 2.47	5.64 ± 0.35	37.22 ± 2.39	37.19 ± 2.10	53.16 ± 4.28	53.57 ± 3.24
Healthy control	50	36.46 ± 3.16	3.04 ± 0.50	32.10 ± 2.05	33.37 ± 1.97	46.27 ± 3.25	60.24 ± 4.31
t	-	16.169	42.133	13.818	11.547	10.574	11.961
P	-	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Note: SD, standard deviation; HF, heart failure; sST2, soluble source of tumorigenicity 2; BNP, B-type natriuretic peptide; LAD, left atrial diameter; LVDs, left ventricular end-systolic diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

Table 2. Relationship between peripheral blood sST2 and BNP levels and cardiac function indices in patients with HF

Indicator	LAD		LVDs		LVDd		LVEF	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
sST2	0.494	< 0.05	0.452	< 0.05	0.36	< 0.05	-0.484	< 0.05
BNP	0.497	< 0.05	0.579	< 0.05	0.468	< 0.05	-0.59	< 0.05

Note: HF, heart failure; sST2, soluble source of tumorigenicity 2; BNP, B-type natriuretic peptide; LAD, left atrial diameter; LVDs, left ventricular end-systolic diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

Statistical analysis

SPSS Statistics 26.0 statistical software was used to analyze the data with the test standard of $\alpha = 0.05$. Measured data were described by means ± standard deviation (SD), and the independent sample t-test was used. Counted data were described by [*n*, (%)], and the X^2 test was used to test independence and comparison tests for categorical data. The relationship between the prognosis of patients with HF and the variables was analyzed by the multi-factor Cox regression model.

Results

Evaluation of peripheral blood sST2, BNP levels, and cardiac function indices

As clinically detected, peripheral blood sST2 and BNP levels, and LAD, LVDs, and LVDd were higher in HF patients than in the healthy control group (all $P < 0.05$), while LVEF was lower than in the healthy control group ($P < 0.05$). See **Table 1**.

Relationship between peripheral blood sST2 and BNP levels and cardiac function indices in patients with HF

The results of Pearson's correlation analysis showed that peripheral blood sST2 levels in patients with HF were positively correlated with LAD, LVDs, and LVDd (all $P < 0.05$) but negatively correlated with LVEF ($P < 0.05$). Peripheral blood BNP levels were positively correlated with LAD, LVDs, and LVDd (all $P < 0.05$) but negatively correlated with LVEF ($P < 0.05$). See **Table 2**.

Comparison of clinical data between the two groups of HF patients

At 1 year follow-up, a total of 25 patients with clinical endpoint event HF (including 2 all-cause deaths and 23 HF-related readmissions) were included in the poor prognosis group, and the remaining 158 were included in the good prognosis group.

There were no significant differences between the two groups in gender, BMI, systolic blood pressure, diastolic blood pressure, LAD, blood sodium, HDL, and TG (all $P > 0.05$). However, there were significant differences in age, NYHA cardiac function classification, LVDs, LVDd, LVEF, D-D, HB, uric acid, sST2 BNP, TnI, CK-MB, MYO, Cr, and hs-CRP between groups (all $P < 0.05$). See **Table 3**.

Risk factors affecting prognosis of patients with HF

Clinical endpoint events (all-cause death, readmission) were deemed as dependent variables, and age, NYHA cardiac function classification, LVDs, LVDd, LVEF, sST2, and BNP as independent variables. We established a multifactorial Cox regression model. The results showed that LVEF, sST2, BNP, TnI, and HB were

Table 3. Comparison of clinical data between the two groups of HF patients

Factor	Poor prognosis group (n = 25)	Good prognosis group (n = 158)	X^2	*P*
Sex [Male, (*n*), %]	13 (52.00)	78 (49.37)	0.06	0.807
Age (years)	70.36 ± 1.28	65.65 ± 2.04	11.186	< 0.001
BMI (kg/m^2)	22.68 ± 1.30	22.92 ± 1.25	0.887	0.376
NYHA Heart Function Classification				
Class I (*n*, %)	2 (8.00)	60 (37.98)	28.418	< 0.001
Class II (*n*, %)	9 (36.00)	8 (5.06)		
Class III (*n*, %)	12 (48.00)	70 (44.30)		
Class IV (*n*, %)	2 (8.00)	20 (12.66)		
Systolic blood pressure (mmHg)	126.34 ± 1.39	126.91 ± 1.42	1.87	0.063
Diastolic blood pressure (mmHg)	78.00 ± 1.25	77.68 ± 2.36	0.662	0.509
Cardiac ultrasound values				
LAD (mm)	37.52 ± 1.39	37.18 ± 1.36	1.158	0.248
LVDs (mm)	39.84 ± 2.08	36.77 ± 1.25	10.269	< 0.001
LVDd (mm)	52.36 ± 0.49	50.82 ± 0.67	11.024	< 0.001
LVEF (%)	49.52 ± 2.38	54.21 ± 3.31	6.804	< 0.001
Laboratory Metrics				
Blood sodium (mmol/L)	138.12 ± 10.10	138.95 ± 10.30	0.375	0.708
Uric acid (μmol/L)	401.38 ± 5.31	393.95 ± 4.28	7.792	< 0.001
sST2 (ng/mL)	43.15 ± 2.33	32.27 ± 2.46	20.689	< 0.001
BNP (ng/mL)	8.12 ± 0.96	5.24 ± 0.54	21.846	< 0.001
TnI (ng/mL)	1.73 ± 0.16	0.44 ± 0.08	63.365	< 0.001
CK-MB (U/L)	40.61 ± 2.05	9.57 ± 1.10	113.767	< 0.001
MYO (μg/L)	176.58 ± 10.62	105.58 ± 4.63	56.949	< 0.001
D-D (mg/L)	1.18 ± 0.21	1.40 ± 0.19	5.302	< 0.001
HB (g/L)	123.68 ± 2.36	129.11 ± 1.40	16.155	< 0.001
Cr (μmol/L)	167.04 ± 6.15	115.90 ± 9.46	26.136	< 0.001
HDL (mmol/L)	1.19 ± 0.06	1.17 ± 0.07	1.351	0.178
TG (TG)	1.25 ± 0.28	1.29 ± 0.30	0.625	0.533
hs-CRP (mg/L)	7.09 ± 1.39	5.75 ± 0.69	7.61	< 0.001

Note: HF, heart failure; BMI, body mass index; NYHA, New York heart association; LAD, left atrial diameter; LVDs, left ventricular end-systolic diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; sST2, soluble source of tumorigenicity 2; BNP, B-type natriuretic peptide; TnI, troponin I; CK-MB, creatine kinase isoenzyme-MB; MYO, myoglobin; D-D, D-dimer; HB, hemoglobin; Cr, creatinine; HDL, high-density lipoprotein; TG, triglycerides; hs-CRP, high-sensitivity C reactive protein.

independent risk factors for the poor prognosis of HF patients. See **Table 4**.

The impact of peripheral blood sST2 and BNP levels on the prognosis of HF patients

The results of the unpaired t-test analysis showed that peripheral blood sST2 and BNP levels were increased in poor prognosis HF patients ($P < 0.05$). See **Figure 1**.

Discussion

Currently, the diagnosis of HF is mainly based on history, signs, and imaging examinations, but for patients with HF with atypical symptoms, the above diagnostic tools have certain limitations, and it is important to explore more objective and specific indexes to assess cardiac function [19, 20]. It has been reported [21] that sST2 and BNP are closely related to the development of HF and have gradually been used in the diagnosis of various cardiovascular diseases including HF. This study aimed to analyze the relationship between peripheral blood sST2 and BNP levels and cardiac function and prognosis in patients with HF, to provide a theoretical basis for clinical diagnosis and treatment of HF and to improve prognosis.

Table 4. Cox regression model for the analysis of factors influencing prognosis in patients with HF

Independent variable	*β*	*SE*	*Wald* x^2	*P*	*RR*	95% *CI*
LVEF	0.774	0.228	11.524	< 0.05	2.168	2.010~2.327
sST2	0.769	0.242	10.098	< 0.05	2.158	1.955~2.360
BNP	0.801	0.229	12.235	< 0.05	2.228	2.107~2.349
TnI	0.791	0.26	9.256	< 0.05	2.206	1.998~2.413
HB	0.758	0.257	8.699	< 0.05	2.134	1.886~2.382

Note: HF, heart failure; LVEF, left ventricular ejection fraction; sST2, soluble source of tumorigenicity 2; BNP, B-type natriuretic peptide; TnI, troponin I; HB, hemoglobin.

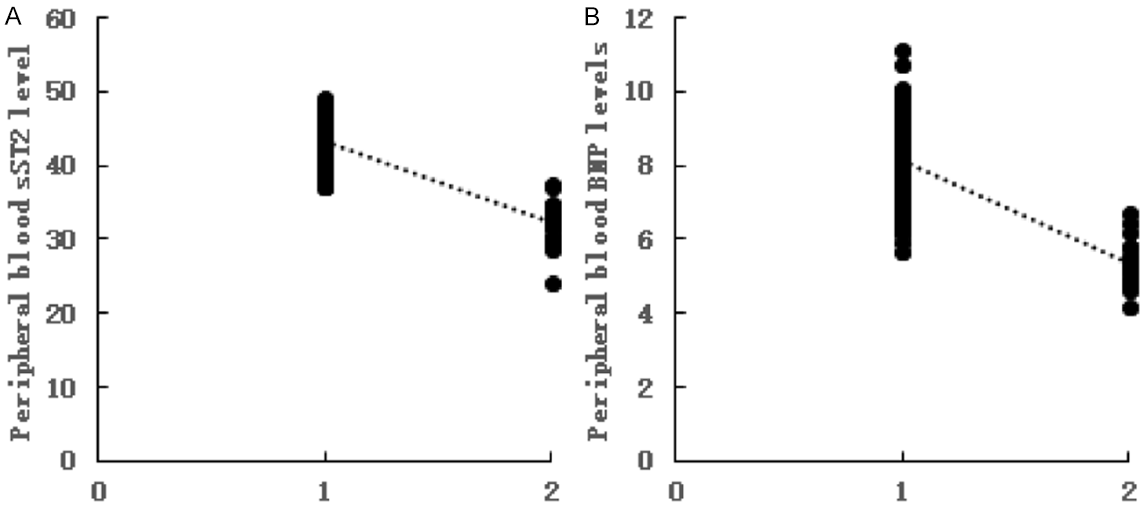

Figure 1. Different peripheral blood sST2 (A) and BNP levels (B) between good and poor prognosis of HF patients by unpaired t-test (1: the poor prognosis group; 2: the good prognosis group). HF, heart failure; sST2, soluble source of tumorigenicity 2; BNP, B-type natriuretic peptide.

It has been found that serum sST2 levels were significantly higher in patients with respiratory distress due to acute heart failure than in patients with respiratory distress due to non-cardiac disease and that sST2 levels were positively correlated with the severity of HF [22]. The results of Pearson's correlation analysis in this study showed that the peripheral blood sST2 levels in patients with HF were positively correlated with LAD, LVDs, and LVDd, and negatively correlated with LVEF, indicating that sST2 was closely related to the degree of ventricular remodeling and cardiac contractile function. We postulated that as cardiac function deteriorates and LVEF decreases, the sudden increase in cardiac pressure load stimulates cardiomyocytes and fibroblasts to secrete sST2, resulting in increased levels. The relationship between sST2 and the stage of HF can be further explored clinically. BNP can reduce sympathetic excitability and delay ventricular remodeling by inhibiting the renin-angiotensin-aldosterone system, and its level was significantly and positively correlated with the ventricular pressure load value in HF [23]. The results of this study also showed that peripheral blood BNP levels were positively correlated with LAD, LVDs, and LVDd, and negatively correlated with LVEF, suggesting that BNP levels gradually increased as clinical symptoms of HF worsened, ventricular contractility decreased, and intraventricular pressure increased. BNP can be used clinically as a predictor to assess the status of cardiac function in HF.

A follow-up study on patients with HF by Boman *et al.* showed that sST2 and BNP were predictors of 1-year mortality in patients with HF, and sST2 combined with BNP improved the prediction of poor prognostic outcome in patients with HF [24]. The results of multifactorial Cox regression in this study showed that sST2 and BNP were independent risk factors affecting the prognosis of HF patients. The above

findings all confirm that sST2 and BNP are associated with the prognosis of HF patients. Recent studies [25, 26] have found that sST2 is associated with HF. After cardiomyocytes are stimulated by mechanical tension, sST2 expression is increased in cardiomyocytes and cardiac fibroblasts, which inhibits the IL-33/ST2L signaling pathway, thus affecting the prognosis of HF patients. BNP has been reported as an independent predictor of mortality (all-cause and cardiovascular) in acute decompensated HF despite different cut points, time intervals, and prognostic models [27]. After the occurrence of HF, the ventricular load increases, and cardiomyocytes are stimulated to secrete a large amount of BNP, which resists the body circulation and constricts the renal vasculature after a large amount of BNP enters the blood, further increasing the cardiac load and renal sodium retention. This may be the reason why BNP affects the prognosis of HF patients [28]. In addition, the results of Pearson's correlation analysis in this study showed that peripheral blood sST2 and BNP levels were negatively correlated with the prognosis of HF patients. Under normal conditions, sST2 and BNP exist only in cardiomyocytes, and their secretion is influenced by the metabolic level of the body, while when HF occurs, the ventricular volume increases dramatically, and sST2 and BNP secretion is induced by cardiac insufficiency [29].

In conclusion, peripheral blood sST2 and BNP levels were correlated with cardiac function and prognosis in patients with HF, and sST2 and BNP were risk factors affecting the prognosis of patients with HF. Since all-cause death and readmission were regarded as the clinical endpoint events and the criteria to distinguish patients with a good prognosis or a poor prognosis, they were not analyzed as risk factors separately. Therefore, further studies are necessary to validate our conclusion.

Disclosure of conflict of interest

None.

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