

The value of soluble suppression of tumorigenesis-2 (sST2) in the maintenance of hemodialysis patients with heart failure

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Abstract

Background: Patients with end-stage renal disease are prone to develop heart failure (HF). The N-terminal pro-brain natriuretic peptide (NT-proBNP, BNP) is regarded as the gold standard for diagnosing HF. However, its prognostic sensitivity in patients with end-stage renal disease is sub-optimal. Soluble suppression of tumorigenesis-2 (sST2) has been well studied in HF but rarely in patients with maintenance hemodialysis (MHD). This study aimed to evaluate the value of sST2 in predicting HF in MHD patients.

Methods: Twenty-three patients with New York Heart Association (NYHA) class III-IV were included in the HF group and 88 NYHA class I-II patients in the non-heart failure (NHF) group. sST2 and laboratory indexes were compared between the two groups.

Results: The HF group, compared with the NHF group, presented with higher sST2, more advanced age, higher incidence of coronary heart disease (CHD), left ventricle end-diastolic diameter (LVEDD), and pulmonary artery pressure (PAP), and unchanged parathyroid hormone (iPTH). The HF group also had lower ejection fraction (EF), uric acid, inorganic phosphorus, 25-OH VitD3, and serum albumin. Multivariate logistic regression indicated that age, BNP, and sST2 were independent risk factors of HF in MHD patients. Spearman analysis defined that sST2 was positively correlated with PAP ($r=0.283$, $p=0.003$) and C-reactive protein ($r=0.354$, $p<0.001$); and negatively correlated with sex ($r=-0.255$, $p=0.007$), albumin ($r=-0.366$, $p<0.001$), uric acid ($r=-0.213$, $p=0.025$), 25-OH VitD3 ($r=-0.216$, $p=0.04$), calcium ($r=-0.219$, $p=0.021$), and inorganic phosphorus ($r=-0.256$, $p=0.007$). Receiver operating characteristic curve analysis determined a positive association between BNP and sST2 ($r=0.373$, $p<0.001$), with the area under the curve (AUC) of BNP being 0.822 (sensitivity: 0.783, specificity: 0.830) and the AUC of sST2 being 0.841 (sensitivity: 0.913, specificity: 0.761). The AUC of sST2 was 0.841, and the cut-value was 42.840 (sensitivity: 0.913, specificity: 0.761).

Conclusion: sST2 can predict HF in MHD patients and facilitate early diagnosis and prevention of HF in MHD patients. HIPPOKRATIA 2022, 26 (1):19-24.

Keywords: Soluble suppression of tumorigenesis-2, sST2, N-terminal pro-brain natriuretic peptide, NT-proBNP, hemodialysis, heart failure

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Introduction

Despite improved survival in chronic kidney disease (CKD) patients, especially those with end-stage renal disease (ESRD), cardiovascular disease (CVD) is the leading cause of death. The secretion of N-terminal pro-brain natriuretic peptide (NT-proBNP, BNP) by cardiomyocytes can be stimulated by stress or volume overload¹. NT-proBNP is regarded as the gold standard for diagnosing heart failure (HF)^{2,3}; however, its sensitivity in patients with end-stage renal disease is sub-optimal. Therefore, more favorable indicators are required. Sup-

pression of tumorigenicity 2 (ST2) has two forms: soluble ST2 (sST2) and ST2 ligand (ST2L). sST2 is a prognostic marker of congestive HF⁴ and, thus, may be an effective diagnostic marker for HF in ESRD. The ligand of ST2 is interleukin 33 (IL-33), which binds to the receptor to produce nuclear signaling and immune regulation in the heart⁴. The binding of IL-33 to ST2L can induce activation of mitogen-activated protein kinase and nuclear factor signaling pathways in target cells while the binding of IL-33 to sST2 can block this effect⁵. Early studies determined that sST2 could not be used as a diagnostic

marker for CKD⁶. Moreover, relatively few studies in assessing the outcome of CKD, especially cardiovascular outcomes, have focused on the value of sST2. However, sST2 plays a vital role in the prognosis of all-cause mortality and cardiovascular events in peritoneal dialysis patients⁷. There are only a few studies on the correlation between the clinical outcome of ESRD patients on hemodialysis and sST2^{8,9}. Recently, sST2 has been identified as an independent predictor of all-cause and cardiovascular death in maintenance hemodialysis (MHD) patients¹⁰. Therefore, this study aimed to evaluate the value of sST2 alone or in combination with BNP in predicting HF in MHD patients.

Material and methods

Patients

One hundred eleven hemodialysis patients (66 males and 45 females) were included in this study at the Department of Nephrology, First Affiliated Hospital of the University of Science and Technology of China, from October 2020 to October 2021. Twenty-three patients with severe symptoms classified as New York Heart Association (NYHA) class III-IV were included in the HF group, and 88 patients with NYHA class I-II symptoms were included in the non-heart failure (NHF) group¹¹. The average age was 58.83 ± 15.96 years. Hemodialysis patients excluded from the study were patients with chest tightness, asthma, or infectious complications, under 18 years old, had dialysis vintage <3 months, or were non-compliant with the dialysis regimen. The Ethics Committee of Anhui Provincial Hospital approved this study (No 2021-RE-143).

Methods

We retrospectively collected the following patients' demographics and clinical characteristics: age, sex, hemodialysis time, diabetes history, coronary heart disease history (CHD), left ventricle end-diastolic diameter (LVEDD), ejection fraction (EF), pulmonary artery pressure (PAP), creatine phosphokinase-isoenzyme-MB (CK-MB), sST2, BNP, C-reaction protein (CRP), uric acid, alkaline phosphatase (AKP), calcium (Ca), inorganic phosphorus (P), 25-OH VitD3, albumin and intact parathyroid hormone (iPTH) after hospitalization and before treatment. The general indicators and laboratory indexes were compared between the two groups.

Statistical analysis

We implemented t-tests or Mann-Whitney U-tests to analyze the relationship between continuous variables and sST2, and we present them as means \pm standard deviation or medians with the 25th and 75th percentiles, respectively. Qualitative variable analyses were performed using χ^2 test. We performed univariate and multivariate logistic regression analyses to identify risk factors of HD in MHD and Spearman analyses to state the correlation between variables and sST2. We used receiver operator characteristic (ROC) curves to assess the accuracy of

sST2 and BNP in diagnosing HF in MHD patients. A p-value <0.05 was considered statistically significant.

Results

Clinical characteristics of MHD patients in the HF and NHF groups

The average age was 58.83 ± 15.96 years, and the incidence of HF was 20.72%. Compared with the NHF group, the HF group presented with higher sST2 ($p < 0.001$), age ($p = 0.001$), incidence of CHD ($p = 0.038$), LVEDD ($p = 0.023$), and PAP ($p = 0.007$), and unchanged iPTH ($p = 0.931$). The HF group also had lower EF ($p = 0.017$), uric acid ($p = 0.020$), P ($p = 0.019$), 25-OH VitD3 ($p = 0.029$), and serum albumin ($p = 0.011$), seen in Table 1.

Univariate and multivariate logistics regression analysis to identify independent predictors of HF in MHD patients

Univariate logistic regression analysis indicated that age, history of CHD ($p = 0.044$), LVEDD ($p = 0.029$), EF ($p = 0.003$), PAP ($p = 0.001$), albumin ($p = 0.012$), uric acid ($p = 0.023$), P ($p = 0.023$), BNP ($p < 0.001$), and sST2 ($p = 0.000$) were correlated to HF (Table 2). When the above indicators were incorporated into multivariate logistic regression analysis, age ($p = 0.010$), BNP ($p = 0.008$), and sST2 ($p = 0.008$) were seen as independent risk factors of HF in MHD patients, seen in Table 2.

The association between variables and sST2

Upon univariate linear regression analysis, a positive correlation was found between sST2 and PAP ($r = 0.283$, $p = 0.003$) or CRP ($r = 0.354$, $p < 0.001$), a negative correlation was found between sST2 and sex ($r = -0.255$, $p = 0.007$), albumin ($r = -0.366$, $p < 0.001$), uric acid ($r = -0.213$, $p = 0.025$), 25-OH VitD3 ($r = -0.216$, $p = 0.040$), calcium ($r = -0.219$, $p = 0.021$), and inorganic phosphorus ($r = -0.256$, $p = 0.007$) (Table 3). Furthermore, positive association between BNP and sST2 was significant ($r = 0.373$, $p < 0.001$) (Table 3). When the above indicators were incorporated into multivariate-adjusted linear regression analysis, albumin was independently associated with sST2 ($r = -2.749$, $p = 0.007$).

ROC curve analysis of BNP and sST2 in MHD patients

Table 4 and Figure 1 show the results of the ROC curve analysis. The area under the curve (AUC) of BNP was 0.822, with the sensitivity and specificity being 0.783 and 0.830, respectively. The AUC of sST2 was 0.841, with the cut-value of sST2 being 42.840 and the sensitivity and specificity being 0.913 and 0.761, respectively. The AUC of sST2 combined with BNP was 0.892, with the cut-value of sST2 being 55.71 and that of BNP being 35,000, the sensitivity and specificity being 0.957 and 0.795 (Figure 2).

Discussion

The cardiovascular and renal systems maintain the stability of blood volume, vascular tension, and hemodynamics through two-way interaction. The primary dysfunction of

Table 1: Baseline characteristics of the 111 hemodialysis patients, of whom 23 patients with New York Heart Association (NYHA) class III-IV were included in the heart failure group (HF) and 88 NYHA class I-II patients in the non-heart failure (NHF) group.

Parameter	HF group (n =23)	NHF group (n =88)	Statistic (t/Z/ χ^2)	P
Age	68.13 ± 14.40	56.40 ± 15.52	-3.274	0.001
Hemodialysis time (years)	33.57 (8-36)	47.01 (12-84)	-1.420	0.156
Sex (male %)	15 (65.22 %)	51 (57.95 %)	0.399	0.528
CHD (%)	7 (30.43 %)	11 (12.50 %)	4.317	0.038
LVEDD (mm)	56.43 ± 6.92	52.99 ± 5.97	-2.309	0.023
EF (%)	56.43 ± 14.11	64.26 ± 7.65	2.559	0.017
PAP (mmHg)	49.30 ± 19.18	37.10 ± 10.93	-2.925	0.007
Hemoglobin (g/L)	96.87 ± 17.31	99.98 ± 23.00	0.604	0.547
AKP (IU/L)	206.87 (67.00-246.00)	121.24 (66.00-128.50)	-1.193	0.233
Uric acid (μ mol/L)	323.53 ± 115.28	395.05 ± 132.28	2.367	0.020
Ca (mmol/L)	2.10 ± 0.31	2.19 ± 0.22	1.523	0.131
P (mmol/L)	1.49 ± 0.71	1.90 ± 0.74	2.384	0.019
CK-MB (U/L)	26.00 (11.00-21.00)	16.08(10.00-18.50)	-1.195	0.232
VitD3 (ng/dl)	12.61 ± 7.79	18.06 ± 10.40	2.218	0.029
sST2 (pg/ml)	78.54 (45.72-99.50)	35.47 (18.17-39.27)	-5.028	<0.001
CRP (μ g/ml)	21.76 (2.99-17.60)	16.14 (1.25-11.10)	-1.472	0.141
Albumin (g/L)	36.50 (34.10-41.60)	39.88 (37.33-43.05)	-2.552	0.011
iPTH (pg/ml)	423.03 (89.55-472.25)	391.94 (97.00-534.00)	-0.087	0.931
BNP (pg/ml)	28976.22 (29000.00-35000.00)	12159.82 (2251.00-17925.25)	-4.778	<0.001

Values are presented as means ± standard deviation, medians with the 25th and 75th percentiles in brackets, or number with percentage in brackets. HF: heart failure group, NHF: non-heart failure group, n: number, CHD: coronary heart disease; LVEDD: left ventricle end-diastolic diameter; EF: ejection fraction; PAP: pulmonary artery pressure; AKP: alkaline phosphatase, Ca: calcium, P: inorganic phosphorus, VitD3: 25-OH VitD3, CK-MB: creatine kinase MB, CRP: C-reaction protein; iPTH: intact parathyroid hormone, BNP: Brain natriuretic peptide, sST2: soluble suppression of tumorigenesis-2

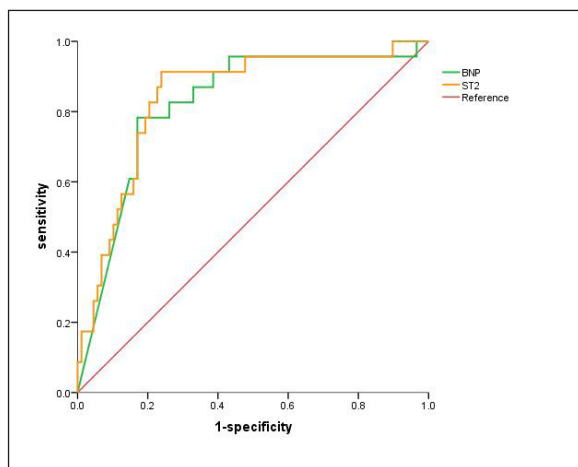


Figure 1: Receiver operator characteristic (ROC) curve analysis of N-terminal pro-brain natriuretic peptide (BNP) [area under the curve (AUC): 0.822, sensitivity: 0.783, specificity: 0.830] and soluble suppression of tumorigenesis-2 (sST2) (AUC: 0.841, sensitivity: 0.931, specificity: 0.761) respectively in hemodialysis patients.

one organ leads to the progressive decline of the two organ systems, known as the cardio-renal system. Chronic kidney-heart disease is characterized by cardiovascular dysfunction based on chronic kidney disease¹². Left ventricular hypertrophy (LVH) is very common in MHD patients. LVH occurs in approximately 69 % of pediatric patients and 75 % of adult patients at the commencement of dialysis, and almost 100 % of patients after five years of dialysis^{13,14}. Cardiomyopathy (uremic cardiomyopathy), impaired diastolic filling, myocardial fibrosis, and

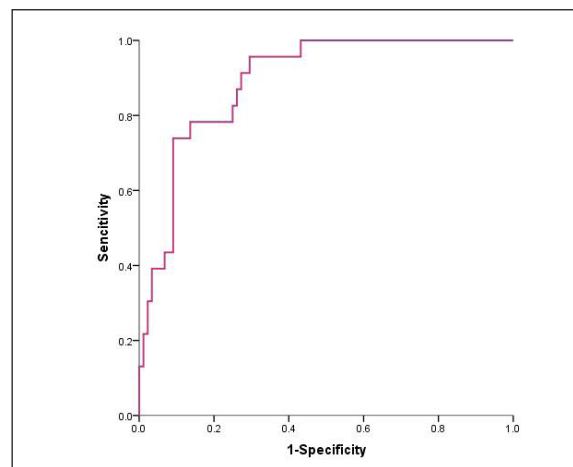


Figure 2: Receiver operator characteristic (ROC) curve analysis of soluble suppression of tumorigenesis-2 (sST2) combined with N-terminal pro-brain natriuretic peptide (BNP) in hemodialysis patients [area under the curve (AUC): 0.892, sensitivity: 0.957, specificity: 0.795].

coronary microvascular disease can also be seen. Vascular changes include atherosclerosis, vascularization, and loss of vascular elasticity. According to the statistics of the United States Renal Data System (USRDS), the mortality caused by CVD in ESRD patients in the United States accounted for 41.6 %, which was significantly higher than the general population and 10-20 x greater than that of the general population. In addition, about 30 % of dialysis patients are hospitalized due to CVD every year¹⁵. CVD remains the leading cause of death

Table 2: Univariate and multivariate logistics regression analysis to identify independent predictors of heart failure in maintenance hemodialysis patients.

parameter	Univariate			Multivariate		
	OR	95 % CI	p	OR	95 % CI	p
Age	1.060	1.020-1.101	0.003	1.097	1.023-1.178	0.010
Sex (male)	1.360	0.532-3.541	0.528	-	-	-
Diabetes	1.583	0.486-5.159	0.446	-	-	-
CHD	3.062	1.030-9.108	0.044	0.439	0.054-3.596	0.443
LVEDD	1.086	1.009-1.170	0.029	1.103	0.960-1.268	0.167
EF	0.931	0.889-0.975	0.003	1.019	0.938-1.107	0.660
PAP	1.058	1.023-1.094	0.001	0.073	0.996-1105	0.073
CK-MB	1.028	0.997-1.059	0.077	-	-	-
Albumin	0.895	0.820-0.976	0.012	1.091	0.952-1.249	0.211
Uric acid	0.995	0.991-0.999	0.023	1.008	0.999-1.017	0.071
Ca	0.229	0.033-1.592	0.136	-	-	-
P	0.423	0.201-0.887	0.023	0.288	0.057-1.464	0.133
BNP	1.000	1.000-1.000	<0.001	1.000	1.000-1.000	0.008
ST2	1.029	1.015-1.044	<0.001	1.030	1.008-1.052	0.008
VitD3	0.919	0.853-0.990	0.027	0.918	0.818-1.029	0.143

CI: confidence interval, CHD: coronary heart disease, LVEDD: left ventricle end-diastolic diameter, EF: ejection fraction, PAP: pulmonary artery pressure, Ca: calcium, P: inorganic phosphorus, VitD3: 25-OH VitD3, CK-MB: creatine kinase MB, BNP: Brain natriuretic peptide, SST2: soluble suppression of tumorigenesis-2.

Table 3: The association between parameters and soluble suppression of tumorigenesis-2, upon univariate and multivariate-adjusted linear regression analysis.

Parameter	univariate linear regression		multivariate-adjusted linear regression	
	r	p	r	p
sex	-0.255	0.007	-1.687	0.096
LVEDD	0.050	0.610	-	-
EF	-0.124	0.204	-	-
PAP	0.283	0.003	1.214	0.229
CRP	0.354	<0.001	1.239	0.219
Albumin	-0.366	<0.001	-2.794	0.007
Uric acid	-0.213	0.025	0.483	0.631
25-OH VitD3	-0.216	0.040	-1.493	0.140
Ca	-0.219	0.021	-0.135	0.893
P	-0.256	0.007	-1.644	0.104
BNP	0.326	<0.001	-0.264	0.793

LVEDD: left ventricle end-diastolic diameter, EF: ejection fraction, PAP: pulmonary artery pressure, Ca: calcium, P: inorganic phosphorus, VitD3: 25-OH VitD3, CK-MB: creatine kinase MB, CRP: C-reaction protein, iPTH: intact parathyroid hormone, BNP: Brain natriuretic peptide, sST2: soluble suppression of tumorigenesis-2.

in ESRD¹⁶. HF is one of the most severe complications in dialysis treatment of MHD patients, and it is also a high-risk factor for death. During HF in MHD patients, ventricular remodeling will occur, mainly by increased cardiac load and left ventricular dilation. Therefore, early diagnosis and treatment are particularly important. Due to the atypical symptoms of mild heart failure, it is easy to miss the diagnosis, thus losing the best treatment opportunity and increasing the mortality from cardiovascular diseases in MHD patients^{17,18}. Therefore, exploring effective laboratory indicators to help clinical prediction of HF in MHD patients is significant.

ST2 has two forms: ST2L and sST2. sST2 is a prognostic marker of congestive heart failure¹⁴. When stress stimulates cardiomyocytes, IL-33 can bind to ST2L, activating downstream pathways and exerting cardiac protection¹⁹. However, sST2 can competitively bind IL-33 and block the entry of IL-33 into the corresponding signaling pathways for cardiac protection, leading to cardiac remodeling and ventricular dysfunction. In the state of cardiac muscle fiber stretching and tension, that is, when human ventricular capacity overload and pressure load increase, as is commonly seen during HF, cardiac myocytes will secrete BNP, so serum NT-proBNP will increase. In this

Table 4: Receiver operator characteristic (ROC) curve analysis of N-terminal pro-brain natriuretic peptide (BNP) and soluble suppression of tumorigenesis-2 (sST2) in hemodialysis patients.

parameter	AUC	sensitivity	specificity	95 % CI	Youden's J
BNP	0.822	0.783	0.830	0.725-0.919	0.66
ST2	0.841	0.913	0.761	0.751-0.932	0.67
sST2 + BNP	0.900	0.957	0.795	0.831-0.968	0.71

CI: confidence interval, BNP: N-terminal pro-brain natriuretic peptide, sST2: soluble suppression of tumorigenesis-2, AUC: area under the curve.

study, MHD patients with HF presented higher age, increased incidence of CHD, LVEDD, PAP, sST2, BNP, and iPTH, and lower EF. In MHD patients with heart failure, the increased myocardial stiffness and diastolic filling pressure result in abnormal left ventricular diastolic function. During the progression of HF, ventricular volume index and ventricular volume increase will further activate the renin-aldosterone-angiotensin system (RAAS) and promote cardiac functional compensation. At the same time, cardiomyocytes inhibit RAAS through massive synthesis and secretion of NT-proBNP^{20,21}. In the present study, logistic regression analysis determined that age, serum sST2, and BNP were independent risk factors of HF in MHD patients. It was also found that PAP was positively correlated with sST2. Therefore, high concentrations of sST2 may predict HF in MHD.

In this study, the ROC curve analysis ascertained that the sensitivity and specificity of sST2 and BNP in predicting HF of MHD patients were 0.783, 0.913 and 0.830, 0.761, respectively, indicating that sST2 and BNP may have certain predictive of the occurrence of HF in MHD. A meta-analysis has previously determined that the AUC of sST2 in heart failure was 0.75, slightly lower than our result²². Moreover, the AUC of sST2 combined with BNP was 0.892, with the sensitivity and specificity being 0.957 and 0.705, respectively. When combining the sST2 and BNP results, the sensitivity is higher, but the cut values are higher than sST2 alone. Thus, the conclusion that combining the two is more valuable was not supported, which may be related to the small sample size, courses, and/or selection bias. However, here for the first time, sST2 is of higher value than BNP in independently predicting HF in MHD patients.

In addition, sST2 was negatively correlated with calcium and inorganic phosphorus in MHD, but no correlation was found between iPTH and sST2. ST2 is associated with parathyroid hormone in CKD patients²³. Parathyroid hormone is involved in maintaining mineral balance, and when abnormal, mineral and bone metabolism can be disrupted. IL-33 and ST2 may be regulatory targets of parathyroid hormone^{24,25}. It was determined that 25-OH VitD3 was lower in MHD patients with heart failure, while iPTH did not change between groups, suggesting that iPTH is unrelated to HF in MHD.

In the subgroup analysis of patients with HF²⁶, high sST2 level was a prognostic factor for patients with glomerular filtration rate <60 mL/min/1.73m². Similarly, higher sST2 concentration has recently been associated with the development of CKD^{27,28}, and the mortality in MHD patients is associated with sST2 levels²⁹. Therefore, elevated sST2 may indicate subclinical cardiovascular

disease, directly affect renal function or affect systemic processes in the heart and kidney. The serum sST2 level was higher in CKD patients, and the titer was correlated with the severity of the disease. The cross-sectional design of this study did not establish a healthy control group, excluding the effect of renal function, nor did it analyze the HF or ESRD prognosis of the MHD patients. A follow-up multi-center study would further explore the relationship between sST2 and patient mortality and a set control group of people without diseases. Nevertheless, this study has uncovered for the first time that sST2 can predict HF in MHD patients and may assist in the early diagnosis of HF in MHD patients.

In conclusion, sST2 can be used to predict HF in MHD patients and can assist in the early diagnosis and prevention of HF in MHD patients.

Conflict of interest

Authors report no potential conflict of interest.

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