THE ASSOCIATION BETWEEN SERUM SOLUBLE ST2 CONCENTRATION AND SOME CLINICAL AND SUBCLINICAL INDICES IN PATIENTS WITH CHRONIC HEART FAILURE

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Abstract

Objectives: To investigate the level of serum soluble ST2 (sST2) and its association with some clinical and subclinical indices in patients with chronic heart failure (HF). ***Methods:*** A prospective cohort study was performed on 116 patients diagnosed with chronic HF at the Cardiology Department, Military Hospital 103, Hanoi and Cardiology Department, 19-8 Hospital - Ministry of Public Security, Hanoi, Vietnam, and 40 control patients at General Health Examination Department, Military Hospital 103, Hanoi from November 1, 2019 to September 30, 2022. Serum sST2 was measured using an enzyme-linked immunosorbent assay. ***Results:*** The mean age (± standard deviation) of patients with chronic HF was 68.3 (± 15.9) years, with 57.8% of the total patients who showed their age was > 65 years. The median serum sST2 level in the group of patients with chronic HF (median: 5.89 ng/mL) was significantly higher than those in the control group (median: 2.39 ng/ml) ($p < 0.05$). Serum sST2 level increased as LVEF decreased, with the highest level in HF with reduced EF patient group, followed by HF with mildly reduced EF, and HF with preserved EF groups. Serum sST2 level had a significant, positive correlation with heart rate in chronic HF patients. The serum sST2 level in the group of NYHA class IV was significantly higher than those in the group of NYHA class III and II ($p < 0.05$).

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Conclusion: The level of serum sST2 increased in chronic HF patients. Serum sST2 level associated with left ventricular ejection fraction, and NYHA classification in chronic HF patients.

Keywords: Soluble suppression of tumorigenicity 2; Heart failure; NYHA classification.

INTRODUCTION

Heart failure is a complex clinical syndrome that results from either a structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood [1]. The American Heart Association (AHA) reported that the rate of HF in the United States was more than 6 million people, accounting for nearly 1.8% of the total population in 2021 [2]. In Vietnam, research on the prevalence of HF in the total population has been limited. However, based on both the total Vietnamese population and the prevalence of HF in Europe, an estimation of 360,000 to 1,8 million people with HF require treatment [3]. In addition, it was reported that the rate of HF is expected to increase significantly due to the availability of better diagnostic tools ensuring proper diagnosis [2]. Although HF treatment and prognosis have improved with the current medical treatments, patients with HF are frequently hospitalized, and the survival rate is low. Therefore, new strategies to manage patients with HF are priority warranted.

In previous studies, biomarkers have been proven to be helpful in HF management, particularly soluble suppression of tumorigenicity 2 (sST2), which was suggested as a strong predictor of cardiovascular outcomes in both chronic and acute HF [4, 5]. Suppression of tumorigenicity 2 (ST2) is a member of the interleukin-1 receptor family biomarker and circulating sST2 concentrations, which are hypothesized to reflect cardiovascular stress and fibrosis. A study by Ky et al. (2011) found a robust, independent association between a single baseline measure of sST2 and adverse outcomes in chronic

HF [5]. Pascual-Figal et al. (2009) reported that the elevation of ST2 was associated with a high rate of sudden death [4]. However, in Vietnam, research on sST2 level was carried out in the general population, hypertension disease, and acute HF; however, there are not many studies on plasma ST2 in patients with chronic HF except a study by Le Khac Hiep et al. in 2020 [6]. The authors found that the sST2 level increased in a group of chronic HF with a higher NYHA grade, but only 58 cases were recruited in this study. Therefore, we conducted this study with a larger sample size to: Investigate serum sST2 concentration and its association with clinical and subclinical features in patients with chronic HF.

MATERIALS AND METHODS

1. Subjects

116 patients diagnosed with chronic HF were recruited at the Cardiology Department, Military Hospital 103, Hanoi, Vietnam, and Cardiology Department, 19-8 Hospital-Ministry of Public Security, Hanoi, Vietnam from November 1st 2019 to September 30th 2022.

* *Inclusion criteria:* Patients aged ≥ 18 years; patients diagnosed with chronic HF following the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic HF 2012 [7]; patients agreed to join this study. The patient consent was obtained from individual participants included in this study.

* *Exclusion criteria:* Patients had comorbidity with other diseases affecting serum sST2 level, such as respiratory failure, acute HF, liver failure, bronchial asthma, autoimmune disease, electrolyte disorders, severe infection, etc. at the time of the study; patients did not agree to participate in the study.

A total of 40 healthy people who were examined at the general health examination, Military Hospital 103 were recruited at the same time as a control group. The criteria for the control group are as follows: Age ≥ 18 years; participants were not

previously diagnosed with chronic or acute disease; participants agreed to join this study.

2. Methods

* *Study design:* A prospective cohort study.

* *Sample collection:* Convenient sampling method.

* *Study procedure:* The study was conducted according to the following steps:

- Collecting data: Data regarding patients, including age, sex, body mass index (BMI), heart rate, blood pressure, medical history, some biochemical indices (glucose, estimated glomerular filtration rate (eGFR), Na+, K+, Cl-, creatinine, NT-proBNP), hematological indices (hemoglobin (HGB), leukocytes, neutrophil), X-ray indices (cardiothoracic index, pulmonary congestion, pleural effusion) and heart ultrasound indices (ejection fraction, left ventricular end-diastolic volume, left atrial diameter).

- Quantification of serum ST2: An amount of 3mL of venous blood was collected to quantify the level of serum sST2 according to ELISA (Enzyme-linked immunosorbent assay). Measurement of serum sST2 level was performed in the molecular physiology laboratories of the Department of Pathophysiology, Vietnam Military Medical University

- Data analysis: SPSS 22.0 statistical software was used for data analysis. Continuous variables are represented by the mean and standard deviation (± SD) and percentages (%). The level of serum sST2 was log transformation (base e) to improve normality. Comparison of quantitative variables with normal distribution using the independent sample T-test and the Pearson rank correlation coefficient was used for analyzing relationships between serum sST2 level (continuous variable) and some clinical and subclinical indices (continuous variables).

3. Ethics

Written informed consent was obtained from all patients participating in this study.

RESULTS

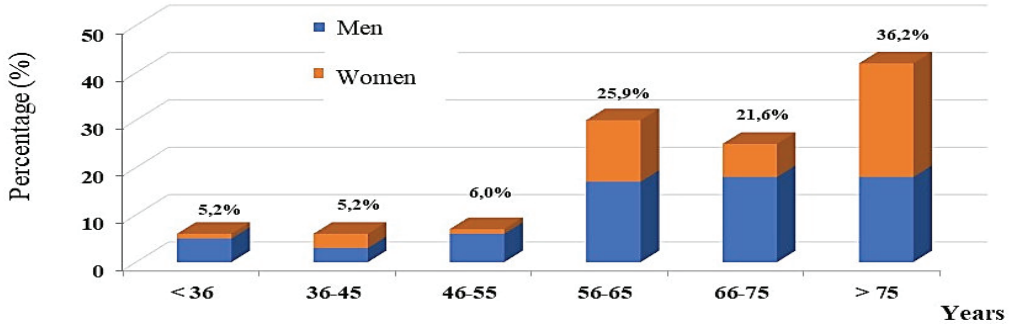

Figure 1. Distribution of age in patients with chronic heart failure (n = 116).

The mean age (± SD) of the chronic HF patients was 68.3 (± 15.9) years, with 57.8% of the total patients who showed their age was > 65 years. There were 67 male patients out of 116 patients, accounting for 57.8%. The proportion of male patients was higher than those of female patients, but the difference did not reach statistically significant (p = 0.071). The mean age of male patients was 65.3 ± 15.8 years, which was significantly lower as compared with the mean age of women, which was 72.3 ± 15.3 years (p < 0.05) (*Figure 1*).

Table 1. The concentration of serum sST2 in the study subject.

	Patients with chronic HR			**Control group**		
	n	**Median**	**[IQR1; IQR3]**	**n**	**Median**	**[IQR1; IQR3]**
Total	116	5.89	[3.97; 11.47]	40	2.39	[1.96; 3.79]
Male patients	67	5.83	[3.31; 12.6]	23	3.05	[1.94; 4.45]
Female patients	49	5.9	[4.25; 10.90]	17	2.36	[1.96; 3.36]

n: Number of patients, IQR: Interquartile Range.

Table 1 displays the median serum sST2 in chronic HF patients. The median [IQR1; IQR3] of serum sST2 level in the total chronic HF patients was 5.89 [3.97; 11.47] ng/mL, which was significantly higher than those in the control group (median [IQR1; IQR3]: 2.39 [1.96; 3.79] ng/mL). The median serum sST2 level for the male and female chronic HF patients was 5.83 and 5.9 ng/mL, respectively. No significant difference was observed in the median serum sST2 level between male and female chronic HF patients (*Table 1*).

Table 2. Correlations between Log (sST2) level and some clinical and subclinical indices using Pearson rank correlation coefficient.

Clinical and subclinical indices	r	p
Age	0.104	0.266
BMI	-0.030	0.747
Heart rate	0.189	0.042
Systolic pressure blood	-0.027	0.771
Diastolic pressure blood	-0.001	0.992
Hematological indices		
HGB	-0.022	0.814
Leukocytes	-0.038	0.683
Neutrophil	-0.082	0.383
Biochemical blood indices		
Glucose	0.009	0.925
eGFR	0.025	0.788
Na+	-0.035	0.708
Creatinine	-0.128	0.170
Cholesterol	0.010	0.912
Heart ultrasound indices		
Left ventricular ejection fraction	-0.179	0.054
Left ventricular end-diastolic volume	0.141	0.134
Left atrial diameter	0.004	0.996

r: pearson's rank correlation coefficient, HGB: hemoglobin, BMI: body mass index, eGFR: estimated glomerular filtration rate

The level of serum sST2 was positively and significantly correlated with the heart rate ($r = 0.189$, $p < 0.05$). There were no significant correlations between

the serum sST2 level and hematological, biochemical, and heart ultrasound indices found in the present study (*Table 2*).

Table 3. Comparison of serum sST2 level between different groups of related factors in chronic heart failure patients using independent sample T-test.

Factors			n	Log(sST2)	p
Causes of heart failure	Coronary artery disease	Yes	49	1.77 ± 0.82	0.712
		No	67	1.82 ± 0.76	
	Hypertension	Yes	84	1.98 ± 0.76	< 0.001
		No	32	1.32 ± 0.62	
	Cardiomyopathy	Yes	6	1.92 ± 0.91	0.688
		No	110	1.79 ± 0.78	
	Valvular Heart Disease	Yes	32	1.91 ± 0.66	0.339
		No	84	1.75 ± 0.82	
	Cardiac arrhythmias	Yes	58	1.81 ± 0.69	0.827
		No	58	1.78 ± 0.87	
	Diabetes	Yes	24	1.90 ± 0.60	0.480
		No	92	1.77 ± 0.82	
	Dyslipidemia	Yes	13	1.64 ± 0.89	0.430
		No	103	1.82 ± 0.77	
NYHA	II		20	1.19 ± 0.74	
	III		63	1.73 ± 0.68	0.004*
	IV		33	2.30 ± 0.68	< 0.000*
Left ventricular ejection fraction	≤ 40%		43	2.05 ± 0.76	
	41 - 49%		46	1.69 ± 0.82	0.034**
	≥ 50%		27	1.57 ± 0.65	0.008***

NYHA: New York Heart Association classification; BMI: body mass index.

*: as compared with NYHA class II

**: as compared with LVEF ≤ 40%

***: as compared with LVEF 41 - 49%

Table 3 shows the results of comparisons of serum sST2 level among different groups of related factors using an independent sample T-test. The serum sST2 level in the group of NYHA class III and IV were significantly lower than those in the group of NYHA II ($p < 0.05$). There was no significant difference among different groups of causes of HF and comorbidity disease in the present study ($p > 0.05$) (*Table 3*). Since the significant correlation between the serum sST2 level and LVEF, we compared the serum sST2 level among different groups of LVEF and found that a significant decrease of the serum sST2 was observed in groups with LVEF $\leq$ 40% when compared with those in group with LVEF 41 - 49%, and in groups with LVEF $\geq$ 50% when compared with those in group with LVEF 41 - 49% ($p < 0.05$) (*Table 3*).

DISCUSSION

In this study, we found that the mean age of participants was 68.3 (± 15.9) years. The result was consistent with a previous report by Lichtenauer et al. (2017) [8], but it was inconsistent with previous reports by Ky et al. (2011) or Le Khac Hiep et al. (2020) [4, 6]. Ky et al. (2011) reported that the mean age of chronic HF patients was 56.3 ± 14 years [4], which was lower than that in our study. This may be explained by the fact that the study by Ky et al. performed in a developed country is suggested to have better management of HF in the population. In contrast, a higher age (74.95 ± 13.86 years) was observed in a report by Le Khac Hiep et al. on Vietnamese chronic HF patients in 2019 [6]. These suggest that the health management to decrease the rate of HF in elderly people may be improved in Vietnam. In addition, in this study, the rate for female HF patients was higher than that for male HF patients. It was reported that the increased rate of HF was associated with increasing age [2]. Since women showed higher average life expectancy than men, an increased risk of HF was found in older women, which might lead to the imbalance of gender rate in this study.

The median serum sST2 level was recorded as 5.89 ng/mL in the chronic HF patients and 2.39 ng/mL in healthy people in this study. In an investigation of 891 HF patients, Bayes-Genis et al.

(2013) reported the mean serum sST2 level was 38.1 ng/mL [9]. Le Khac Hiep et al. (2020) reported that the level of serum sST2 in healthy people was 2.3 ng/mL [6], which was much lower than those in HF patients in the present study and the report by Bayes-Genis et al. (2013) [9]. Since increased serum sST2 level and IL33 are associated with fibrosis, remodeling, and myocardial inflammation, increased IL33 has cardioprotective effects, such as reducing myocardial fibrosis and hypertrophy, preserving ejection fraction, and improving survival. The sST2 is a receptor that inhibits beneficial cardioprotective effects of IL-33. The source of sST2 is derived mainly from cardiomyocytes and fibroblasts in the myocardium. Under the effect of stretching, fibrosis, inflammation, and remodeling of the myocardium, the production of sST2 increases, which might lead to an increase in the serum sST2 concentration in HF patients.

In this study, our results also showed that the serum sST2 level was inversely and significantly correlated with LVEF in chronic HF patients. Although the assessment of left ventricular function does not provide all regional movement in the heart, it shows the ability of the left ventricle to contract. In the case of the contractility of the left ventricular muscle decreases, which might partly reflect severe damage in the structure, such as dilation or fibrosis in the heart. Moreover, the right ventricular ejection fraction has been reported to be associated with serum sST2 in the previous study [6]. So, we will have a plan to analyze the right ventricular indices and serum sST2 level in chronic HF patients in the future. Moreover, we did not find any significant association between serum sST2 level and some biochemical and hematological indices, particularly eGFR. Consistent results were observed in the previous studies in Vietnam [6] and another country [9]. These support the hypothesis that serum sST2 is eliminated by various pathways other than the kidney. However, the number of subjects in the present study is small. Therefore, another study with a larger number of HF patients should be performed to investigate relationships between serum sST2 level and other hematological and biochemical indices.

In addition, we found that increased serum sST2 level in chronic HF patients caused by hypertension, which was a consistent result with a previous report by Ky et al. (2011) [4]; however, it was inconsistent with the previous report by Le Khac Hiep et al. (2020) [6]. The author reported that there was no significant difference in serum sST2 level in different groups of hypertension, type 2 diabetes disease, and valvular heart disease in HF patients [6]. It may be due to different times under high blood pressure and different classification of hypertension in chronic HF patients between our study and previous study. Because prolonged high blood pressure will lead to hypertrophy, fibrosis, and gradually leading to heart failure and is associated with an increase in serum sST2 level. In our study, there were no patients in the group of NYHA class I, and a significant increase in serum sST2 level was observed in the NYHA class IV and class III groups compared to the NYHA II group. In a study by Silvio Quick et al. (2015), they also reported a positive correlation between serum sST2 level and NYHA class ($r = 0.22$; $p = 0.002$) [10]. These results indicate that increased serum sST2 level relate to increasing NYHA class.

CONCLUSION

The median serum sST2 level in patients with chronic HF was 5.89 ng/mL with IQR [1 - 3] from 3.97 to 11.47 ng/mL. The level of serum sST2 was positively and significantly correlated with heart rate. Increased serum sST2 level related to increasing NYHA class in chronic HF patients. Increased serum sST2 level related to reduced LVEF class in chronic HF patients.

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REFERENCES

1. McDonagh TA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the

Heart Failure Association (HFA) of the ESC. *European heart journal.* 2021; 42(36):3599-3726.

2. Bozkurt B, et al. ACC/AHA key data elements and definitions for heart failure: A report of the American College of Cardiology/American Heart Association task force on clinical data standards (Writing Committee to Develop Clinical Data Standards for Heart Failure). *Circulation: Cardiovascular Quality and Outcomes*. 2021; 14(4):e000102.

3. Nguyễn Lân Việt, et al. Khuyến cáo của Hội Tim Mạch Quốc Gia Việt Nam về chẩn đoán và điều trị suy tim: Cập nhật 2015.

4. Pascual-Figal DA, et al. Soluble ST2 for predicting sudden cardiac death in patients with chronic heart failure and left ventricular systolic dysfunction. *Journal of the American College of Cardiology*. 2009; 54(23):2174-2179.

5. Ky B, et al. High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure. *Circulation: Heart Failure*. 2011; 4(2):180-187.

6. Lê Khắc Hiệp. Nghiên cứu đặc điểm lâm sàng, cận lâm sàng, nồng độ ST2 huyết thanh hòa tan ở bệnh nhân suy tim mạn tính. Luận văn bác sĩ chuyên khoa II. 2020. Học viện Quân y.

7. Members ATF, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2012; 33(14):1787-1847.

8. Lichtenauer M, et al. A comparative analysis of novel cardiovascular biomarkers in patients with chronic heart failure. *European Journal of Internal Medicine*. 2017; 44:31-38.

9. Bayes-Genis A, et al. Soluble ST2 serum concentration and renal function in heart failure. *Journal of Cardiac Failure*. 2013; 19(11):768-775.

10. Quick S, et al. Soluble ST2 and myocardial fibrosis in 3T cardiac magnetic resonance. *Scandinavian Cardiovascular Journal*. 2015; 49(6):361-366.