ESC HEART FAILURE
ESC Heart Failure 2023; **10**: 303–310
Published online 9 October 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14147

ORIGINAL ARTICLE

Expression of soluble ST2 in patients with essential hypertension and its relationship with left ventricular hypertrophy

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Abstract

Aims Identification and intervention of left ventricular hypertrophy (LVH) in essential hypertension (EH) are important for the prevention of adverse cardiovascular events. However, effective methods for diagnosing LVH are still lacking. This study aimed to explore the relationship between soluble ST2 (sST2) and LVH in EH patients to identify a potential specific biomarker for hypertensive LVH.

Methods and results This study included 97 EH patients. Based on the criteria for LVH, participants were divided into the LVH group (n = 52) and the non-LVH group (n = 45). The level of serum sST2 was detected by enzyme-linked immunosorbent assay. Pearson correlation analysis, logistic regression analysis, and receiver operating characteristic (ROC) curve analysis were used to investigate the potential of sST2 as a biomarker of LVH in EH patients. Compared with the non-LVH group, the sST2 level was elevated in EH patients with LVH ($P < 0.001$). Pearson correlation analysis indicated that the sST2 level was positively correlated with the left ventricular mass index in EH patients (r = 0.454, $P < 0.001$). Logistic regression analysis showed that the odds ratio (OR) value of LVH was 2.990, suggesting that sST2 is an independent risk factor for LVH in EH patients [OR = 2.990, 95% confidence interval (CI), 1.650–5.419; $P < 0.001$]. The area under the ROC curve was 0.767 (95% CI, 0.669–0.866; $P < 0.001$), with a sensitivity of 0.808 and specificity of 0.689, indicating the possibility of considering sST2 as a biomarker for diagnosing LVH.

Conclusions Up-regulation of sST2 is strongly related to LVH in EH patients, is an independent risk factor for hypertensive LVH, and can be used as a biomarker for the diagnosis of LVH.

Keywords Soluble ST2; Left ventricular hypertrophy (LVH); Essential hypertension (EH)

Received: 3 September 2021; Revised: 22 August 2022; Accepted: 26 August 2022
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Introduction

Essential hypertension (EH) is a common chronic disease caused by unexplained elevated blood pressure that increases the risk of events in target organs, such as the brain, heart, and kidney.[1] Hypertension has been proved to be a major risk factor for the gradual development of cardiovascular disease.[2] During the early phase of hypertensive cardiovascular disease, there is slight damage to the heart (i.e. ventricular hypertrophy).[3] A recent review of multiple studies showed that the average incidence of left ventricular hypertrophy (LVH) was 18%.[4] Long-term left

ventricular hypertension can lead to serious cardiac events, such as acute and chronic heart failure and even death.[5,6] Framingham *et al*. reported that LVH predicted a higher incidence of cardiovascular disease-related events, including death, in subjects without clinically significant cardiovascular disease symptoms.[7] It has been demonstrated that the extent of LVH regression is an independent prognostic factor for cardiovascular health in evaluating the curative effect of hypertensive treatment.[8] The European Society of Cardiology has issued guidelines for the management of high blood pressure that highlight the severity of damage to target organs, particularly the heart.[9] The identification of myocardial hypertrophy in EH is important for the prevention of adverse cardiovascular events. Although LVH can be diagnosed by electrocardiogram, the criteria for clinical diagnosis with electrocardiogram vary, and its sensitivity is low—only 20–40%.[10] Transthoracic echocardiography is also an effective diagnostic tool and is the preferred procedure because it is more sensitive than an electrocardiogram. Computed tomography and magnetic resonance imaging can also be used to diagnose LVH. However, their effectiveness can be hampered by lack of specificity, long diagnostic time, and technical complexity.[11] Hence, a new diagnostic strategy that can easily and accurately detect cardiac hypertrophy is urgently needed. The blood levels of certain proteins have been associated with pathologic activation of a high left ventricular pressure load.[12] Due to their stability and the relative convenience of detection, extraction, and quantification, blood biomarkers have the potential to be an effective diagnostic approach for LVM.

As a member of the interleukin-1 receptor family, ST2 was originally identified as a protein involved in regulating inflammation and immune diseases. Soluble ST2 (sST2) has been shown to compete with the transmembrane ST (ST2L) receptor to combine with interleukin 33 (IL-33) by acting as a decoy receptor and is thus an independent risk factor for acute heart failure and capable of predicting the poor prognosis.[13] ST2L/IL-33 is a protective signal transduction pathway that prevents myocardial hypertrophy and fibrosis and reduces myocardial remodelling and cardiovascular events.[14–16] It has been reported that altered sST2 levels are correlated with the ventricular remodelling in hypertensive patients and can be used as an indicator of cardiac remodelling and diastolic function in hypertensive patients.[17,18] However, the relationship between sST2 levels and LVH in EH patients is unclear, and the clinical value of sST2 as a diagnostic indicator remains to be explored.

In this study, we explored the differences in sST2 levels between EH patients with LVH and those without LVH and analysed the relationship between sST2 levels and LVH in EH patients to estimate its clinical application value and provide a new theoretical basis for the diagnosis of hypertensive LVH.

Materials and methods

Patients

The retrospective study protocols were approved by the committee of our hospital. A total of 97 patients (57 males and 40 females aged 26–88 years) who were admitted to our hospital due to EH between September 2018 and December 2020 were selected as the study subjects. All patients enrolled in this study were hospitalized with a first diagnosis of EH, and none of them received any medication. All participants met the diagnostic criteria outlined in the 2018 Chinese Guidelines for Hypertension Prevention and Treatment. Left ventricular mass index (LVMI) $\geq$ 115 g/m^2 (male) and LVMI $\geq$ 95 g/m^2 (female) were defined as LVH. Patients were divided into the LVH group (N = 52) and the non-LVH group (N = 45). The flow diagram is shown in *Figure 1*.

The exclusion criteria included the following: (i) secondary hypertension; (ii) a history of the acute coronary syndrome and previous myocardial infarction; (iii) ejection fraction (EF) $<$ 50%; (iv) cardiomyopathy, myocarditis, valvular heart disease, congenital heart disease, pericardial disease, and pulmonary hypertension; (v) acute and chronic infection, chronic obstructive pulmonary disease, and severe liver and kidney insufficiency with an estimated glomerular filtration rate (eGFR) of $<$30 mL/min/1.73 m^2; (vi) immune diseases, malignant tumours, thyroid diseases, and anaemia; and (vii) any other conditions that the researcher determined made the patient ineligible to participate in the study.

The baseline data included gender, age, systolic blood pressure, diastolic blood pressure, low-density lipoprotein, triglyceride, total cholesterol, aspartate aminotransferase, alanine aminotransferase, creatinine, urea nitrogen, uric acid, and cardiac EF.

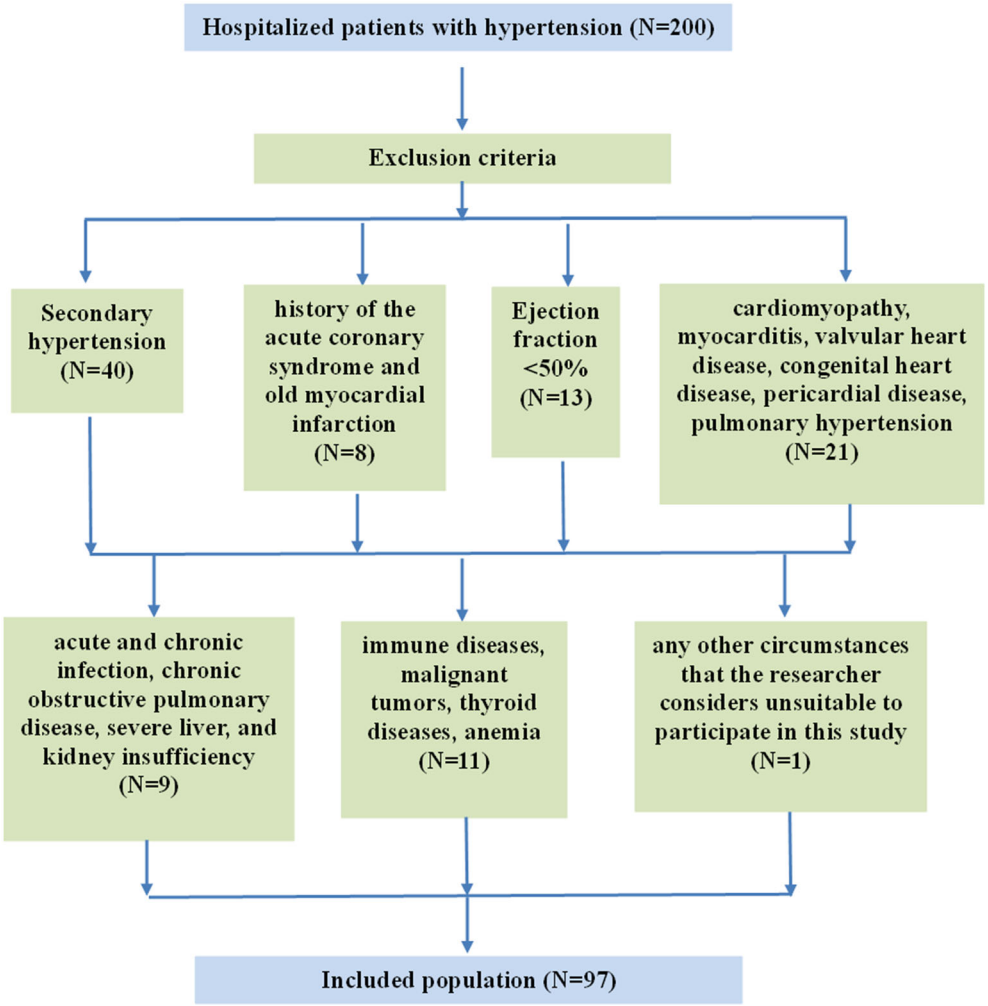
Soluble ST2 examination by enzyme-linked immunosorbent assay (ELISA)

A total of 5 mL of fasting elbow venous blood was collected from all subjects on the morning after admission and then immediately stored at 4°C for 1 h. The serum samples were extracted after centrifugation at 1000 g for 15 min, distributed into EP tubes, and then stored at −80°C until use. Serum sST2 expression was determined using an ELISA kit provided by Critical Diagnostics (USA). As an indicator of heart failure, the normal range of sST2 is $<$35 ng/mL.

Echocardiogram

Left ventricular end-diastolic septal thickness (LVSTd), left ventricular posterior wall thickness (LVPWTd), and left ventricular end-diastolic diameter (LVDd) were measured

Figure 1 The flow diagram for this study.



using an EPIQ7C colour Doppler ultrasound diagnostic instrument acquired from Philips, and left ventricular mass was calculated using the Devereux formula.[19] Left ventricular mass (g) = 1.04*[(LVSTd + LVDd + LVPWTd)^3 − LVDd^3] − 13.6. Stevenson's formula was used to calculate body surface area (m^2) = 0.0061*height (cm) + 0.0128*body mass (kg) − 0.1529. LVMI (g/m^2) = left ventricular mass/body surface area.

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. The Kolmogorov–Smirnov test was used to determine the normality of the data. Where the measurement data were in line with normal distribution, the differences between the two groups were analysed with the independent sample *t*-test. Otherwise, the Mann–Whitney *U* test was used to compare the groups. Non-normally distributed data were reported as median (interquartile range, IQR), whereas other measurement data were expressed as mean ± standard deviation (mean ± SD). The count data were expressed as cases/percentage (*n*/%) and tested by chi-square (χ^2). Logistic regression analysis was used to analyse the risk factors for LVH in hypertensive patients. A receiver operating characteristic (ROC) curve was drawn to evaluate the predictive value of sST2 in hypertensive LVH. The $P < 0.05$ was considered statistically significant.

Results

Comparison of baseline data

As shown in *Table 1*, the systolic and diastolic blood pressure of patients in the LVH group were higher than they were in

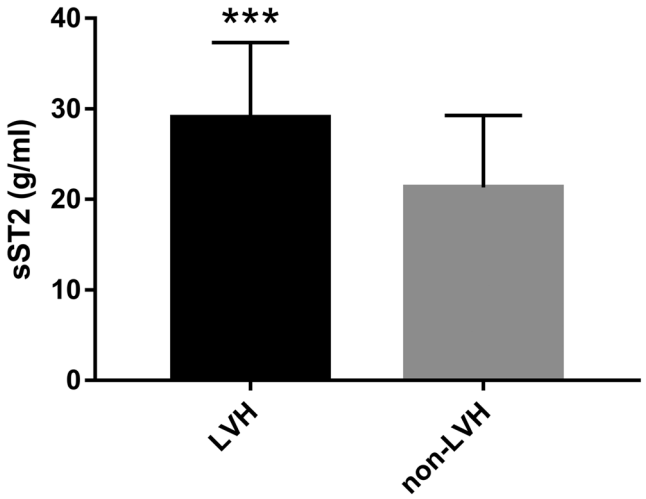
DOI: 10.1002/ehf2.14147

Table 1 Baseline information

Index	LVH (N = 52)	Non-LVH (N = 45)	t/χ^2	P
Gender (male/%)	31 (59.62%)	26 (57.78%)	0.034	0.856
Age (years)	59.12 ± 13.78	57.27 ± 12.05	0.698	0.487
Systolic pressure	154.58 ± 22.57	145.60 ± 20.47	2.039	0.044
Diastolic pressure	90.90 ± 15.77	84.53 ± 13.59	2.114	0.037
LDL-C (mmol/L)	2.71 ± 0.65	2.93 ± 0.70	1.552	0.124
TG (mmol/L)	1.57 (0.95–2.20)	1.50 (1.14–2.07)	0.304	0.761
TC (mmol/L)	4.47 ± 0.92	4.83 ± 1.18	1.688	0.095
Aspartate aminotransferase (μ/L)	26.31 ± 9.28	20.73 ± 7.85	1.441	0.153
Alanine aminotransferase (μ/L)	18.00 (14.00–30.75)	25.00 (19.00–33.50)	1.785	0.074
Creatinine (μmol/L)	56.36 (45.48–63.05)	54.70 (44.50–67.70)	0.481	0.631
Urea nitrogen (mmol/L)	5.55 ± 1.30	5.11 ± 1.14	1.767	0.081
Uric acid (μmol/L)	323.65 ± 105.01	328.39 ± 89.38	0.238	0.813
EF value (/%)	58.08 ± 1.87	58.82 ± 1.09	2.351	0.021
LVMI (g/m^2)	121.79 ± 15.20	84.02 ± 12.46	13.412	<0.001

Abbreviations: EF, ejection fraction; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; TC, total cholesterol; TG, triglyceride.

Figure 2 Comparison of the sST2 levels of the LVH and non-LVH groups. LVH, left ventricular hypertrophy; sST2, soluble ST2.



the non-LVH group, whereas the cardiac EF value was slightly decreased in the LVH group compared with the non-LVH group ($P < 0.05$). There were no significant differences in gender, age, low-density lipoprotein, triacylglycerol, total cholesterol, aspartate aminotransferase, alanine aminotransferase, creatinine, urea nitrogen, or uric acid between the two groups ($P > 0.05$; see *Table 1*).

Elevated soluble ST2 levels in essential hypertension patients

In contrast with the non-LVH group, sST2 levels were prominently up-regulated in the LVH group ($P < 0.001$; see *Figure 2*). To identify the correlation between sST2 levels and LVMI, we conducted a Pearson correlation analysis. The results showed that the expression level of sST2 was elevated owing to the increase in LVMI, revealing that sST2 was positively correlated with LVMI (r = 0.454, $P < 0.001$; see *Figure 3*).

Risk factors for left ventricular hypertrophy in essential hypertension patients

After adjusting for various indicators, such as gender, age, blood lipid levels, blood pressure, and EF, the logistic regression analysis was conducted to identify the risk factor

Figure 3 Scatter plot of the correlation between sST2 levels and LVMI in essential hypertension patients. LVMI, left ventricular mass index; sST2, soluble ST2.

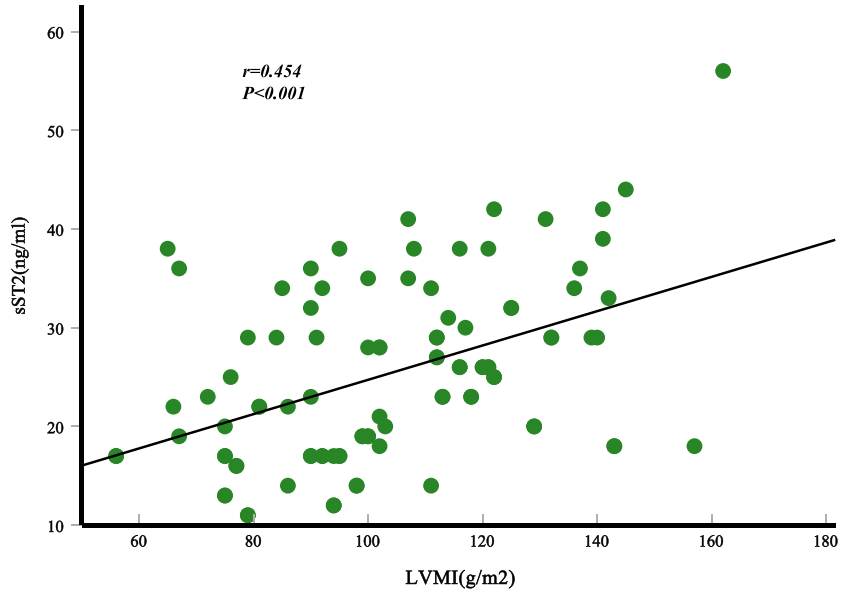
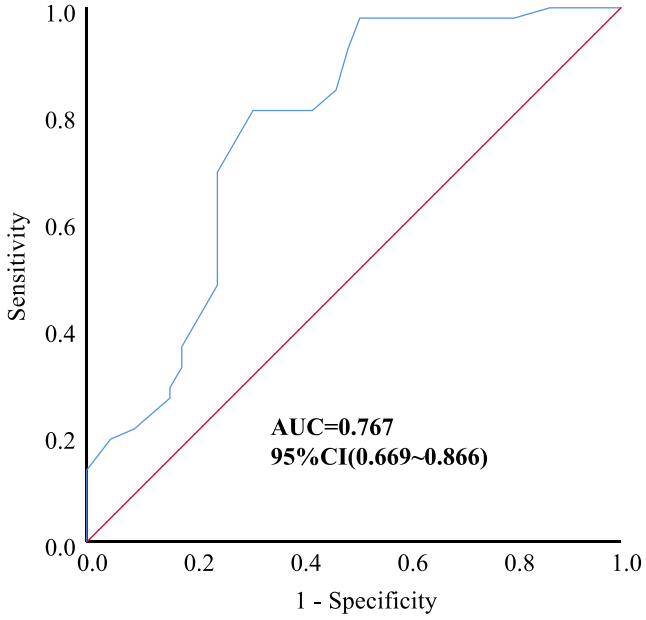


Table 2 Risk factors for left ventricular hypertrophy in essential hypertension patients

Variate	*B* value	SE	Wald χ^2	*P*	OR value	95% CI
sST2	1.095	0.303	13.046	<0.001	2.990	1.650–5.419
Diastolic pressure	0.777	0.281	7.663	0.006	2.174	1.255–3.767
EF	−0.864	0.33	6.871	0.009	0.422	0.221–0.804

Abbreviations: CI, confidence interval; EF, ejection fraction; OR, odds ratio; sST2, soluble ST2.

Figure 4 Receiver operating characteristic curve of soluble ST2 for predicting left ventricular hypertrophy in essential hypertension patients. AUC, area under the curve; CI, confidence interval.



DOI: 10.1002/ehf2.14147

for LVH in EH patients. We observed that the odds ratio (OR) value of LVH was 2.990, which suggested that sST2 was an independent risk factor for LVH in EH patients [OR = 2.990, 95% confidence interval (CI), 1.650–5.419; $P < 0.001$] (*Table 2*). In addition, diastolic blood pressure (OR = 2.174, 95% CI, 1.255–3.767; $P = 0.006$) and EF (OR = 0.422, 95% CI, 0.221–0.804; P = 0.00) was also shown to be a risk factor for LVH in EH patients (*Table 2*).

Receiver operating characteristic analysis of soluble ST2 to predict hypertensive left ventricular hypertrophy

ROC analysis was performed to evaluate the effectiveness of sST2 as a diagnostic marker for hypertensive LVH. The area under the curve (AUC) of serum sST2 levels was 0.767 (95% CI, 0.669–0.866; $P < 0.001$), the optimal threshold of serum sST2 levels was 22.50 ng/mL, the sensitivity and specificity of predicting the occurrence of LVH were 0.808 and 0.689, respectively, and the Youden index was 0.497 (*Figure 4*), suggesting that the diagnosis of LVH with sST2 level has high accuracy.

Discussion

This study identified a positive correlation between serum sST2 levels and LVMI in EH patients. Logistic regression analysis showed that sST2 was an independent risk factor for LVH in EH patients. More importantly, ROC analysis showed that the AUC of serum sST2 levels was 0.767 (95% CI, 0.669–0.866) with 80.8% sensitivity and 68.9% specificity. Therefore, we provided a theoretical basis for the diagnostic potential of sST2 levels in screening for LVH.

LVH has been identified as an important factor in adverse cardiovascular events.[20] Although there are many diagnostic labels for LVH, there is an urgent need to find an economical and effective strategy to predict and diagnose LVH. Electrocardiogram is a common, inexpensive, noninvasive method for detecting LVH, and some electrocardiographic parameters, such as frontal QRS-T angle, can predict LVH in hypertensive patients.[21] Unfortunately, electrocardiogram criteria for LVH vary, and this method lacks specificity and sensitivity.[22] Both echocardiography and cardiac magnetic resonance imaging can be used to obtain an accurate picture of cardiac hypertrophy with high specificity and sensitivity. However, both methods require experienced, trained staff and expensive equipment, resulting in high costs.[23] Therefore, accurate, accessible, and low-cost LVH detection methods remain a clinical need. The molecules in circulating blood are both stable and readily available, making them an excellent method for monitoring physiological and/or pathological conditions. To date, multiple circulating molecules have been used as easily accessible biomarkers for predicting LVH.[11,24] Accordingly, it is necessary to seek potent blood indicators for LVH.

Mounting evidence suggests that sST2 is involved in regulating immune inflammation and functions as an important mediator of signal transduction between cardiac fibroblasts and cardiomyocytes.[25] According to a recent report, elevated sST2 levels were associated with myocardial fibrosis and remodelling.[26] Therefore, sST2 is likely to participate in the occurrence of cardiac events. An increasing number of studies have demonstrated that sST2 has application value in the diagnosis and prognosis of acute and chronic heart failure.[13,27,28] Several studies have shown that sST2 can be used as a prognostic indicator of myocardial infarction.[29,30] However, the relationship between sST2 and hypertensive heart disease remains unclear. Accordingly, researchers have increasingly focused on exploring the relationship between sST2 levels and hypertension. Coglianese *et al*. measured the concentration of sST2 in a community population and found that the expression level of sST2 was related to systolic blood pressure.[31] Wu *et al*. observed that ST2 gene polymorphism was correlated with hypertension susceptibility, and gene variation may promote the occurrence and development of EH by regulating ST2 expression.[32] Hypertension has been widely recognized as an independent risk factor for heart disease due to its influence on heart function. When the heart pumps blood against increased systemic vascular resistance, increased cardiac afterload promotes cardiac hypertrophy and interstitial fibrosis (i.e. centripetal reconstruction of the left ventricular mass increase and ventricular septum thickening), manifested as myocardial hypertrophy.[33] The increased left ventricular load in EH patients leads to the secretion and release of sST2 by cardiomyocytes, fibroblasts, and vascular endothelial cells. sST2 inhibits the protective effect of ST2L/IL-33 signal transduction on myocardial cells by acting as a decoy receptor.[34] Increased sST2 levels may exacerbate myocardial fibrosis and hypertrophy; therefore, sST2 has potential predictive significance in evaluating EH cardiac hypertrophy. In this study, we compared sST2 levels in EH patients with and without LVH and found that sST2 levels in EH patients with LVH were higher than in patients without LVH. Logistic regression analysis showed that sST2 was an independent risk factor for LVH in hypertensive patients, and the OR value of LVH increased by 2.990 when the SD of sST2 increased by 1. ROC curve analysis indicated that sST2 had good sensitivity and specificity for predicting myocardial hypertrophy in EH patients. Based on these results, we conclude that sST2 exhibits strong potential for predicting EH cardiac hypertrophy.

This study has some limitations. In this experimental design, we calculated LVMI using left ventricular thickness

and mass detected by cardiac ultrasound to estimate the relationship between LVH and sST2. However, for ethical reasons, we were unable to verify our results by knocking out the ST2 gene in humans. The role and mechanism of sST2 in EH cardiac remodelling can be further verified by silencing the sST2 gene in basic animal experimental hypertension models and through interference or overexpression of sST2 in myocardium cells, which will be investigated in future studies.

In conclusion, the level of sST2 is high in EH patients with LVH. The sST2 is expected to be a new indicator for EH risk stratification and evaluation of cardiac target organ damage, or even as a drug target to intervene in myocardial fibre-like changes to reverse left ventricular remodelling and ventricular diastolic function reduction, and is worthy of clinical recommendation.

Conflict of interest

None declared.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81900306), Jiangsu Provincial Medical Youth Talent (No. QNRC2016382), Jiangsu Provincial Postdoctoral Research Funding Program (No. 2020Z449), Research Plan and Research Start-up Fund of Binzhou Medical University, China (No. BY2018KYQD14), Develop Project of Science and Technology in Traditional Chinese Medicine of Shandong Province, China (No. 2019-0509), and Yantai Key Research and Development Plan (No. 2019YD065).

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