Long-Term and Short-Term Prognostic Value of Circulating Soluble Suppression of Tumorigenicity-2 Concentration in Chronic Heart Failure: A Systematic Review and Meta-Analysis

Guoqi Dong Hao Chen Hongru Zhang Yihuang Gu

School of Acupuncture and Tuina, Nanjing University of CM, Nanjing, China

Keywords

Chronic heart failure · Soluble suppression of tumorigenicity-2 · Prognosis

Abstract

Introduction: Soluble suppression of tumorigenicity-2 (sST2) has been considered as a prognostic factor of cardiovascular disease. However, the prognostic value of sST2 concentration in chronic heart failure remains to be summarized. **Methods:** We searched PubMed, Embase, and Web of Science for eligible studies up to January 1, 2020. Data extracted from articles and provided by authors were used in agreement with the PRISMA statement. The endpoints were all-cause mortality (ACM), cardiovascular mortality (CVM)/heart failure-related hospitalization (HFH), and all-cause mortality (ACM)/heart failure-related readmission (HFR). **Results:** A total of 11 studies with 5,121 participants were included in this analysis. Higher concentration of sST2 predicted the incidence of long-term ACM (hazard ratio [HR]: 1.03, 95% confidence interval [CI]: 1.02–1.04), long-term ACM/HFR (HR: 1.42, CI: 1.27–1.59), and long-term CVM/HFH (HR: 2.25, CI: 1.82–2.79), regardless of short-term ACM/HFR (HR:

2.31, CI: 0.71–7.49). **Conclusion:** Higher sST2 concentration at baseline is associated with increasing risk of long-term ACM, ACM/HFR, and CVM/HFH and can be a tool for the prognosis of chronic heart failure.

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Introduction

Heart failure is the terminal stage of various heart diseases, with high all-cause mortality and heart failure-related readmission [1], and increasing number of patients aggravate the global economic burden [2]. In the stage of chronic heart failure (CHF), the heart of a human has a remarkable degree of plasticity [3], and ventricular remodeling is an important sign of heart failure. Cardiac fibroblasts, upon injury, will transform to a myofibroblast phenotype, which contributes to cardiac fibrosis [4]. Soluble suppression of tumorigenicity-2 (sST2) blocks the cardioprotective effects of interleukin-33 (IL-33) in the way of sequestering its availability to bind with the ST2L receptor. In this way, sST2 has been proved to be the marker of myocardial fibrosis and heart failure

Fig. 1. Flowchart of the selection procedure. CHF, chronic heart failure.

progression [5] and has potential to be the prognosis index of heart failure, which is valuable for further study [6]. Although many studies have suggested that higher concentration of sST2 in baseline is related to a higher rate of HF events, most of them [7–17] vary in follow-up duration. In this paper, meta-analysis is used to provide evidence-based basis for the clinical prognosis evaluation of sST2 for long-term and short-term outcomes in CHF patients.

Methods

This meta-analysis was performed in accordance with MOOSE (Meta-analysis of Observational Studies in Epidemiology) [18].

Database Search

Two investigators (G.D. and H.C.) conducted a systematic search of PubMed, Embase, and Web of Science for eligible studies up to January 1, 2020, using the following keywords: (“heart failure” OR “Cardiac Failure” OR “Myocardial Failure” OR “Congestive Heart Failure” OR “Heart Decompensation” OR “Left-Sided Heart Failure” OR “Left Sided Heart Failure” OR “Right-Sided Heart Failure” OR “Right Sided Heart Failure” OR “cardiac dysfunction” OR “cardiac insufficiency” OR “left ventricular dysfunction”) AND (“ST2” OR “suppression of tumorigenicity 2”).

Inclusion and Exclusion Criteria

Studies fulfilling the following criteria were included: (1) English language; (2) cohort studies, including prospective studies or post hoc analysis of randomized controlled trials; (3) the concentration of sST2 measured at baseline; (4) patients diagnosed with HF and aged over 18 years; and (5) reporting the adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the risk of all-cause mortality (ACM), all-cause mortality/heart failure-related readmission (ACM/HFR), and cardiovascular mortality/heart failure-related hospitalization (CVM/HFH). Retrospective studies, overlapping studies, and studies with incomplete basic information of patients were excluded. Two authors independently included studies, and the disagreement was resolved by discussion.

Data Extraction and Quality Evaluation

Data extraction was performed by 2 authors (G.D. and H.C.), and disagreement about data was resolved by discussion. The following data of the included studies were extracted: author, publication year, study location, study design, sample size, basic clinical information (mean ages and proportions of males), follow-up durations, variables which were adjusted, HR, 95% CI, and the cutoff value of sST2 concentration. For studies not providing HRs or 95% CI, useful data would be extracted from survival distributions [19]. Two authors evaluated the quality of studies independently with the Newcastle-Ottawa Scale [20].

Statistical Analyses

All the references of studies were imported into the EndNote software (version X9). Our study used HR to measure the prognos-

Table 1. Summary of the characteristics of the 11 studies

Author	Year	Country	Design	Population	Age	Male, %	Outcome reported	Follow-up, months	Adjusted	sST2 (cutoff), ng/mL	NOS
Bahuleyan et al. [14]	2018	Asia	PC	141	60.3±10.4	76.6	CVM/HFH	12	Age, BMI, DM, dyslipidemia, creatinine clearance, smoking, NYHA, ACEI or ARB, BB	Continuous	7
Bayes-Genis et al. [8]	2012	Europe	PC	891	70.2 (median)	71.6	ACM	33.4 (median)	Age, sex, LVEF (in %), eGFR, NYHA, DM, ischemic etiology, hemoglobin, sodium, BB, ACEI or ARB, NT-proBNP	50	7
Binas et al. [15]	2018	Europe	Post hoc	262	50.2±12.8	75.2	ACM	60	Sex, age, BMI, DM, etiology, QRS duration, NYHA, LVEF, LVEDD	Continuous	7
Cui et al. [16]	2018	Asia	PC	217	72.61±9.08	38.7	CVM/HFH	12	Age, sex, SBP, DBP, NYHA, LVEF, CAD, hypertension, BB, ARB, LDL cholesterol, eGFR, NT-proBNP	Continuous	9
Grande et al. [13]	2017	Europe	PC	315	64±13	81	CVM/HFH	12	NT-proBNP, galectin-3	34	7
Ky et al. [7]	2011	USA	PC	1,141	56.3±14	67	ACM/HFR	33.6 (median)	Age, sex, race, cardiomyopathy etiology (ischemic vs. nonischemic), tobacco use, BMI, SBP, creatinine, LVEF, biventricular pacemaker, cardioverter defibrillator, ACEI/ARB, aldosterone antagonist, BB, clinical site, NT-proBNP	Continuous	7
Miller et al. [12]	2016	USA	PC	180	72±10	76	ACM/HFR	24	NYHA, etiology of HF, presence of biventricular pacing or ICD, MI, and stroke	Men:49.3 ng/mL; women:33.5 ng/mL	7
Pacho et al. [17]	2018	Europe	Post hoc	522	82.1±8.7	42.9	ACM/HFR	1	DM, Charlson comorbidity index, urea, NT-proBNP	Continuous	6
							ACM/HFR	12	Age, NYHA, Charlson comorbidity index, urea, creatinine, NT-proBNP, CA125, Hs-TnI	Continuous	
							ACM	12	Age, NYHA, Charlson comorbidity index, urea, creatinine, NT-proBNP, CA125, Hs-TnI	Continuous	
Sobczak et al. [10]	2014	Europe	PC	145	62.16±11.25	82.76	CVM/HFH	12	NT-proBNP, heart rate, LVESV, neutrophils	0.296	6
Xu et al. [11]	2014	Asia	PC	233	62±11	56.2	ACM/HFR	12	Age, heart rate, BMI, creatinine, NT-proBNP, NYHA, hypertension	Continuous	6
Zlinski et al. [9]	2012	Multi	PC	30	57 (median)	77	ACM/HFR	1.5	Age	104	6

ACM, all-cause mortality; CVM/HFH, cardiovascular mortality/heart failure-related hospitalization; ACM/HFR, all-cause mortality/heart failure-related readmission; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; BB, b-blockers; DM, diabetes mellitus; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CAD, coronary artery disease; ICD, implantable cardioverter defibrillator; MI, myocardial infarction.

Fig. 2. Forest plots for the meta-analysis of long-term prognostic value of sST2 concentration in CHF patients with sST2 concentration before sensitivity analysis: ACM (a); ACM/HFR (b); CVM/HFH (c). sST2, soluble suppression of tumorigenicity-2; CHF, chronic heart failure; ACM, all-cause mortality; ACM/HFR, all-cause mortality/heart failure-related readmission; CVM/HFH, cardiovascular mortality/heart failure-related hospitalization.

tic efficacy of sST2 concentration for CHF. We extracted HRs for log(sST2) if sST2 concentration was present as continuous variables; we extracted HRs which compared patients from the above to below cutoff value if sST2 concentration was present as categorized variables. We used Cochrane's Q test and I^2 to evaluate the heterogeneity among the studies. If $I^2 > 50\%$, which means heterogeneity was significant, sensitivity analyses were used to find out the source of heterogeneity, and the randomized-effects model was used to pool effect sizes. If $I^2 < 50\%$, the fixed-effects model was used to pool effect sizes. The above statistics are completed by Review Manager (Revman version 5.3; Cochrane Collaboration, Oxford, UK).

Results

Study Inclusion and Characteristics

According to the above inclusion criteria, 2,144 studies were retrieved, and 943 duplicated studies were excluded. 1,142 unrelated studies were excluded by reading titles

and abstracts; forty-eight articles were excluded after reading the full text, and 11 studies met the criteria of inclusion and exclusion (Fig. 1). The location of the study included Asia, Europe, USA, and multiple areas. The year of publication ranged from 2011 to 2018, and 5,121 patients in total were included. Three studies reported long-term ACM; four studies reported long-term ACM/HFR; four studies reported long-term CVM/HFH; and 3 studies reported ACM/HFR (Table 1).

Long-Term Prognostic Endpoints of Meta-Analyses

Three studies reported the relationship between higher sST2 concentration and ACM (over 1 year after hospitalization) (HR: 1.03, 95% CI: 1.02–1.04, $p = 0.0007 < 0.1$, $I^2 = 86\%$; Fig. 2a), and 4 studies showed higher concentration of sST2 is related to worse ACM/HFR (over 1 year after hospitalization) (HR: 1.48, 95% CI: 1.33–1.64, $p = 0.10$, $I^2 = 52\%$; Fig. 2b). Four studies showed that the baseline sST2 concentration predicts the risk of CVM/HFH (over

Fig. 3. Forest plots for the meta-analysis of long-term prognostic value of sST2 concentration in CHF patients in the fixed-effect model after sensitivity analysis: ACM (a); ACM/HFR (b); CVM/HFH (c). sST2, soluble suppression of tumorigenicity-2; CHF, chronic heart failure; ACM, all-cause mortality; ACM/HFR, all-cause mortality/heart failure-related readmission; CVM/HFH, cardiovascular mortality/heart failure-related hospitalization.

Fig. 4. Forest plots for the meta-analysis of short-term prognostic value of sST2 concentration in CHF patients in the randomized-effect model. sST2, soluble suppression of tumorigenicity-2; CHF, chronic heart failure.

1 year after hospitalization) (HR: 2.25, 95% CI: 1.82–2.79, $p = 0.470$, $I^2 = 0\%$; Fig. 2c) and had no significant heterogeneity. The first two of analyses of endpoints had a significant heterogeneity, and thus sensitivity analyses were needed to find the reason of heterogeneity. The sensitivity

analyses showed that after omitting the study by Pacho et al. [17] and Xu et al. [11], the heterogeneity of long-term ACM and long-term ACM/HFR became nonsignificant. Besides, there was no change after omitting any of the studies in the analysis of long-term CVM/HFH. There-

fore, the fixed-effect model was used. As shown in the fixed-effect model, higher sST2 concentration still predicted worse long-term ACM (HR: 1.03, 95% CI: 1.02–1.04, $p = 0.32$, $I^2 = 0\%$, $Z = 6.24$; Fig. 3a), long-term ACM/HFR (HR: 1.42, 95% CI: 1.27–1.59, $p = 0.66$, $I^2 = 0\%$, $Z = 7.22$; Fig. 3b), and long-term CVM/HFH (HR: 2.25, 95% CI: 1.82–2.79, $p = 0.47$, $I^2 = 0\%$, $Z = 7.50$; Fig. 3c). The publication biases of the meta-analyses because of limited number of included studies could not be performed.

Short-Term Prognostic Endpoints of Meta-Analyses

Two studies reported the risk of ACM/HFR in short term (1–1.5 months). Because of the significant heterogeneity and limited number of studies, the randomized-effects model was performed. The pooled analysis of these studies showed no significant difference in risk of ACM/HFR between people with different concentrations of sST2 in baseline risk of ACM/HFR (HR: 2.31, 95% CI: 0.71–7.49, $p = 0.10$, $I^2 = 62\%$, $Z = 1.46$; Fig. 4). The publication biases of the meta-analyses because of limited number of included studies could not be performed.

Discussion/Conclusion

In this meta-analysis, 11 prospective and post hoc studies from different regions and countries were integrated. The survival data of 5,121 patients were included. The results showed that sST2 is related to long-term ACM, ACM/HFR, and CVM/HFH. The sensitivity analysis and fixed-effect model analysis proved that the results were stable and reliable, which provided evidence from evidence-based medicine for sST2 as a clinical prognosis index.

2016 ESC Guidelines recommended LVEF as indicators to evaluate the severity of ventricular remodeling and cardiac function, but there are still great limitations when it comes to clinical application [21]. The guidelines also have mentioned that the natriuretic peptide plays an important role in the diagnosis and management of heart failure. However, 1 study pointed that NT-proBNP does not have a significant relationship with measures of cardiac function and exercise tolerance [22]. Also, BNP and NT-proBNP are cleared by the kidney, and their concentration is correlated similarly to glomerular filtration rate [23]. Besides, it is hard to identify the presence of change in filling pressures according to the change of NPs, and the diagnose of early decompensation should be dependent on the combination of NP concentration, weight gain, and symptoms [24].

sST2 is one of the subtypes of ST2 [25]. Compared to the natriuretic peptide, concentration of sST2 seems to be not affected by age, gender, and kidney function and has been known as the HbA1c of heart failure [26]. In the context of stretch-induced injury to the heart, sST2 prevents signaling through ST2L by the binding of IL-33 to sST2 and thus inhibiting the cardioprotective effect [27, 28]. In this way, it has been proved to be significantly related to the prognosis of cardiovascular disease [29]. Because of the low coefficient of variation in the concentration, sST2 has a great potential in serial measurement of HF [30]. sST2 and NT-proBNP complement each other in the risk stratification of heart failure [31]. This combination of biomarkers will also affect clinical decision-making in the future [32].

The strength of our study is using HRs after adjustment for multiple baseline covariates in the analysis of the relationship between the concentration of sST2 and the prognosis of CHF. Two recent meta-analyses [33, 34] did a remarkable job to reveal the prognostic value of sST2 in acute heart failure and CHF independently. What is different from these 2 studies is that our paper reveals the role of sST2 in CHF from 2 aspects: short-term effect and long-term effect. Furthermore, we have studied more and different clinical endpoints (ACM, ACM/HFR, and CVM/HFH) to elucidate the important role of sST2 in the prognosis of CHF. This article will promote people's cognition of the prognostic role of sST2 in heart failure. There are some limitations and deficiencies in our study. Firstly, it is difficult to determine the stability of this study through the publication bias due to the small number of studies included, and thus need to be performed, especially, in the aspect of short-term endpoints. Secondly, the study by Ky et al. [7] has larger sample size than others, and the 2 studies [9, 17] in the analysis for short-term ACM/HFR have great difference in sample size and that may lead to bias. Last but not least, our study does not restrict the measurement of sST2. It has been proved that compared with other detection methods, the Pressure[®] ST2 assay can determine the concentration of sST2 more accurately [35, 36]. However, different detection methods are included in our study, which will also interfere with the stability and accuracy of this study.

In conclusion, our study showed that higher concentration of sST2 can be used as independent prognostic factors for CHF and is suitable for long-term endpoints (ACM, ACM/HFR, and CVM/HFH), regardless of short-term ACM/HFR, and more studies need to be performed in this aspect. This meta-analysis supports the wide ap-

plication of sST2 in CHF and provides a supplement for the natriuretic peptide and other biomarkers of heart failure risk stratification.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Supervision: Hao Chen and Yihuang Gu. Data curation, investigation, and methodology: Guoqi Dong and Hongru Zhang. Software: Guoqi Dong. Writing – original draft: Guoqi Dong.

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