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Research article

Soluble ST2 for predicting heart failure, atrial fibrillation and death in patients with coronary heart disease with or without renal insufficiency

Huiying Li [a,b,1], Qiwei Zhu [a,1], Jing Bai [c,1], Jianqiao Chen [d], Zifan Zhu [e], Benchuan Hao [a,b], Wei Wang [f], Yongyi Bai [a,**], Hongbin Liu [a,*]

[a] *Department of Cardiology, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, 100853, Beijing, China*
[b] *Medical School of Chinese PLA, 100853, Beijing, China*
[c] *Outpatient Department of the Ministry of Foreign Affairs, 100020, Beijing, China*
[d] *Department of Geriatric Medicine, Henan Provincial People's Hospital, 450003, Henan, China*
[e] *Yangfangdian Outpatient Department, Southern Medical Branch of PLA General Hospital, 100843, Beijing, China*
[f] *Department of Cardiology, The Sixth Medical Center of Chinese PLA General Hospital, 100037, Beijing, China*

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ABSTRACT

Background: This study aimed to investigate the relationship between baseline soluble suppression of tumorigenesis-2 (sST2) concentration and the outcomes of heart failure (HF), atrial fibrillation (AF) or death in patients with coronary heart disease (CHD) with or without renal insufficiency (RI).

Methods: Between March 2011 and December 2015, 3454 patients with CHD from the Chinese PLA General Hospital were enrolled in this cohort study. The patients were followed up until October 2021. AF, HF, and death events were recorded. Associations between baseline sST2 concentrations and clinical outcomes were assessed using Kaplan-Meier (K-M) curves, and Cox regression and generalised additive models. Subgroup analysis were carried out between RI and non-RI groups.

Results: Among the patients with CHD (61.5 ± 11.8 years; 78.6 % men), 415 (12.02 %) had RI. During a median follow-up of 8.37 years, HF and AF were reported in 216 (6.25 %) and 174 (5.04 %) patients, respectively, and 297 (8.60 %) died. The K-M curves indicated that patients in the higher quartiles of sST2 concentrations were correlated with a poor survival rate of HF, AF, or death (all $Ps < 0.001$). Generalised additive model (GAM) demonstrated a nonlinear positive association between sST2 concentration and the risk of HF, AF, and death in CHD patients. The cut-off value of sST2 for predicting HF, AF and death were 32.1, 25.4 and 28.6 ng/mL, respectively. CHD patients with sST2 higher than the cut-off value had higher risks of HF (HR: 3.02, 95%CI: 2.24–4.05), AF (HR: 2.86; 95%CI: 2.10–3.90), and death (HR:2.11, 95%CI: 1.67–2.67). Furthermore, in patients with RI (12.02 %, n = 415), the prognostic value of sST2 over the cut-off

* Corresponding author. Department of Cardiology, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, No. 28 Fu Xing Road, Hai Dian, Beijing, 100853, China.
** Corresponding author. Department of Cardiology, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, No. 28 Fu Xing Road, Hai Dian, Beijing, 100853, China.
E-mail addresses: baiyongyi301@sina.com (Y. Bai), liuhbcad301@163.com (H. Liu).
[1] These authors contributed equally to this work and share first authorship.

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value for HF and death remained unchanged (HR: 3.21 and 2.35; $P < 0.05$). In patients with CHD with or without RI, sST2 improved the area under the curve (AUC) of traditional risk models for predicting clinical endpoint events.
Conclusions: The biomarker sST2 may be useful for predicting HF, AF, and death in patients with CHD. The predicted value was not affected by renal function.

1. Introduction

Coronary heart disease (CHD) remains a leading cause of morbidity and mortality globally [1]. Myocardial ischaemia and hypoxia caused by CHD can lead to cardiac remodelling, heart failure (HF) and even death [2]. Because the comorbidity rate of renal insufficiency (RI) in the CHD population is high, the management of CHD is complicated in patients with RI.

Suppression of tumorigenesis-2 (ST2), a member of the interleukin-1 (IL-1) receptor family, is expressed by vascular cells, myocardial fibroblasts, cardiomyocytes and various circulating immune cells [3,4]. The ST2 gene encodes two subtypes: soluble ST2 (sST2) and transmembrane ST2 (ST2L) [5]. The interaction between ST2L and IL-33 alleviates cardiac hypertrophy and myocardial fibrosis [6]. However, sST2 acts as a "decoy" receptor, impeding the IL-33/ST2L pathway by competing for binding sites in IL-33, thereby inhibiting the cardioprotective effects of IL-33 [7,8]. sST2 is a marker of inflammatory and haemodynamic overload and, reflects the degree of myocardial stretch to a certain extent. Additionally, sST2 plays a key role in promoting ventricular remodelling and increasing mortality in patients with diagnosed HF [9,10]. However, few studies have demonstrated the prognostic value of baseline sST2 concentrations in predicting HF, atrial fibrillation (AF) and death in patients with CHD, especially in those with concurrent RI [11]. Therefore, this study aimed to investigate the association between baseline sST2 concentrations and long-term clinical outcomes in patients with CHD, especially in those with concurrent RI.

2. Material and methods

2.1. Patients and the study process

This study was initially designed to test the prognostic value of different biomarkers in patients with CHD diagnosed using coronary angiography or coronary computed tomography angiography [12]. Between March 2011 and December 2015, 4070 patients with >50 % stenosis in one or more major coronary vessels on coronary angiography (CA) or coronary computed tomography angiography (CTA) in the Chinese PLA General Hospital were included. These patients had undergone coronary CTA or CA for angina-like chest pain; myocardial ischaemia indicated by electrocardiogram, dynamic electrocardiogram, or exercise tablet test; or coronary

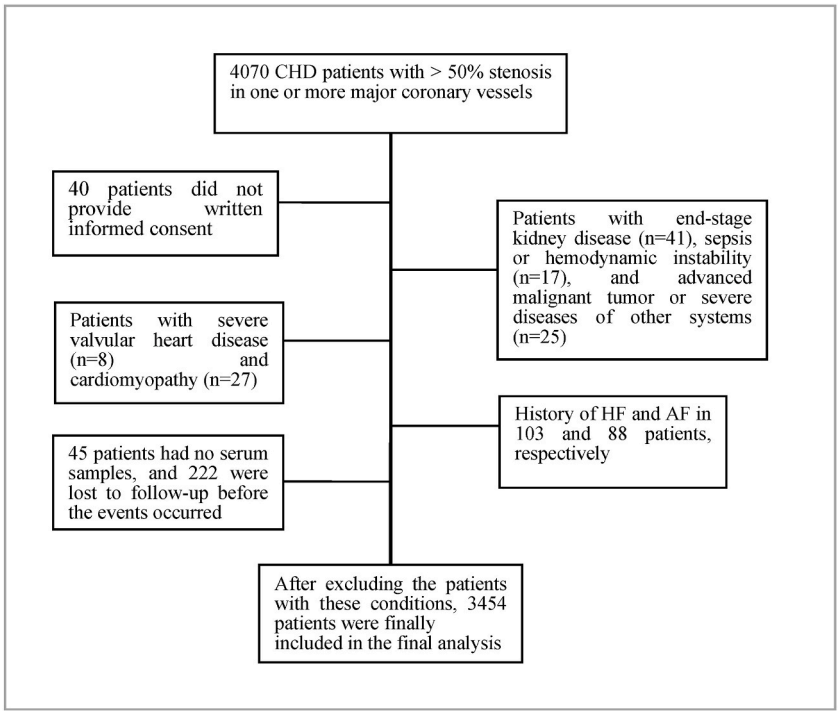

Fig. 1. Participant Selection Flowchart. AF, atrial fibrillation; HF, heart failure; CHD, coronary heart disease.

calcification indicated by chest computed tomography. Statisticians recorded single or multiple vascular lesions using angiography or coronary CTA. In summary, all the selected patients with CHD were diagnosed using imaging findings. The exclusion criteria were as follows: 1) patients who were not willing to provide written informed consent, 2) no serum samples, 3) history of HF or AF, end-stage kidney disease (estimated glomerular filtration rate [eGFR] <15 mL/min·1.73 m^2), haemodynamic instability, severe valvular heart disease or cardiomyopathy, advanced malignant tumour or severe diseases of other systems. Patients who were lost to follow-up before the events were also excluded. Finally, 3454 patients were included in this study (Fig. 1). Previous HF was defined using the Framingham criteria according to the patients' medical histories, physical examinations and laboratory tests. AF was diagnosed based on the basis of previous electrocardiograms. Patients with eGFR <60 mL/min·1.73 m^2 or who had been diagnosed with chronic kidney disease (CKD) were considered to have RI, irrespective of the acute kidney injury. Baseline clinical information was collected through face-to-face interviews with patients or from medical records.

Follow-ups commenced either immediately after inclusion on the study or 15 days after coronary CA or coronary artery bypass grafting (CABG), which extended until October 2021. During this period, medical records of patients who had visited another emergency department or had been hospitalised elsewhere, were obtained from the corresponding hospitals or healthcare systems. Signs and symptoms, laboratory results, chest radiographs, electrocardiograms, and medication records were collected, and echocardiography and magnetic resonance imaging results were obtained. All possible HF or AF records provided by the patients or obtained through the electronic medical record system were reviewed by at least two physicians on adjudication committee. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the PLA General Hospital (S2016-070-02). Informed consent was obtained from all the patients.

2.2. Biomarker assessment

Blood samples were collected from all the participants after overnight fasting. In patients who had undergone CA or CABG, serum samples were collected 15 days after the procedure. The serum was centrifuged and stored at −80 °C. The samples did not undergo any freeze-thaw cycles before sST2 concentrations were detected using a quantitative sandwich monoclonal enzyme-linked immunosorbent assay (Presage sST2 Assay; Critical Diagnostics, Inc., San Diego, CA, USA). The analysts were blinded to the patient characteristics. Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, uric acid, creatinine, and glucose concentrations were measured using an automatic biochemical analyser (Cobas c 501; Roche Diagnostics Corp., IN, USA). N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations were determined using a fully-automatic chemiluminescence immunoassay instrument (Elecsys System 2010; Roche). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation as follows: for men, eGFR (mL/min·1.73 m^2) = 141 × (serum creatinine [Scr]/0.9)$^{\sigma}$ × 0.993^{age} (if Scr is ≤ 0.9 mg/dL, σ = −0.411; if Scr is >0.9 mg/dL, σ = −1.209); and for women, eGFR = 144 × (Scr/0.7)$^{\sigma}$ × 0.993^{age} (if Scr is ≤ 0.7 mg/dL, σ = −0.329; if Scr is > 0.7 mg/dL, σ = −1.209).

2.3. Clinical outcomes and definitions

Clinical outcomes were defined as the incidence of HF, AF, and all-cause deaths. Patients who were clinically diagnosed with HF or met the Framingham criteria for HF were recorded as having experienced HF events. Medical records, physical examinations, radiological information, and laboratory tests were used to determine whether the patients met the Framingham criteria for HF [13,14], which required two major criteria or one major and two minor criteria for congestive HF (Supplementary Table 1). AF was confirmed by electrocardiography during hospitalisation or during an outpatient or emergency department visit. All-cause death was defined as death from any cause confirmed by the patient's family members or a death record in the medical record system. Patients included in this study with clinically diagnosed CKD and those with an eGFR <60 ml/min·1.73 m^2, regardless of acute kidney injury were considered to have RI.

2.4. Statistical analysis

Continuous variables are presented as mean with standard deviation (SD) or median with interquartile range. Categorical variables are presented as counts and percentages. The participants were categorised into four groups according to the quartiles of baseline sST2 concentrations. The differences in baseline characteristics between the groups were evaluated using the Student's t-test or chi-square test. The prognostic effects of sST2 were evaluated using adjusted Kaplan–Meier curves (log-rank test), multivariate Cox proportional hazard regression models, and generalised additive models (GAM). Before performing the Cox regression analysis, the proportionality of hazards was assessed for each variable, and Schoenfeld residual tests were used to verify the assumption of proportional hazards. All variables fulfilled this assumption, and none exhibited significance based on a *P* value threshold of 0.05. In the Kaplan–Meier curves, GAM and multivariate Cox regression models, age, sex, traditional cardiovascular risk factors (hypertension, hyperlipidemia, smoking history, and diabetes mellitus), medication history (Antiplatelet, ACEI/ARB, β-blocker, statins), invasive or surgical procedure, and other clinical indicators (BMI, blood pressure, multivessel disease, uric acid, eGFR, fasting glucose, NT-proBNP and LVEF if they showed a significant *P* value in the single factor analysis) were adjusted. Subsequently, subgroup analysis were performed between subgroups of age, sex, LVEF, CA/CABG or not, and eGFR (eGFR ≥60 or ≥15 and < 60 ml/min·1.73 m^2). Interaction tests were performed to assess the heterogeneity in the subgroups. The cut-off values of sST2 for predicting HF, AF and death were calculated using the "survminer" package. When doing the multivariate Cox regression analysis and the subgroup analysis, the sST2 values were grouped according to the above cut-off values. Using the method described by Delong et al. [15], we compared the areas under the

receiver operating characteristic curves of the traditional and new risk models in all patients and in those with RI. All statistical analyses were performed using the statistical software packages R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA). A two-sided P value < 0.05 was considered statistically significant.

3. Results

3.1. Demographics and clinical characteristics

Of the 3454 patients with CHD (mean age: 61.5 ± 11.8 years; 78.6 % men), 2567 (74.3 %) and 168 (4.9 %) had undergone CA and CABG, respectively, 2112 (61.1 %) had multivessel disease. The mean eGFR was (84.2 ± 21.6) mL/min·1.73 m2, and the mean sST2 concentration was 22.9 ng/mL. We divided the patients into four groups according to the quartiles of sST2 concentration (Table 1) and the RI definition (60 mL/min·1.73 m2, Supplementary Table 2). Patients in different sST2 quartiles showed significant difference in age, sex, CABG proportions, medication history (antiplatelet, ACEI/ARB, statins), high-density lipoprotein cholesterol (HLD-C), creatinine, eGFR, uric acid, NT-proBNP, fasting glucose, and LVEF levels (Table 1, $P < 0.05$). RI was reported in 415 (12.02 %) patients (Supplementary Table 2). Patients in the RI group were older, with a lower BMI, and a higher systolic blood pressure and lower diastolic blood pressure and LVEF, and the levels of uric acid, NT-proBNP, creatinine, fasting glucose, and sST2 values were elevated (all $P < 0.05$, Supplementary Table 2). The number of patients with diabetes mellitus or multivessel disease was higher in the RI group than in the non-RI group ($P < 0.05$; Supplementary Table 2).

3.2. Outcomes

During the median follow-up time of 8.37 years, 216 (6.25 %) and 174 (5.04 %) experienced HF and AF events, respectively, and 297 (8.60 %) were reported dead. Univariate Cox analysis were carried out to find the variables that increase the risk of HF, AF or death (Supplementary Table 3). Adjusted Kaplan–Meier curves showed that higher quartiles of sST2 concentrations were correlated with a

Table 1
Baseline characteristics of the patients according to sST2 concentrations.

Characteristics	Total(n = 3454)	Bottom quartile	Second quartile	Third quartile	Top quartile	*P* value
		ST2≤12.60 ng/dL n=863	**12.60 < sST2≤19.19 n=864**	**19.19 < sST2≤28.97 n=864**	**sST2≥28.97 n=863**	
Age, years	61.5 (11.8)	61.2 (11.4)	61.0 (11.5)	61.2 (11.5)	62.6 (12.6)	0.035
Male	2714(78.6 %)	640 (74.2 %)	679 (78.6 %)	705 (91.6 %)	690 (80.0 %)	0.001
BMI, kg/m^2	25.6 (3.45)	25.6 (3.4)	25.7 (3.4)	25.6 (3.4)	25.6 (3.6)	0.966
Systolic BP, mmHg	134.9 (22.1)	134.4 (19.2)	134.8 (19.1)	134.5 (19.6)	135.4 (20.5)	0.729
Diastolic BP, mmHg	75.8 (16.8)	75.5 (11.3)	76.0 (12.1)	75.6 (11.0)	75.4 (12.7)	0.812
Used to smoke	1627 (47.1 %)	392 (45.4 %)	431 (49.9 %)	402 (46.5 %)	402 (46.6 %)	0.276
Hypertension	2248 (65.1 %)	539 (62.5)	569(65.9)	559(64.7)	581 (67.3)	0.186
Dyslipidemia	1056 (30.6 %)	261(30.2)	281 (32.5)	275 (31.8)	239 (27.7)	0.133
Diabetes mellitus	1111 (32.2 %)	269 (31.2 %)	276 (31.9 %)	268 (31.0 %)	298(31.4 %)	0.370
CA	2567 (74.3 %)	645 (74.7 %)	642 (74.3 %)	642 (74.3 %)	638 (73.9 %)	0.985
CABG	168 (4.9 %)	36 (4.2 %)	29 (3.4 %)	53 (6.1 %)	50 (5.8 %)	0.021
Multivessel disease	2112 (61.1 %)	525 (60.8 %)	505 (58.4 %)	537 (62.2 %)	545 (63.2 %)	0.211
Antiplatelet	3345(99.7 %)	838 (97.1 %)	844 (97.7 %)	842 (97.5 %)	821 (95.1 %)	0.009
ACEI/ARB	1474 (42.7 %)	338 (39.2 %)	357 (41.3 %)	380 (44.0 %)	399 (46.2 %)	0.018
β-blocker	2484 (71.9 %)	615 (71.3 %)	611 (70.7 %)	638 (73.8 %)	620 (71.8 %)	0.496
Statins	3258 (94.3 %)	825 (95.6 %)	813 (94.1 %)	822 (95.1 %)	798 (92.5 %)	0.025
TC, mmol/L	4.03 (1.06)	4.02 (1.07)	4.02 (1.05)	4.03 (1.01)	4.05 (1.13)	0.909
LDL-C, mmol/L	2.39 (0.87)	2.36(0.86)	2.39 (0.85)	2.39 (0.84)	2.41 (0.91)	0.761
HDL-C, mmol/L	1.05 (0.31)	1.07 (0.35)	1.04 (0.28)	1.05 (0.28)	1.05 (0.31)	0.376
TG, mmol/L	1.61 (1.01)	1.68 (1.10)	1.62 (0.99)	1.62 (1.10)	1.51 (0.92)	0.004
Uric acid, μmol/L	328.8 (271.2,394.1)	319.6(266.7,379.7)	327.4(270.9,391.5)	340.4(272.8,398.0)	339.7 (275.2,408.4)	<0.001
NT-proBNP, ng/L	149.5 (52.3, 502.1)	119.6 (46.6, 321.5)	127.0 (48.4, 336.8)	142.3 (50.4, 492.1)	267.8 (80.8,1334.5)	<0.001
Creatinine, μmol/L	76.4 (67.2, 88.2)	74.7 (66.3, 85.3)	76.0 (66.7, 86.7)	76.6 (67.8, 87.2)	78.6 (68.8, 94.3)	<0.001
eGFR,mL/ min·1.73m^2	84.2 (21.6)	86.2 (18.8)	85.6 (20.0)	85.4 (20.4)	79.7 (25.8)	<0.001
Glucose, mmol/L	7.09 (4.86)	6.76 (3.14)	6.68 (3.10)	6.86 (3.15)	7.27 (3.56)	<0.001
sST2, ng/dL	22.86 (13.86)	9.08 (2.41)	15.8 (1.85)	23.47 (2.79)	43.10 (10.09)	<0.001
LVEF, %	56.3 (8.5)	57.1 (7.9)	57.4 (7.5)	56.2 (8.8)	54.5 (9.2)	<0.001

Data are the mean (standard deviation), n (%) or median (interquartile range). BMI, body mass index; BP, blood pressure; CA, coronary angiography; CABG, coronary artery bypass grafting; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; NT-proBNP, N-terminal pro-brain natriuretic peptide; eGFR, estimated glomerular filtration rate; sST2, soluble suppression of tumorigenesis-2; LVEF, left ventricular ejection fraction.

poor survival rate of HF, AF, or death (Fig. 2, all *Ps* for trend <0.001). Adjusted generalised additive model demonstrated a nonlinear positive association between sST2 concentration and the risk of HF, AF, and death in CHD patients (Fig. 3). The best cut-off values of sST2 for predicting HF was 32.1 ng/mL, for AF was 25.4 ng/mL, and for death was 28.6 ng/mL. The multivariable Cox regression analysis, showed that CHD patients with sST2 higher than the cutoff value had higher risks of HF (HR: 3.02, 95%CI: 2.24–4.05), AF (HR: 2.86; 95%CI: 2.10–3.90), and death (HR:2.11, 95%CI: 1.67–2.67) (Fig. 4). HRs remained relatively stable in the age, sex, LVEF, CA/CABG, and eGFR subgroups (Fig. 4). The area under the curve (AUC) of the conventional risk models for predicting HF, AF, and death during the follow-up period increased when the continuous variable sST2 was added to the models (all $P < 0.05$; Fig. 5, Table 2). In the total cohort, adding sST2 to the conventional risk models increased the AUC for HF from 0.751 to 0.799 ($P < 0.001$, Fig. 5A), AF from 0.782 to 0.811 ($P = 0.001$, Fig. 5C), and mortality from 0.868 to 0.882 ($P < 0.001$, Fig. 5E). In the RI group, the addition of sST2 increased the AUC for HF from 0.738 to 0.802 ($P = 0.021$, Fig. 5B), AF from 0.739 to 0.764 ($P = 0.014$, Fig. 5D), and mortality from 0.754 to 0.771 ($P = 0.019$, Fig. 5F).

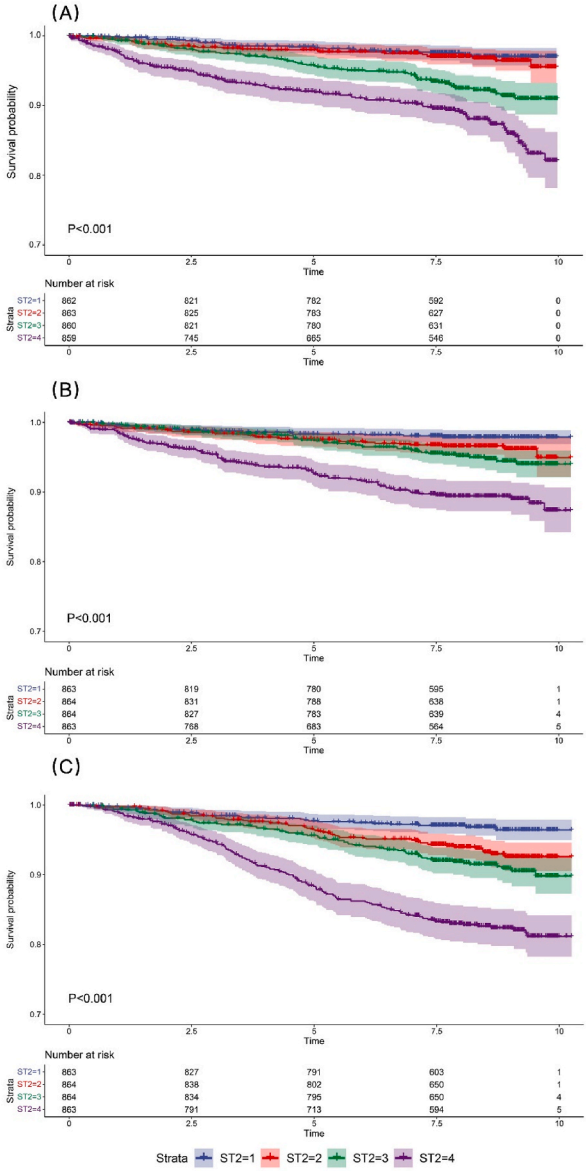

Fig. 2. (a colored graph) Kaplan–Meier curves for HF, AF and all-cause death in patients in different quartiles of sST2 concentrations. (A) Kaplan–Meier curves of HF in different sST2 quartiles. (B) Kaplan–Meier curves of AF in different sST2 quartiles. (C) Kaplan–Meier curves of all-cause death in different sST2 quartiles. HF, heart failure; AF, atrial fibrillation; sST2, soluble suppression of tumorigenesis-2.

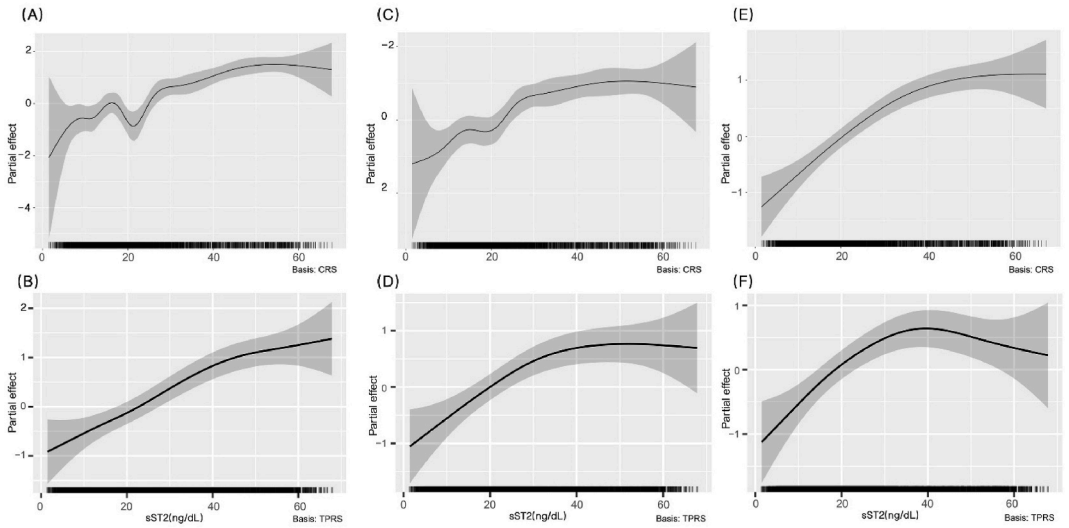

Fig. 3. Simple (A, C, E) and multivariate GAM models (B, D, F) to examine the relationship between soluble ST2 and HF (A, B), AF (C, D), or death events (E, F). Non-linear correlations were found between the ST2 levels and HF, AF or death events. Overall, the higher the sST2 level, the greater the risk of HF, AF and death. GAM, generalised additive models.

4. Discussion

Owing to its adverse outcomes, CHD contributes to substantial burden of healthcare costs, particularly in middle-income countries [16]. Functional changes in endothelial cells, smooth muscle cells, myocardial cells and macrophages at the ischaemic site cause local inflammatory responses that promote myocardial remodelling [17]. HF is an adverse outcome of CHD; therefore, the secondary prevention and treatment of CHD mainly aim to prevent the development of HF. AF is a major risk factor for stroke and closely related to HF. AF complicates antithrombotic therapy in patients with CHD, particularly when RI increases the risk of bleeding. Therefore, it is important to conclude that sST2 can predict the risk of HF and AF in patients with CHD, including those with RI.

RI is a strong independent risk factor for HF and AF [11], and a considerable number of patients with CHD have RI. A nationwide registration study conducted in the USA reported that 30.5 % of ST elevation myocardial infarctions (n = 5880) and 42.9 % of non-ST elevation myocardial infarctions (n = 13,069) were accompanied by CKD [18]. Acute kidney injury was diagnosed in 13.09 % (575/4391) of patients who had undergone CA [19]. In our study, 12.0 % (415/3454) of the patients with CHD had RI (eGFR: 15–60 mL/min·1.73 m^2).

The biomarker sST2 is mostly produced by vascular cells, and is partially produced by myocardial fibroblasts, cardiac myocytes, and circulating immune cells, which are associated with inflammatory status, endothelial dysfunction, cardiac mechanical stress, myocardial fibrosis, and remodelling, with prognostic capability in risk stratification of HF [20–23]. Patients with HF and high sST2 concentrations had higher rates of rehospitalisation and all-cause mortality [10,24]. Patients with CHD and elevated sST2 concentrations are at a higher risk of developing major adverse cardiovascular events [7]. sST2 is an independent predictor of new-onset AF in patients with acute myocardial infarction and could improve the accuracy of the AF risk model [25]. However, few studies have shown a relationship between sST2 concentrations and HF and AF outcomes in a large cohort of patients with CHD, especially in patients with CHD and RI [26]. To our knowledge, this is the first study to demonstrate that sST2 concentration can predict the risk of HF and AF in patients with CHD, even in the RI subgroups. The prognostic value of sST2 was also observed in different subgroups according to age, sex, LVEF, and CA/CABG or not, suggesting that sST2 is a potential biomarker in the Chinese CHD population.

The mechanisms underlying the association between sST2 levels and incident HF and AF in patients with CHD are not fully understood. Herein, we have summarised the possible mechanisms by which sST2 leads to incident HF in patients with CHD. During pathogenic stimulation and cellular injury, the release of IL-33 and ST2L inactivates myocardial hypertrophy and fibrosis, inhibits cardiomyocyte apoptosis, and plays a cardioprotective role [27]. However, sST2 acts as a decoy receptor for IL-33 and blocks the protective effects of the IL-33/ST2 pathway in myocardial ischaemia and remodelling [28,29]. Furthermore, endothelial dysfunction is a component of the underlying HF pathophysiology, and sST2 is specifically expressed in arterial endothelial cells, which is inversely associated with flow-mediated dilation (an indicator for evaluating endothelial function and arterial stiffness). These facts highlight the interplay between a dysfunctional endothelium and the pathophysiological mechanisms of HF [22]. Therefore, sST2 may aggravate myocardial ischaemia, promote remodelling and fibrosis, and lead to ischaemic HF. Finally, cardiac remodelling and other adverse events in patients with CHD are partly due to an inflammatory reaction in the microenvironment, and sST2 may promote inflammation by mediating allergic reactions [30,31].

However, the specific mechanism through which sST2 triggers AF remains unclear. Possible mechanisms include the involvement of sST2 in inflammation, tissue fibrosis, tight ventricular pressure overload and myocardial injury [32]. However, a clear relationship was observed between AF and HF because they share a similar pathogenesis of electrophysiological remodelling, neurohormonal

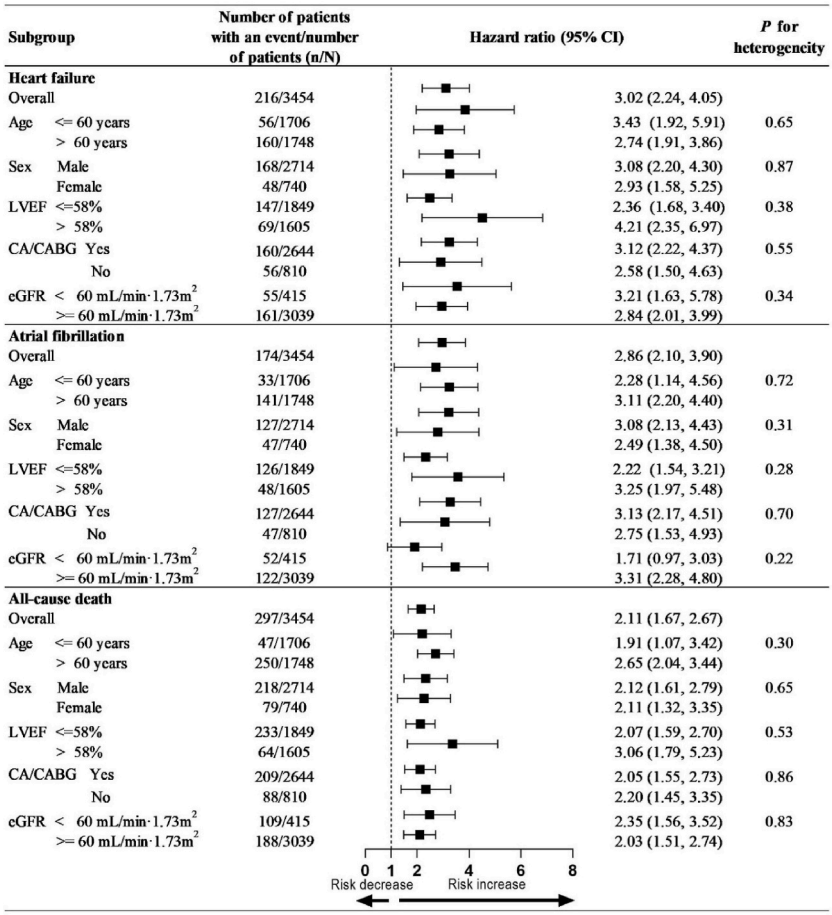

Fig. 4. Forest plot of sST2 in predicting HF, AF and death in the RI group and in subgroups of age, sex, LVEF, and CA/CABG. The best cut-off values of sST2 for predicting HF was 32.1 ng/mL, for AF was 25.4 ng/mL, and for death was 28.6 ng/mL. According to these cut-off values, the multivariate analysis were carried out, which considered age, sex, traditional cardiovascular risk factors, medication history, invasive or surgical procedure, and other variables with $P < 0.05$ in univariate analysis in the Supplementary Table 3. CA, coronary angiography; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.

hyperactivation, and the development of fibrosis. AF impairs cardiac efficiency, worsens preexisting left ventricular dysfunction and exacerbates HF symptoms [33,34]. HF is associated with atrial fibrosis and AF, similar to other cardiovascular diseases such as hypertension and valvular heart disease, which cause atrial overload and stretching. The presence of HF increases the likelihood of AF and vice versa [35]. Further studies are required to clarify the relationship between sST2 levels and AF in patients with CHD. The increased risk of HF and AF events in patients with CHD and RI may be partially attributed to myocardial ischaemia and remodelling, endothelial dysfunction, and inflammation indicating the role of ST2 in these pathways.

4.1. Limitations

Our study had several potential limitations. First, this was a single-center observational study. Although this study included a large population, the results may only be applicable to patients with similar characteristics. Second, we failed to validate these results in other cohorts, as the detection of ST2 has not been applied in clinical practice and obtaining peripheral blood samples from large populations with CHD was challenging. Third, other promising biomarkers, such as hsCRP, high-sensitivity troponin I, high-sensitivity troponin T, GDF-15 and IL-6, were not included in this study. The combination of biomarkers could have improved the prognostic value [36]. The CHD severity and the risk of the CHD patients were also not taken into consideration. Fourth, studies have shown that a decline in renal function, rather than the presence of RI, is associated with the progression and outcomes of CHD [37]. However, we failed to monitor renal function during follow-up. Finally, although higher sST2 levels were associated with an adverse prognosis, the underlying mechanisms require further research.

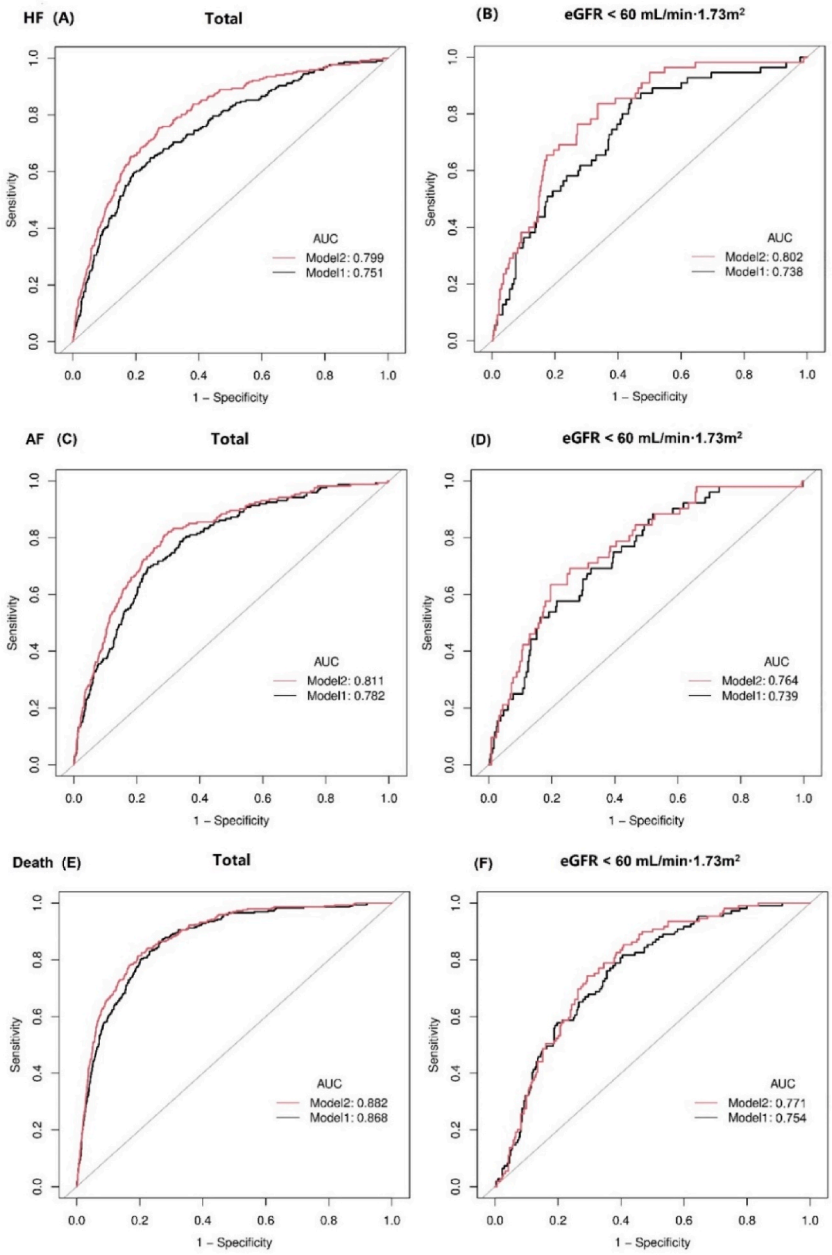

Fig. 5. Receiver operating characteristics of risk models for predicting HF, AF and death in patients with coronary heart disease with or without renal insufficiency. Model 1 considered age, sex, traditional cardiovascular risk factors, medication history, invasive or surgical procedure, and variables with $P < 0.05$ in the Supplementary Table 3. Model 2 consisted of the variables in model 1 and soluble suppression of tumorigenesis-2. AUC, area under the curve; eGFR, estimated glomerular filtration rate; HR, heart failure; AF, atrial fibrillation.

5. Conclusions

Serum sST2 is a potential biomarker for predicting HF, AF, and death in Chinese patients with CHD and may have therapeutic potential for regulating the myocardial response to ischaemia and overload. Because the predictive value of sST2 was not affected by renal function, sST2 may increase the predictive ability of traditional risk models for HF, AF, and death among Chinese patients with CHD concurrent with RI.

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Table 2
Comparison of the areas under the receiver operating characteristic curves in Fig. 4.

	Total	RI (eGFR<60 mL/min·1.73m^2)
Heart Failure		
Model1	0.751 (0.718, 0.785)	0.738 (0.670, 0.807)
Model2	0.799(0.768, 0.829)	0.802 (0.745, 0.859)
P	<0.001	0.021
Atrial Fibrillation		
Model1	0.782 (0.749, 0.816)	0.739 (0.671, 0.807)
Model2	0.811 (0.778, 0.843)	0.764 (0.698, 0.831)
P	<0.001	0.014
Death		
Model1	0.868 (0.849, 0.888)	0.754 (0.705, 0.804)
Model2	0.882 (0.863, 0.901)	0.771 (0.724, 0.818)
P	<0.001	0.019

Areas under the curves of the risk models were used to predict heart failure, atrial fibrillation and death in patients with coronary heart disease with or without renal insufficiency. Model 1 considered age, sex, traditional cardiovascular risk factors, medication history, invasive or surgical procedure, and other variables with $P < 0.05$ in the Supplementary Table 3. Model 2 consisted of the variables in model 1 and soluble suppression of tumorigenesis-2. eGFR, estimated glomerular filtration rate; RI, renal insufficiency.

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Ethics declarations

This study was reviewed and approved by ethics committee of PLA General Hospital, with the approval number: S2016-070-02. All patients provided informed consent to participate in the study. All patients provided informed consent for the publication of their anonymised case details and images.

Data availability statement

The dataset analysed in the current study is available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Huiying Li: Writing – original draft, Methodology, Data curation. **Qiwei Zhu:** Writing – original draft, Data curation, Conceptualization. **Jing Bai:** Writing – original draft, Investigation, Data curation. **Jianqiao Chen:** Methodology. **Zifan Zhu:** Investigation, Data curation. **Benchuan Hao:** Investigation, Data curation. **Wei Wang:** Resources. **Yongyi Bai:** Supervision, Funding acquisition. **Hongbin Liu:** Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

All authors disclosed no financial relationships relevant to this publication.

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Appendix A. Supplementary data

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