Prognostic value of ST2 for MACEs and all-cause mortality in patients with coronary artery disease during a long-term follow up

Man Li  
Chinese PLA General Hospital  https://orcid.org/0000-0003-1482-0512

Lei Duan  
Chinese PLA General Hospital

Yulun Cai  
Chinese PLA General Hospital

Benchuan Hao  
Chinese PLA General Hospital

Jianqiao Chen  
Chinese PLA General Hospital

Huiying Li  
Chinese PLA General Hospital

Hongbin Liu  
liuhbcad301@163.com  Chinese PLA General Hospital  https://orcid.org/0000-0002-9418-7341

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Abstract

**Background:** Suppression of tumorigenesis-2 is implicated in the myocardial overload and it was long been recognized as an inflammation marker related to heart failure and acute coronary syndromes, but the data on prognostic value of suppression of tumorigenesis-2 on patients with coronary artery disease remains limited. The study ought to investigate the prognostic value of suppression of tumorigenesis-2 in patients with established coronary artery disease.

**Methods:** In this prospective cohort study, a total of 3641 consecutive patients were included. The primary end point was major adverse cardiovascular events. Kaplan-Meier survival estimates indicated that the patients with higher levels of ST2 (ST2> 19 ng/ml) had a significantly increased risk of MACEs (log-rank p<0.001) and all-cause death (log-rank p<0.001). The secondary end point was all-cause death. The association between suppression of tumorigenesis-2 and outcomes was investigated using multivariable COX regression.

**Results:** During a median follow up of 6.4 years, there were 775 patients had the occurrence of major adverse cardiovascular events and 275 patients died. Kaplan-Meier survival estimates indicated that the patients with higher levels of ST2 (ST2> 19 ng/ml) had a significantly increased risk of MACEs (log-rank p<0.001) and all-cause death (log-rank p<0.001). Multiple COX regression models showed that higher level of suppression of tumorigenesis-2 was an independent predictor in developing major adverse cardiovascular events (HR=1.36, 95% CI 1.17-1.56, p<0.001) and all-cause death (HR=2.01, 95%CI 1.56-2.59, p<0.001). The addition of suppression of tumorigenesis-2 to established risk factors significantly improved risk prediction of the composite outcome of major adverse cardiovascular events and all-cause death (c-statistic, net reclassification index, and integrated discrimination improvement, all p<0.05).

**Conclusions:** Higher level of suppression of tumorigenesis-2 is significantly associated with long-term all-cause death and major adverse cardiovascular events. Suppression of tumorigenesis-2 may provide incremental prognostic value beyond traditional risk factors.

1 Introduction

Coronary artery disease (CAD) remains the leading cause of death of the world [1]. Patients with previous coronary heart disease have a high probability of major adverse cardiac events (MACEs). Development of reliable prognostic biomarker would be of vital importance in established CAD patients.

Suppression of tumorigenesis-2 (ST2) is an interleukin-1 (IL-1) receptor family member, it exists in two isoforms: membrane-bound (ST2L) and soluble isoforms (sST2) [2]. Previous studies have suggested that IL-33 acts as an “alarm” to alert potential tissue stress or damage [3, 4]. IL-33 promotes the production of inflammatory cytokines and Th2 immune responses by signaling through a heterodimer receptor complex composed of ST2L and IL-1 receptor attachment proteins, whereas sST2 is known to bind to IL-33 and acts as a “decoy” receptor for IL-33 to inhibit IL-33/ST2L signaling [5, 6]. The increase in circulating sST2 concentration attenuates the systemic biological effects of IL-33. Therefore, ST2 has long been recognized as a marker of both the activation of inflammatory and hemodynamic overload [7–9]. Subsequently, soluble
ST2 has been shown to be a powerful independent prognosticator for patients with acute coronary syndrome (ACS) [10, 11] as well as heart failure (HF) [12–14]. However, in the long-term follow-up of CAD, whether ST2 is predictive of MACEs and all-cause death remains inconclusive [13, 15–18]. We thus performed a large prospective large scale study. The aim of the present study is to evaluate the prognostic value of ST2 on MACEs and all-cause mortality in established CAD patients during a long-term follow up.

2 Materials And Methods

2.1 The study population

The design, details, and primary results of the study have been reported previously [19]. To be brief, the purpose of the study is to evaluate different biomarkers’ prognostic value of adverse cardiac events in patients with CAD. From 2011 to 2015, a total of 4078 patients who underwent coronary angiography examination diagnosed as stable angina pectoris (SAP) or ACS at our hospital were included in the study; subjects were required to be 18 years or older and the result of angiography suggested at least one major coronary artery stenosis ≥ 50%. Patients were excluded if they had severe heart failure, atrial fibrillation, aortic dissection, active infective disease, history of malignancy, end stage of renal disease, as well as those in a deep coma. In the current study, patients were also excluded if their blood sample or detailed data were not available. Finally, a total of 3641 patients were included in the present study (Fig. 1).

2.2 Data collection

Baseline data on demographic characteristics, lifestyle risk factors, cardiac history, and medications were collected at the time of enrollment. CAD were classified as SAP or ACS based on the clinical symptoms and the imaging data. Blood samples were collected in the early morning. On the basis of protocol, the blood were obtained by the EDTA-anticoagulated plastic tubes. All the blood samples were centrifuged at 1000 g for 10 min and serum samples were stored at 80°C. Routine laboratory determinations (blood glucose, lipids) were measured using commercial reagents following standard procedures. Patients were considered to be hypertension with BP > 140/90 mmHg or under anti-hypertensive medication. Hyperlipidemia was defined as known but untreated dyslipidemia or current treatment with lipid-lowering medications. Diabetes mellitus (DM) was defined as the presence of symptoms of diabetes and a resting plasma glucose concentration ≥ 200 mg/dL, a fasting plasma glucose concentration ≥ 126 mg/dL, a 2-h plasma glucose concentration ≥ 200 mg/dL in a 75 g oral glucose tolerance test, or taking hypoglycemic agent or other medications for DM. Current smoking was defined smoking if they reported any tobacco use in the last 30 days.

2.3 Plasma ST2 detection

Blood samples were collected within 24 h of hospital admission after at least 8 h of fasting. The ST2 levels were determined in serum in single measurements by using a quantitative sandwich monoclonal enzyme-linked immunosorbent assay (Presage ST2 Assay, Critical Diagnostics, Inc., San Diego, California). A standard curve was constructed. Analysts were blinded to patients’ characteristics and endpoints of the study participants.

2.4 Outcome assessment
Patients were followed up until May 2020 or until the occurrence of cardiovascular events. All participants were followed up by analyses of clinical materials and telephone contact semiannually. The primary endpoint was MACEs, the second endpoint was all-cause death. MACEs was defined as cardiac death, myocardial infarction, unstable angina and unplanned revascularization. All deaths were considered cardiac unless a definitive non cardiac cause was established. Unstable angina pectoris was defined as new or accelerating symptoms of myocardial ischemia accompanied by new ischemic ST-T changes. Myocardial infarction was defined as the rise of cardiac biomarkers with evidence of myocardial ischemia. Unplanned revascularization was diagnosed if the patient underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) with evidence of myocardial ischemia. We obtained follow-up for all patients until the primary outcome or date of censoring. All-cause death was defined as death from any cause. The follow-up time was calculated from the date of cardiac event onset to the date of event occurrence or the date of the last follow-up. Written informed content was obtained from all study participants, and the study was approved by the ethics committee of Chineses PLA General Hospital.

2.5 Statistical analysis

Patients were divided into two groups according to the median level of ST2. Differences in baseline characteristics between the two groups were evaluated by chi-square tests (categorical variables), analysis of variance as appropriate. Variables with a normal distribution are presented as mean ± SD, whereas in case of non-normality the medians are presented. Categorical data are presented as counts or percentages. Kaplan-Meier curves was used to estimate the cumulative incidence risks of outcomes across baseline ST2 levels and compared by log-rank tests. Cox proportional hazards models were used to evaluate the association of baseline ST2 levels with the study endpoints. The results are presented as the hazard ratios (HRs) and 95% confidence intervals (CIs) according to levels of ST2. We fitted two multivariate proportional hazards models. Model 1 was adjusted for clinical variables including age, sex, BMI, current smokers, hypertension, hyperlipidemia, diabetes mellitus, previous myocardial infarction (MI), previous PCI/CABG, TC, TG, HDL-C, LDL-C. Model 2 was based on model 1, with the addition of ST2. The relation of ST2 levels with outcomes is presented with COX proportional hazard models both with ST2 as a continuous variable and with ST2 as a categorical variable. Area under ROC curve (AUC) was used to compare the predictive ability of the parameters of interest. Furthermore, continuous net reclassification index (NRI), and integrated discrimination improvement (IDI) were generated to evaluate any improvement in prognostic prediction when ST2 was added to the established model. SPSS and R 4.0.0 (R Foundation for Statistical Computing) used for descriptive data analysis. All statistical tests were 2-tailed, and p values < 0.05 were considered statistically significant.

3. Results

3.1 Baseline characteristics.

Baseline measurements of ST2 were available in 3641 patients. The median concentration of ST2 was 19 ng/ml. The baseline characteristics of the consecutive CAD patients are shown in Table 1. We divided the patients into two groups based on the median concentrations of ST2. Those patients with higher
concentrations of ST2 were older, more often men, with a higher prevalence of previous PCI/CABG, the proportion of ACS patients is higher. They also had a higher level of TG (Table 1).
Table 1
Baseline clinical and laboratory characteristics of the study patients according to ST2 levels

|                          | Total n = 3641 | ST2(<19 ng/ml) (n = 1818) | ST2(≥19 ng/ml) (n = 1823) | p value for trend |
|--------------------------|---------------|---------------------------|---------------------------|------------------|
| Age, years               | 61.4(27–95)   | 61.03(26–93)              | 61.86(30–95)              | 0.031            |
| Male, n%                 | 2632(72.29)   | 1226(67.5)                | 1406(76.7)                | 0.000            |
| BMI(kg/m2)               | 25.64(13.3–41.0) | 25.7(13.3–41.0)         | 25.6(14.5–39.7)         | 0.230            |
| Risk factors for atherosclerosis |           |                           |                           |                  |
| Current smokers, n (%)  | 1668(45.8)    | 810(44.6)                 | 858(47.0)                 | 0.086            |
| Hypertension, n (%)     | 2370(65.1)    | 1160(64.2)                | 1210(66.4)                | 0.090            |
| Hyperlipidemia, n (%)   | 1120(30.8)    | 581(32.0)                 | 539(29.6)                 | 0.099            |
| Diabetes mellitus, n (%)| 1163(31.9)    | 590(32.4)                 | 573(31.4)                 | 0.943            |
| Cardiac history         |               |                           |                           |                  |
| Previous MI, n (%)      | 254(6.98)     | 125(6.88)                 | 129(7.04)                 | 0.085            |
| Previous PCI/CABG, n (%)| 299(8.2)      | 127(6.99)                 | 172(9.43)                 | 0.003            |
| Laboratory data         |               |                           |                           |                  |
| TC (mmol/L)             | 4.03 ± 1.0    | 4.03 ± 1.09               | 4.03 ± 1.08               | 0.816            |
| HDL-C (mmol/L)          | 1.07 ± 0.68   | 1.07 ± 0.71               | 1.07 ± 0.65               | 0.951            |
| LDL-C (mmol/L)          | 2.40 ± 0.91   | 2.38 ± 0.85               | 2.41 ± 0.91               | 0.314            |
| TG (mmol/L)             | 1.62 ± 1.21   | 1.54 ± 1.40               | 1.7 ± 0.98                | 0.000            |
| Medications             |               |                           |                           |                  |
| Aspirin, n (%)          | 3415(93.79)   | 1712(94.1)                | 1703(93.0)                | 0.138            |
| ACEI, n (%)             | 1503(41.28)   | 720(39.7)                 | 813(44.6)                 | 0.530            |
| β-blocker, n (%)        | 1629(44.74)   | 1289(49.0)                | 1340(51.0)                | 0.096            |
| Statins, n (%)          | 3442(94.53)   | 1725(95.0)                | 1717(94.2)                | 0.153            |
| CAD classification      |               |                           |                           |                  |
| SAP                     | 899(24.69)    | 486(26.73)                | 410(22.49)                | 0.95             |
| ACS                     | 2742(75.3)    | 1128(62.05)               | 1614(88.54)               | 0.03             |
3.2 Association between plasma ST2 and prognosis of MACEs and all-cause death

Primary endpoint

During the median follow up of 6.4 years, MACEs was occurred in 775 (21.2%) patients. Patients with higher ST2 levels had a significantly higher rate of MACEs compared with the patients with lower levels (24.8% vs 17.9%, \( p < 0.001 \)). After adjusted for the established factors included in Model 1 and using the lower level of ST2 as reference, we found that patients with ST2 \( \geq 19 \) ng/ml have a higher risk of experiencing a primary outcome (HR = 1.36, 95% CI 1.17–1.56, \( p < 0.001 \))(Table 2). Kaplan–Meier curves showed that the cumulative event curves for MACEs stratified according to ST2 levels: patients with higher level of ST2 were more likely to have a higher MACEs rates (log-rank test, \( p < 0.001 \)) (Fig. 2a).

Secondary endpoint

During the follow up, 275 (7.4%) patients died. Compared with participants with the lower level of ST2, the higher level group had significantly higher incidence of all-cause death (10.0% versus 4.90%). After adjusted for the established factors included in Model 1 and using the lower level of ST2 as reference, we found that patients with ST2 \( \geq 19 \) ng/ml have a higher risk of experiencing all-cause death (HR = 2.01, 95%CI 1.56–2.59, \( p < 0.001 \))(Table 2). Kaplan–Meier curves illustrated the cumulative event curves for all-cause death stratified according to ST2 levels. Patients with higher level of ST2 were more likely to have a high all-cause death rates (log-rank test, \( p < 0.001 \)) (Fig. 2b).
Table 2
HRs and 95% CI of outcomes according to the categories of serum ST2 in model 2

| Outcomes                              | ST2 level             | P trend |
|---------------------------------------|-----------------------|---------|
|                                       | [19 ng/ml]            | [19 ng/ml] |         |
| Primary outcome: MACEs                | 775                   |         |
| Number of cases (%)                   | 321(17.9)             | 454(24.8) | 0.001   |
| Model 2 HR                            | 1.00 (REF)            | 1.36 (1.17–1.56) | 0.001 |
| Cardiac death                         | 163                   |         |
| Number of cases (%)                   | 48(2.6)               | 115(6.2) | 0.001   |
| Model 2 HR                            | 1.00 (REF)            | 1.70 (1.50–1.98) | 0.033 |
| MI                                    | 57                    |         |
| Number of cases (%)                   | 21(1.1)               | 36(1.8)  | 0.066   |
| Model 2 HR                            | REF                   | 1.17 (0.67–2.04) | 0.579 |
| Unstable angina                       | 550                   |         |
| Number of cases (%)                   | 245(13.48)            | 305(16.73) | 0.280 |
| Model 2 HR                            | REF                   | 1.42 (1.25–1.98) | 0.001 |
| Revascularization treatment           | 500                   |         |
| Number of cases (%)                   | 235(12.7)             | 265(14.3) | 0.343 |
| Model 2 HR                            | REF                   | 1.48 (1.24–1.77) | 0.001 |
| Secondary outcome: all-cause death    | 275                   |         |
| Number of cases (%)                   | 90(4.9)               | 185(10.0) | 0.001 |
| Model 2 HR                            | 1.00 (REF)            | 2.01 (1.56–2.59) | 0.001 |

3.3 Incremental value of ST2 over conventional risk factors

For MACEs: We further examined whether adding ST2 to the clinical model consisting of traditional risk factors could improve the risk model prediction performance. As shown in Table 3, adding ST2 significantly improved the C-static from 0.586 (95% CI 0.559–0.603) to 0.619 (95% CI 0.605–0.638). There was a significant difference compared to the clinical model with ST2 (p<0.001) (Fig. 3a). Furthermore, adding ST2 categories to model 1 significantly improved NRI = 0.178 (95% CI: 0.094–0.262, p<0.001); IDI = 0.009 (95% CI: 0.003–0.014, p<0.001) (Table 3). For all-cause mortality: adding ST2 significantly improved the C-static from 0.642 (95% CI 0.594–0.701) to 0.766 (95% CI 0.717–0.806). There was a significant difference compared to the clinical model with ST2 (p<0.001) (Fig. 3b). Moreover, adding ST2 categories to model 1
significantly improved NRI = 0.342 (95%CI:0.118–0.547 p < 0.001); IDI = 0.012 (95%CI:0.004–0.013, p < 0.001) (Table 3).

### Table 3
Reclassification and discrimination statistics for clinical outcomes by serum ST2

| Clinical outcomes     | Model           | C-static Estimate (95%CI) | P value | Continuous NRI,% Estimate (95%CI) | P value | IDI,% Estimate (95%CI) | P value |
|-----------------------|-----------------|---------------------------|---------|----------------------------------|---------|------------------------|---------|
| **MACEs**             | Model1          | 0.586(0.559–0.603)        | 0.001   | REF                              | 0.001   | REF                    | 0.002   |
|                       | Model1 + ST2    | 0.619(0.605–0.638)        |         | 17.8(9.4–26.2)                  | 0.9(0.3–1.4) |
| **Cardiac death**     | Model1          | 0.746(0.703–0.789)        | 0.001   | REF                              | 0.001   | REF                    | 0.001   |
|                       | Model1 + ST2    | 0.783(0.743–0.823)        |         | 27.9(15.9–34.5)                 | 0.8(0.2–1.6) |
| **MI**                | Model1          | 0.644(0.564–0.715)        | 0.352   | REF                              | 0.561   | REF                    | 0.721   |
|                       | Model1 + ST2    | 0.655(0.582–0.729)        |         | 15.3(9.7–20.0)                  | 1.2(0.8–2.8) |
| **Unstable angina**   | Model1          | 0.583(0.561–0.608)        | 0.001   | REF                              | 0.015   | REF                    | 0.001   |
|                       | Model1 + ST2    | 0.601(0.583–0.617)        |         | 18.2(10.4–31.4)                 | 0.07(0.01–0.26) |
| **Revascularization** | Model1          | 0.575(0.545–0.596)        | 0.001   | REF                              | 0.001   | REF                    | 0.001   |
|                       | Model1 + ST2    | 0.584(0.572–0.609)        |         | 16.7(3.9–22.3)                  | 1.4(0.6–1.8) |
| **All-cause death**   | Model1          | 0.642(0.594–0.701)        | 0.001   | REF                              | 0.001   | REF                    | 0.001   |
|                       | Model1 + ST2    | 0.766(0.717–0.806)        |         | 34.2(11.8–54.7)                 | 1.2(0.4–1.3) |

### 4 Discussion

Our study established a higher level of ST2 was a significant and independent predictor of cardiovascular event. In our study, we found that higher concentrations of ST2 (≥ 19 ng/ml) was associated with an increased risk of all-cause death and MACEs in patients with coronary heart disease. Higher concentrations of ST2 remained an independent indicator of MACEs and all-cause mortality after adjustment for established
traditional risk factors for cardiovascular disease. Furthermore, our study confirmed that the incremental prognostic value of ST2 for MACEs and all-cause mortality beyond the clinical model. In summary, our results suggest that the addition of plasma ST2 measurements to established cardiovascular risk factors may further improve risk stratification in patients with CAD and our results provide updated information on the long-term prognostic role of ST2 in established CAD patients.

4.1 Biomarker’s prognostic value in CAD patients

Biomarkers have become increasingly important tools helping to improve patient outcome prognosis over the past two decades [20–22]. Numerous biomarkers have been identified in the diagnosis, prognosis and risk prediction of cardiovascular disease but few have made their way to clinical practice [23]. The most extensively used cardiovascular biomarkers are the natriuretic peptides in the diagnosis and prognosis of heart failure and cardiac troponins in the diagnosis of acute myocardial infarction. Deeper experimental studies of the pathophysiology of atherosclerosis have identified a large number of molecules as potential prognostic biomarkers in cardiovascular disease [24]. To date, however, no marker has been shown to predict cardiovascular events with high accuracy. Therefore, investigation of potential markers for predicting cardiovascular events is still of great value. There have been only 2 small studies report the prognostic value of ST2 in patients with CAD [16, 25]. A study showed that ST2 and IL-33 were associated with mortality in patients with ST elevation MI (STEMI) but not in patients with NSTEMI or stable angina [25]. Another study showed that increased concentrations of ST2 was an independent predictor of all-cause mortality in patients with stable CAD [16]. Therefore, a large sample study including SAP and ACS was urgently needed to further demonstrate the predictive value of ST2 in CAD patients during a long-term follow up.

4.2 Prognosis value of ST2 on cardiovascular disease

Previous studies suggested that ST2 maybe a potential biological marker for mechanical overload in the heart. ST2 was markedly upregulated in mechanically-stimulated cardio-myocytes. Furthermore, ST2 has been proved to be a predictor of outcome in patients with HF [12, 14, 17, 18]. Recent evidences suggest that ST2 may be predictive in patients with ACS [26, 27]. It has also been shown to be a powerful independent prognosticator for patients with acute myocardial infarction (AMI). According to Eggers KM’s research, ST2 levels are elevated early in NSTE-ACS and predict 1-year mortality [10]. Wang YP’s research showed that serum levels of ST2, IL-33 and BNP were positively correlate with MACEs in patients with acute myocardial infarction (AMI) after percutaneous coronary intervention (PCI) [28]. However, there was no study to investigate the long-term value of ST2 in the prediction of MACEs or all cause death in patients with CAD in a large population.

4.3 The underlying mechanisms

The inflammatory hypothesis of atherosclerosis suggests that inflammatory cell signaling drives the formation, development, and eventual instability of atherosclerotic plaques [29]. IL-33 was originally reported as a modulator of inflammation, tipping the balance towards CD4 + T helper-cell type 2 mediated immune responses [30]. The effect of IL-33 on the function of foam cells indicated the protect role of IL-33 in atherosclerosis [31]. ST2 acts as a decoy receptor for IL-33, thus blocking its protective effects. It has been reported that mice treated with soluble ST2 developed significantly larger atherosclerotic plaques in the aortic sinus of the ApoE (-/-) mice compared with the control mice [32]. Researchers have found that ST2 are
particularly expressed in arterial endothelial cells, involving in the progression of atherosclerosis [33]. These results suggested that ST2 may be proposed as a marker of plaque burden and predictors of future cardiovascular events [34]. Under this respect, the IL-33-ST2 pathway deserves consideration. Although the above data suggest that ST2 has a role in the prognosis of patients presenting with an acute coronary syndrome, whether ST2 contributes to cardiovascular risk prediction in a large scale CAD patients during a long-term follow up remains uncertain.

To evaluate the prognostic value of a biomarker in CVD, researchers must demonstrate the elevated risk of cardiovascular events associated with higher levels of the new biomarker with adjustment for other established risk factors. The results should be presented as hazards ratios relative risk estimates from a Cox model and a probability value test of significance of the marker in the multivariable models [35]. Our result indicated that after incorporating age, sex, and other clinically relevant covariates, the adjusted HR for MACEs and all cause death was 1.36 and 2.01 respectively in COX proportional-hazards models. Moreover, in the previous studies, the follow-up time for the predictive value of ST2 was relatively short. Brown et al assess the prognostic value of ST2 during a short-term follow up of 30 days for acute MI, ACS, and MACEs [36], Aldous et al revisited the prognostic value of ST2 in patients with chest pain with a longer follow-up of 18 months [37]. Two reports were based on data from 3 clinical trials in ST elevation MI (STEMI) that provided data on the prognostic value of plasma ST2 for 30 days after MI for adverse events, and a further article reported prognostic performance over an average follow-up time of 20 months [27, 38, 39]. Our result demonstrated that in a median follow up of 6.4 years, higher level of ST2 is significantly associated with all-cause death, MACEs and provides incremental prognostic value beyond traditional risks factors.

**Limitations**

While the study provides a large, well characterized study sample with adjudicated outcomes, the research is limited to a single center, these data represent the results of an observational analysis. As in any observational study, we cannot exclude residual confounding. However, this is probably minimal because we used a comprehensive adjustment strategy to control for known variables that are commonly used to stratify the risk of CAD patients.

**Conclusions**

Higher values of ST2 confer a markedly adverse prognosis characterized by a large excess risk of MACEs and all-cause death over a long period of follow-up. Measurement of ST2 should be considered as part of approaches to risk stratification in CAD patients during the long-term follow up.

**List Of Abbreviations**
| Abbreviation | Full Form |
|--------------|-----------|
| ST2          | suppression of tumorigenesis-2 |
| ACS          | acute coronary syndrome |
| CAD          | coronary artery disease |
| MACEs        | major adverse cardiovascular events |
| IL-1         | interleukin-1 |
| IL-33        | interleukin-33 |
| HF           | heart failure |
| SAP          | stable angina pectoris |
| DM           | diabetes mellitus |
| PCI          | percutaneous coronary intervention |
| CABG         | coronary artery bypass grafting |
| AUC          | area under the curve |
| NRI          | net reclassification index |
| IDI          | integrated discrimination improvement |
| NEST-ACS     | non-ST segment elevation acute coronary syndrome |
| MI           | myocardial infarction |
| STEMI        | ST elevation MI |
| NSTEMI       | Non-ST elevation MI |
| IHD          | ischemic heart disease |
| CAG          | coronary angiography |
| HDL-C        | high-density lipoprotein cholesterol |
| LDL-C        | low-density lipoprotein cholesterol |
| TG           | triglycerides |
| TC           | total cholesterol |
| HR           | hazard ratio |
| CVD          | cardiovascular disease |
| ROC          | receiver operating characteristic curves |
| HR           | hazard ratio |
Ethics approval and consent to participate

This study was approved by the Ethics Board of the Chinese PLA General Hospital

Consent for publication

Written informed consent for publication was obtained from each author and each patient.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Hongbin Liu contributed to substantial contributions to the conception or design of the work. Man Li contributed to data collection, data interpretation, and critical review of the manuscript drafting the manuscript. Lei Duan, Yulun Cai, Benchuan Hao, Jianqiao Chen, Huiying Li contributed to data collection. All authors read and approved the final manuscript.

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References

1. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. Eur Heart J. 2018;39(7):508-79.
2. Pichery M, Mirey E, Mercier P, Lefrancais E, Dujardin A, Ortega N, et al. Endogenous IL-33 is highly expressed in mouse epithelial barrier tissues, lymphoid organs, brain, embryos, and inflamed tissues: in situ analysis using a novel Il-33-LacZ gene trap reporter strain. J Immunol. 2012;188(7):3488-95.
3. Cayrol C, Girard J-P. IL-33: an alarmin cytokine with crucial roles in innate immunity, inflammation and allergy. Curr Opin Immunol. 2014;31:31-7.
4. Molofsky AB, Savage AK, Locksley RM. Interleukin-33 in Tissue Homeostasis, Injury, and Inflammation. Immunity. 2015;42(6):1005-19.
5. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity. 2005;23(5):479-90.

6. Dinarello CA. An IL-1 family member requires caspase-1 processing and signals through the ST2 receptor. Immunity. 2005;23(5):461-2.

7. Pascual-Figal DA, Januzzi JL. The biology of ST2: the International ST2 Consensus Panel. Am J Cardiol. 2015;115(7 Suppl):3B-7B.

8. Kolodin D, van Panhuys N, Li C, Magnuson AM, Cipolletta D, Miller CM, et al. Antigen- and cytokine-driven accumulation of regulatory T cells in visceral adipose tissue of lean mice. Cell Metab. 2015;21(4):543-57.

9. Odegaard JI, Lee MW, Sogawa Y, Bertholet AM, Locksley RM, Weinberg DE, et al. Perinatal Licensing of Thermogenesis by IL-33 and ST2. Cell. 2016;166(4):841-54.

10. Eggers KM, Armstrong PW, Califf RM, Simoons ML, Venge P, Wallentin L, et al. ST2 and mortality in non-ST-segment elevation acute coronary syndrome. Am Heart J. 2010;159(5):788-94.

11. Richards AM, Di Somma S, Mueller T. ST2 in stable and unstable ischemic heart diseases. Am J Cardiol. 2015;115(7 Suppl):48B-58B.

12. Emdin M, Aimo A, Vergaro G, Bayes-Genis A, Lupón J, Latini R, et al. sST2 Predicts Outcome in Chronic Heart Failure Beyond NT-proBNP and High-Sensitivity Troponin T. Journal of the American College of Cardiology. 2018;72(19):2309-20.

13. Hughes MF, Appelbaum S, Havulinna AS, Jagodzinski A, Zeller T, Kee F, et al. ST2 may not be a useful predictor for incident cardiovascular events, heart failure and mortality. Heart. 2014;100(21):1715-21.

14. Aleksova A, Paldino A, Beltrami AP, Padoan L, Iacoviello M, Sinagra G, et al. Cardiac Biomarkers in the Emergency Department: The Role of Soluble ST2 (sST2) in Acute Heart Failure and Acute Coronary Syndrome—There is Meat on the Bone. J Clin Med. 2019;8(2).

15. Pfetsch V, Sanin V, Jaensch A, Dallmeier D, Mons U, Brenner H, et al. Increased Plasma Concentrations of Soluble ST2 Independently Predict Mortality but not Cardiovascular Events in Stable Coronary Heart Disease Patients: 13-Year Follow-up of the KAROLA Study. Cardiovasc Drugs Ther. 2017;31(2):167-77.

16. Dieplinger B, Egger M, Haltmayer M, Kleber ME, Scharmagl H, Silbernagel G, et al. Increased soluble ST2 predicts long-term mortality in patients with stable coronary artery disease: results from the Ludwigshafen risk and cardiovascular health study. Clin Chem. 2014;60(3):530-40.

17. Aimo A, Januzzi JL, Vergaro G, Richards AM, Lam CSP, Latini R, et al. Circulating levels and prognostic value of soluble ST2 in heart failure are less influenced by age than N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T. Eur J Heart Fail. 2020.

18. van Vark LC, Lesman-Leegte I, Baart SJ, Postmus D, Pinto YM, Orsel JG, et al. Prognostic Value of Serial ST2 Measurements in Patients With Acute Heart Failure. Journal of the American College of Cardiology. 2017;70(19):2378-88.

19. Li M, Duan L, Cai Y-L, Li H-Y, Hao B-C, Chen J-Q, et al. Growth differentiation factor-15 is associated with cardiovascular outcomes in patients with coronary artery disease. Cardiovasc Diabetol. 2020;19(1):120.
20. Zhao Q, Zhang T-Y, Cheng Y-J, Ma Y, Xu Y-K, Yang J-Q, et al. Impacts of triglyceride-glucose index on prognosis of patients with type 2 diabetes mellitus and non-ST-segment elevation acute coronary syndrome: results from an observational cohort study in China. Cardiovasc Diabetol. 2020;19(1):108.

21. Wong Y-K, Cheung CYY, Tang CS, Hai JSH, Lee C-H, Lau K-K, et al. High-sensitivity troponin I and B-type natriuretic peptide biomarkers for prediction of cardiovascular events in patients with coronary artery disease with and without diabetes mellitus. Cardiovasc Diabetol. 2019;18(1):171.

22. Cediel G, Rueda F, Oxvig C, Oliveras T, Labata C, de Diego O, et al. Prognostic value of the Stanniocalcin-2/PAPP-A/IGFBP-4 axis in ST-segment elevation myocardial infarction. Cardiovasc Diabetol. 2018;17(1):63.

23. Lyngbakken MN, Myhre PL, Røsjø H, Omland T. Novel biomarkers of cardiovascular disease: Applications in clinical practice. Crit Rev Clin Lab Sci. 2019;56(1):33-60.

24. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111(25):3481-8.

25. Demyanets S, Speidl WS, Tentzeris I, Jarai R, Katsaros KM, Farhan S, et al. Soluble ST2 and interleukin-33 levels in coronary artery disease: relation to disease activity and adverse outcome. PLoS one. 2014;9(4):e95055.

26. Salvagno GL, Pavan C. Prognostic biomarkers in acute coronary syndrome. Ann Transl Med. 2016;4(13):258.

27. Shimpo M, Morrow DA, Weinberg EO, Sabatine MS, Murphy SA, Antman EM, et al. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. Circulation. 2004;109(18):2186-90.

28. Wang Y-P, Wang J-H, Wang X-L, Liu J-Y, Jiang F-Y, Huang X-L, et al. Roles of ST2, IL-33 and BNP in predicting major adverse cardiovascular events in acute myocardial infarction after percutaneous coronary intervention. J Cell Mol Med. 2017;21(11):2677-84.

29. Zhao TX, Mallat Z. Targeting the Immune System in Atherosclerosis: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2019;73(13):1691-706.

30. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov. 2008;7(10):827-40.

31. McLaren JE, Michael DR, Salter RC, Ashlin TG, Calder CJ, Miller AM, et al. IL-33 reduces macrophage foam cell formation. J Immunol. 2010;185(2):1222-9.

32. Junttila MJ, Hookana E, Kaikkonen KS, Kortelainen M-L, Myerburg RJ, Huikuri HV. Temporal Trends in the Clinical and Pathological Characteristics of Victims of Sudden Cardiac Death in the Absence of Previously Identified Heart Disease. Circ Arrhythm Electrophysiol. 2016;9(6).

33. Abulizi P, Loganathan N, Zhao D, Mele T, Zhang Y, Zwiep T, et al. Growth Differentiation Factor-15 Deficiency Augments Inflammatory Response and Exacerbates Septic Heart and Renal Injury Induced by Lipopolysaccharide. Sci Rep. 2017;7(1):1037.

34. Aimo A, Migliorini P, Vergaro G, Franzini M, Passino C, Maisel A, et al. The IL-33/ST2 pathway, inflammation and atherosclerosis: Trigger and target? International journal of cardiology. 2018;267:188-92.
35. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation. 2006;113(19):2335-62.

36. Brown AM, Wu AHB, Clopton P, Robey JL, Hollander JE. ST2 in emergency department chest pain patients with potential acute coronary syndromes. Ann Emerg Med. 2007;50(2).

37. Aldous SJ, Richards AM, Troughton R, Than M. ST2 has diagnostic and prognostic utility for all-cause mortality and heart failure in patients presenting to the emergency department with chest pain. J Card Fail. 2012;18(4):304-10.

38. Sabatine MS, Morrow DA, Higgins LJ, MacGillivray C, Guo W, Bode C, et al. Complementary roles for biomarkers of biomechanical strain ST2 and N-terminal prohormone B-type natriuretic peptide in patients with ST-elevation myocardial infarction. Circulation. 2008;117(15):1936-44.

39. Dhillon OS, Narayan HK, Khan SQ, Kelly D, Quinn PA, Squire IB, et al. Pre-discharge risk stratification in unselected STEMI: is there a role for ST2 or its natural ligand IL-33 when compared with contemporary risk markers? International journal of cardiology. 2013;167(5):2182-8.

**Figures**

![Figure 1](image_url)

**Figure 1**
Flowchart of the study

Figure 2

Kaplan-Meier curves for prediction of MACEs (a) and all-cause death (b) in patients with higher levels of ST2 (ST2≥19ng/ml) and lower levels of ST2 (ST2<19ng/ml)
Figure 3

ROC curve analyses that relate ST2 levels to MACEs (a) and all-cause death (b).
Figure 4

Hazard ratios, 95% confidence intervals (CI) of ST2 for outcomes