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Review Article

Long-term prognostic importance of high levels of sST2 in patient with AMI: a meta-analysis

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Abstract: Objective: This meta-study aimed to assess the connection between soluble suppression of tumorigenicity 2 (sST2) and extended clinical outcomes in individuals diagnosed with acute myocardial infarction (AMI). Methods: We systematically collected pertinent literature from PubMed, Embase and Web of Science. The primary effect measures employed in this research were the hazard ratio and 95% confidence intervals. The quality and publication bias of included studies were evaluated. Subgroup analysis was conducted to explore the diversity in study outcomes. Results: This comprehensive meta-analysis ultimately encompassed thirteen studies, involving a total of 11,571 patients. Elevated levels of sST2 were identified as an adverse prognostic indicator, demonstrating a substantial association not only with overall mortality (combined HR 2.4, 95% CI 1.6-3.5, P < 0.01) but also with major adverse cardiovascular events (MACEs) (HR 2.5, 95% CI 1.5-4.2, P < 0.01). Subgroup analyses revealed that increased sST2 levels were linked to higher rates of all-cause mortality and MACEs in patients with ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and other unselected subcategories of AMI. Conclusion: Increased sST2 could predict the long-term prognosis in patients suffering from AMI.

Keywords: Soluble suppression of tumorigenicity 2 (sST2), acute myocardial infarction (AMI), myocardial infarction (MI), major adverse cardiovascular events (MACEs), prognosis

Introduction

In recent years, there has been a consistent enhancement and increased utilization of vascular reperfusion therapies, encompassing the administration of thrombolytic drugs to dissolve blood clots and the implementation of percutaneous coronary intervention (PCI). Nonetheless, acute myocardial infarction (AMI), clinically categorized as ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), remains a significant contributor to cardiovascular mortality on a global scale, with a pronounced impact in the Asia-Pacific region [1-5]. When compared to stable angina, AMI patients present with notably elevated overall mortality rates and a heightened susceptibility to major adverse cardiovascular events (MACEs) [6, 7]. In cases of AMI, it is advisable to utilize the TIMI (thrombolysis in myocardial infarction) risk score and the GRACE (global registry of acute coronary events) score for risk assessment and outcome prediction, which are endorsed by the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. However, these two recommended risk assessment tools have demonstrated limited efficacy in predicting 1-year survival among contemporary community cohorts with initial-onset myocardial infarction (MI) [8-10]. Thus, it is imperative to identify genes that can be used to predict long-term prognosis of AMI patients, enabling the development of robust and proactive preventive strategies for those at high risk of AMI.

Soluble suppression of tumorigenicity 2 (sST2), a member of IL-1 receptor family, actively participates in post-AMI ventricular remodeling, myocardial fibrosis, and inflammatory processes, which can effectively suppress tumorigenicity. Additionally, sST2 exhibits an association

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with the subsequent likelihood of cardiovascular incidents [11-13]. Recent research has advanced the notion that sST2 may serve as a predictive indicator in individuals with AMI [14]. Remarkably, sST2 significantly enhances discriminative capabilities, regardless of the existing risk assessment methods or the specific type of heart attack. Nevertheless, Kim et al. reported that sST2 concentration was not associated with short-term and long-term MACE [15].

To address this quandary, we here performed a meta-analysis to assess the prognostic value of sST2 in AMI patients, as the meta-analysis is a potent statistical approach which can synthesize and enhance findings from diverse studies, regardless of variations in sample size.

Methodologies and techniques

Study design

A meta-analysis was performed to assess prognostic value of serum sST2 in AMI patients according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, Supplementary Material).

Inclusion criteria

Post hoc analyses of controlled randomized trials within longitudinal studies; studies involving patients with AMI as their subjects; research that evaluated sST2 levels at the outset using serum-based methods; studies with a minimum one-year follow-up duration; research studies providing adjusted HRs and their corresponding 95% CIs for overall mortality and MACEs, including cardiovascular mortality, heart failure occurrence or exacerbation, recurrent heart attacks, and repeated TVR, in line with the original research.

Exclusion criteria

Abstracts, correspondences, case studies, review, or preclinical studies; studies not published in English; research lacking sufficient data for calculating HRs and corresponding 95% CI; studies containing duplicated or redundant data.

Search methods

We performed a thorough and systematic literature search, encompassing the databases PubMed, Embase, the Cochrane Library, and the Web of Science. We exclusively included research conducted on individuals, published in English until Dec 1, 2023. The strategy of search incorporated the utilization of the following keywords: 'ST2' (including "suppression of tumorigenicity 2", "Interleukin 1 Receptor-Like 1", "IL1RL1") and 'Myocardial Infarction' (encompassing 'Cardiovascular Stroke', 'Myocardial Infarct', 'Heart Attack'). Additionally, we meticulously scrutinized the reference lists of acquired articles to identify supplementary pertinent research.

Data extraction

The selected articles underwent independent assessment and data extraction by two investigators, Jing Chen, Haigang Ji. Articles were not clearly categorized based on their titles and abstracts underwent a comprehensive examination of the full text. Any disagreements were resolved through discussions between the two investigators, and if necessary, another author (Wen Bo Jiang) was consulted.

Each study recorded primary author, publication year, location, total cases, gender distribution, average age, follow-up duration, sST2 threshold values, reported results, and AMI types.

Quality assessment

The two reviewers independently conducted quality assessment using the Newcastle-Ottawa Scale (NOS), consisting of three dimensions: selection (0-4 points), comparability (0-2 points), and outcome assessment (0-3 points). Studies scoring 6 or above on the NOS were considered to be of excellent quality.

Publication bias analysis

To evaluate the presence of publication bias, we performed a thorough examination of Begg funnel plot and employed Egger's test to assess potential bias.

Statistical analysis

The data analysis was performed on SPSS 12.0 (IBM). The primary effect measures employed in this research were the hazard ratio and 95% confidence intervals. An HR greater than 1 indicated an adverse prognosis in AMI patients

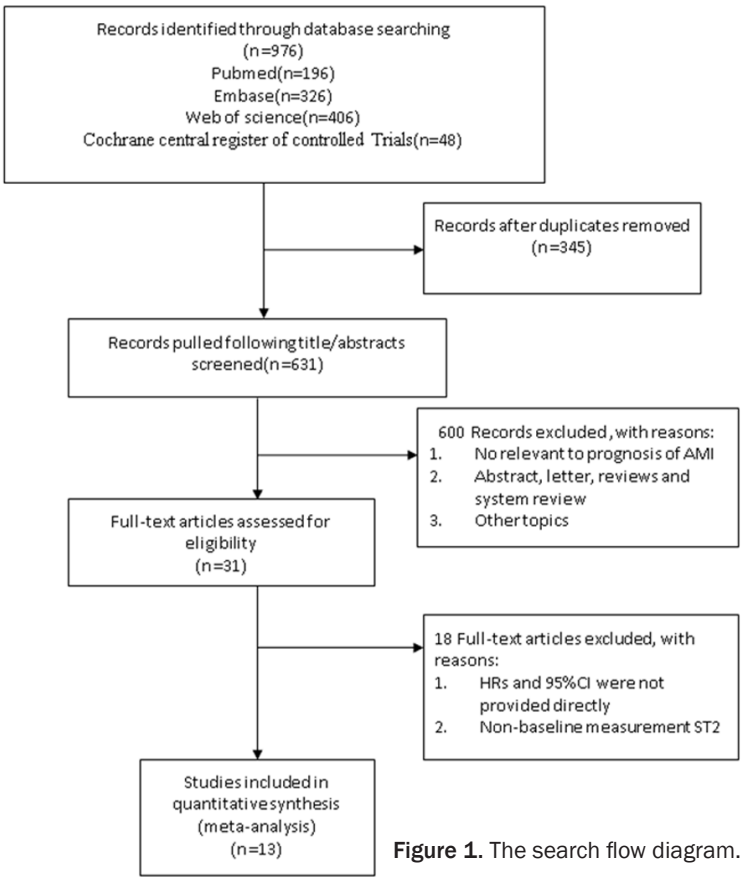

Figure 1. The search flow diagram.

with elevated sST2 expression. To assess heterogeneity in the included studies, we used Cochran's Q test and the Higgins I^2 statistic. Significant heterogeneity was indicated by a *P*-value below 0.10 or an I^2 value exceeding 50%, leading to the adoption of a random-effects model. Otherwise, a fixed-effects model was applied. To explore and clarify the diversity in study outcomes, we conducted subgroup analysis. The sensitivity analysis was carried out when significant heterogeneity was observed.

Results

Study selection and quality evaluation

After conducting the search, 345 duplicate articles were eliminated from the initial pool of 976 studies. An additional 600 studies were excluded during the screening process of titles and abstracts due to a lack of relevance to the research topic. Seventeen articles were excluded due to lack of HRs and 95% CIs for all-cause MACEs. Additionally, one article was excluded as it did not measure sST2 at baseline. In the end, a total of 13 studies were included, with 11,387 participants. **Figure 1** illustrates the procedure of searching and screening. **Table 1** outlines the attributes and relevant information of these 13 studies [14-25]. All the included studies had NOS scores over 6, indicating excellent quality of them.

Meta-analysis

Elevated sST2 level was positively associated with an increased risk of all-cause mortality in AMI patients: We screened out ten articles to investigate the association between sST2 and the HR for all-cause mortality in AMI patients. The overall calculations for mortality exhibited considerable variability (I^2 = 89.2%), necessitating the use of a random-effects model. As depicted in **Figure 2**, elevated sST2 level related to an increased risk of all-cause mortality, as denoted by a combined HR of 2.4 (95% confidence interval (CI) 1.6-3.5, P < 0.01). To address the substantial diversity observed among the included articles, a subgroup analysis was carried out. As depicted in **Figure 3**, there were favorable associations between elevated sST2 level and all-cause mortality in subcategories of NSTEMI, STEMI, and unselected AMI.

Elevated sST2 level was positively associated with AMI associated MACEs: We screened out seven articles to investigate the association between sST2 and the HR for MACEs in AMI patients. Given the notable heterogeneity (I^2 = 0.794), a random-effects model was applied to compute the combined estimates for MACEs. Elevated sST2 level indicated adverse outcome for MACEs, with a pooled HR of 2.6 (95% CI 1.5-4.2, P < 0.01; **Figure 4**). Subsequently, a subanalysis was performed due to significant heterogeneity observed among the included articles. Positive associations between elevated sST2 and MACEs were identified in the subcat-

Table 1. The meta-analysis encompasses the primary attributes of all the studies incorporated

	Author	Year	Study region	No. (M/F)	Follow-up (median and rang)	Age (years; median and rang)	Cut-off value	Outcome	Type	NOS score
1	Onkar S. Dhillon	2011	UK	577 (397/180)	532D (150-1059)	70±13	782 pg/ml	1. All-cause mortality 2. MACE (defined as a composite of all-cause mortality, HF hospitalization, reinfarction) 3. HF hospitalization 4. Reinfarction	NSTEMI	8
2	Payal Kohli	2011	USA	4426 (2862/1564)	1 year	NA	35 ug/l	1. All-cause mortality 2. Cardiovascular death (CVD) 3. New or worsening HF (HF) 4. CVD/HF	NSTEMI	9
3	Onkar S. Dhillon	2012	UK	677 (505/172)	1 year	64.0±12.2	1125 pg/ml	1. All-cause mortality 2. Rehospitalisation for HF 3. Recurrent infarction	STEMI	7
4	Jongwook Yu	2017	Republic of Korea	323 (272/51)	1 year	59.1±13.1	75.8 ng/ml	MACE (defined as a composite of cardiovascular death, non-fatal MI, non-fatal stroke, and ischemia-driven revascularization)	STEMI	8
5	Yariv Gerber	2017	USA	1401 (853/548)	1 year	64.6±13.8	NA	All-cause mortality	AMI (STEMI, NSTEMI)	7
6	William S. Jenkins	2017	USA	1401 (854/547)	5 years	67.3±14.9	72.3	1. All-cause mortality 2. HF	AMI (STEMI, NSTEMI)	7
7	Xintian Liu	2018	China	295 (243/52)	1 year	(32-87)	58.7 ng/ml	1. All-cause mortality 2. MACEs (defined as the composite adverse events of all-cause death, heart failure, and non-fatal myocardial infarction)	STEMI	8
8	Bobak Heydari	2018	USA	317 (282/35)	3 years	NA	35 pg/ml	1. All-cause mortality 2. MACEs (defined as the composite of cardiovascular death and hospitalization for ADHF)	AMI (STEMI, NSTEMI)	8
9	WeiPing Huang	2018	China	186 (119/67)	1 year	68.5 (30-72)	56 ng/ml	MACEs (defined as the composite of cardiovascular death, worsening HF, and recurrent MI)	STEMI	8
10	Agata Tymińska	2019	Poland	117 (82/35)	1 year	NA	45.99 ng/ml	CVD or hospitalization for HF	STEMI	8
11	Mustafa Umut Somuncu	2020	Turkey	380 (279/101)	1 year	NA	35 ng/ml	CVD	AMI (STEMI, NSTEMI)	7
12	Qinyao Zhang	2020	China	205 (143/62)	1 year	33-83	34.2 ng/ml	MACEs (defined as the composite of cardiovascular death, worsening HF, stroke, worsening HF, ischemia-driven revascularization)	NSTEMI	8
13	Marcus Hjort	2021	Sweden	1082 (842/240)	6.6 years	56-73	NA	1. All-cause mortality 2. MACEs (defined as the composite of all-cause mortality, hospitalization for non-fatal MI, ischemic stroke or heart failure)	STEMI, NSTEMI	9

Note: sST2: soluble suppression of tumorigenicity 2, AMI: acute myocardial infarction, MACEs: major adverse cardiovascular events, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST-segment elevation myocardial infarction, HF: heart failure, CVD: cardiovascular death, MI: myocardial infarction, ADHF: acute decompensated heart failure.

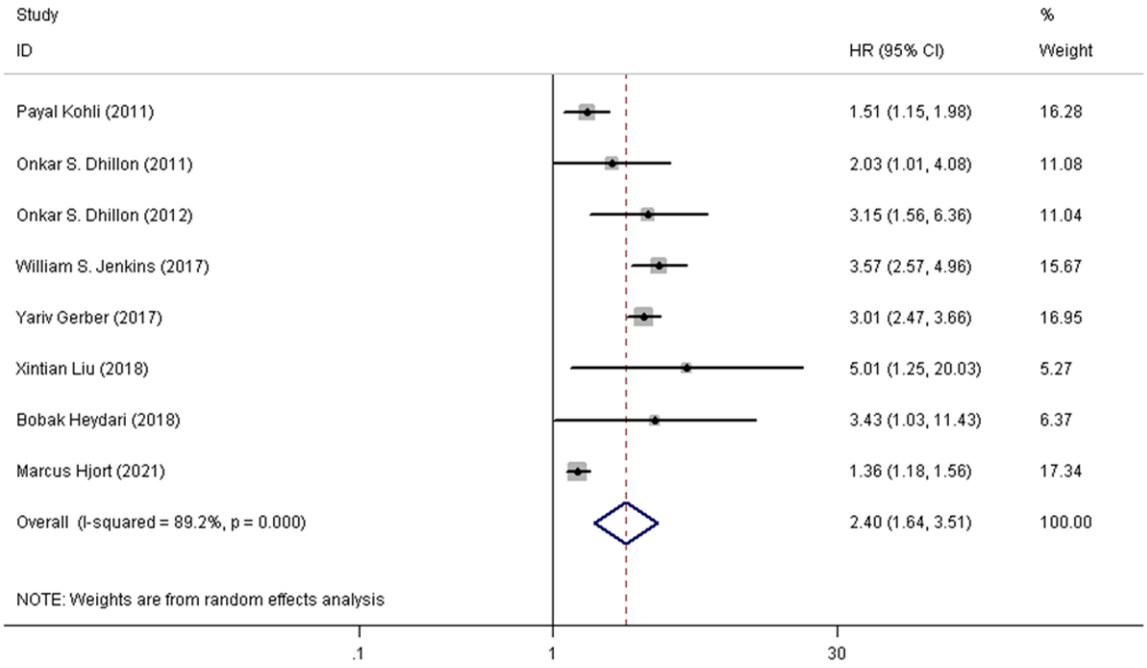

Figure 2. Elevated soluble suppression of tumorigenicity 2 (sST2) level predicted a poor outcome for all-cause mortality.

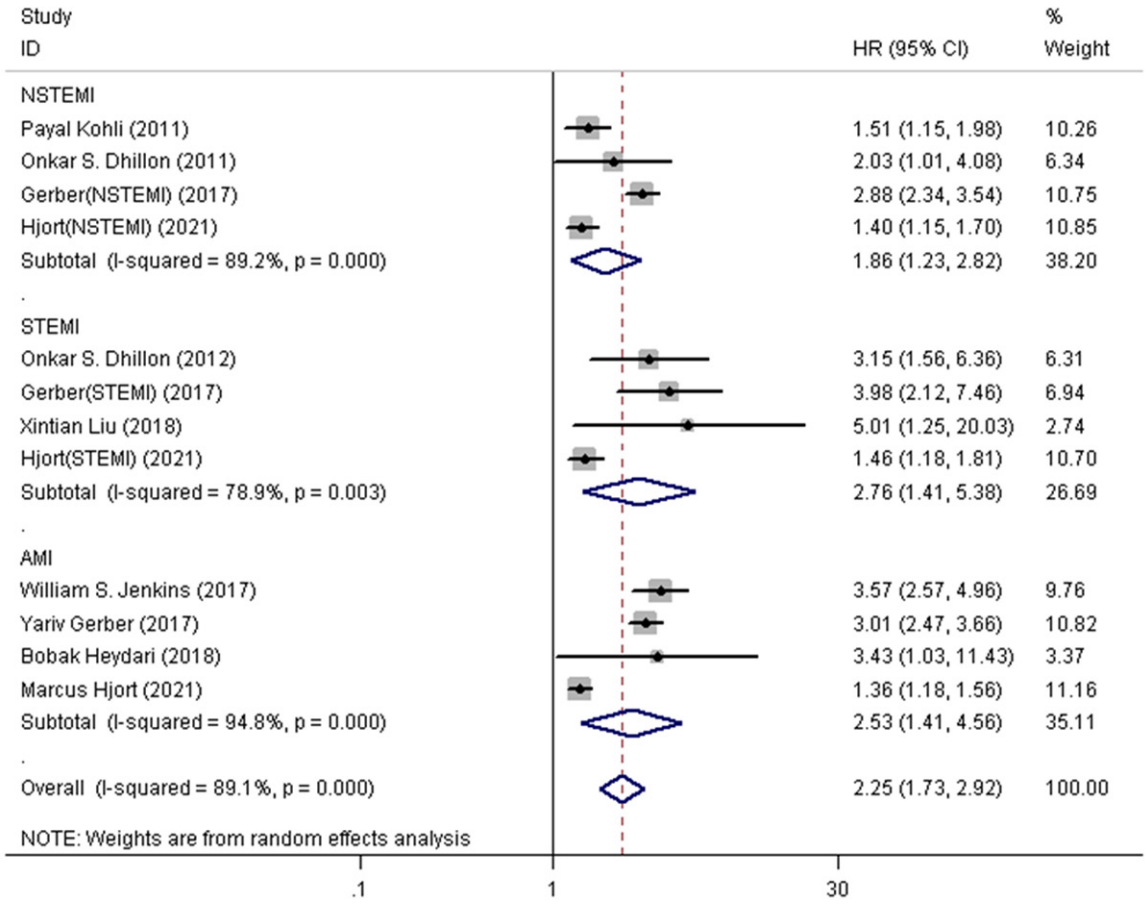

Figure 3. The ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unselected acute myocardial infarction (AMI) subgroups were positively correlated with elevated soluble suppression of tumorigenicity 2 (sST2) and all-cause mortality.

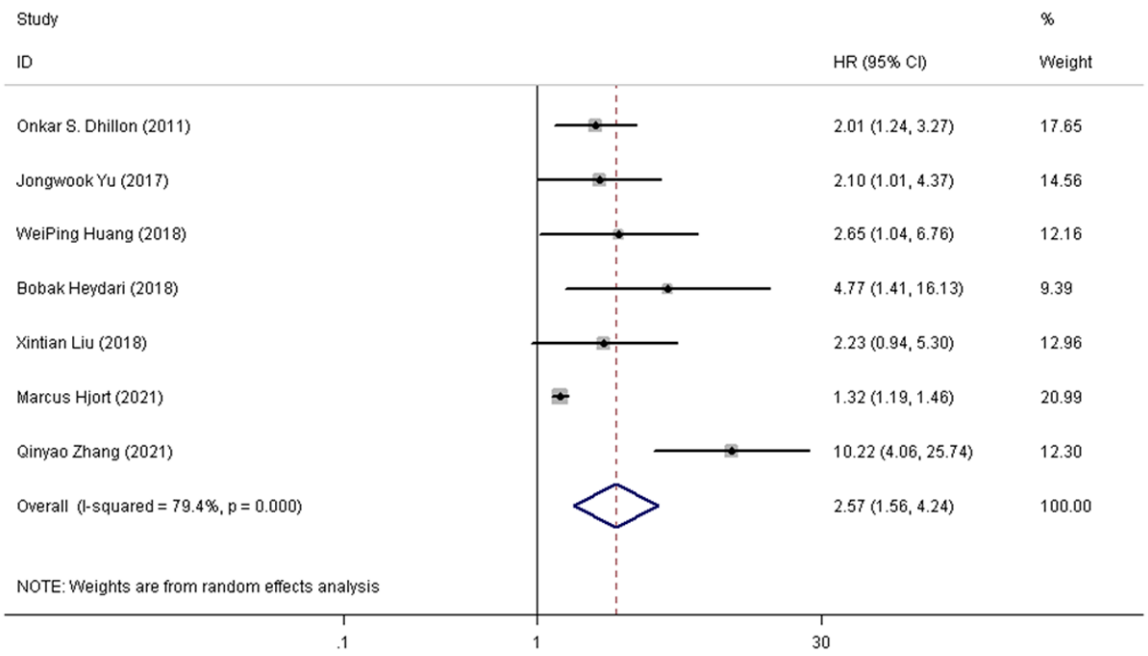

Figure 4. Elevated soluble suppression of tumorigenicity 2 (sST2) predicted a poor outcome for major adverse cardiovascular events (MACEs).

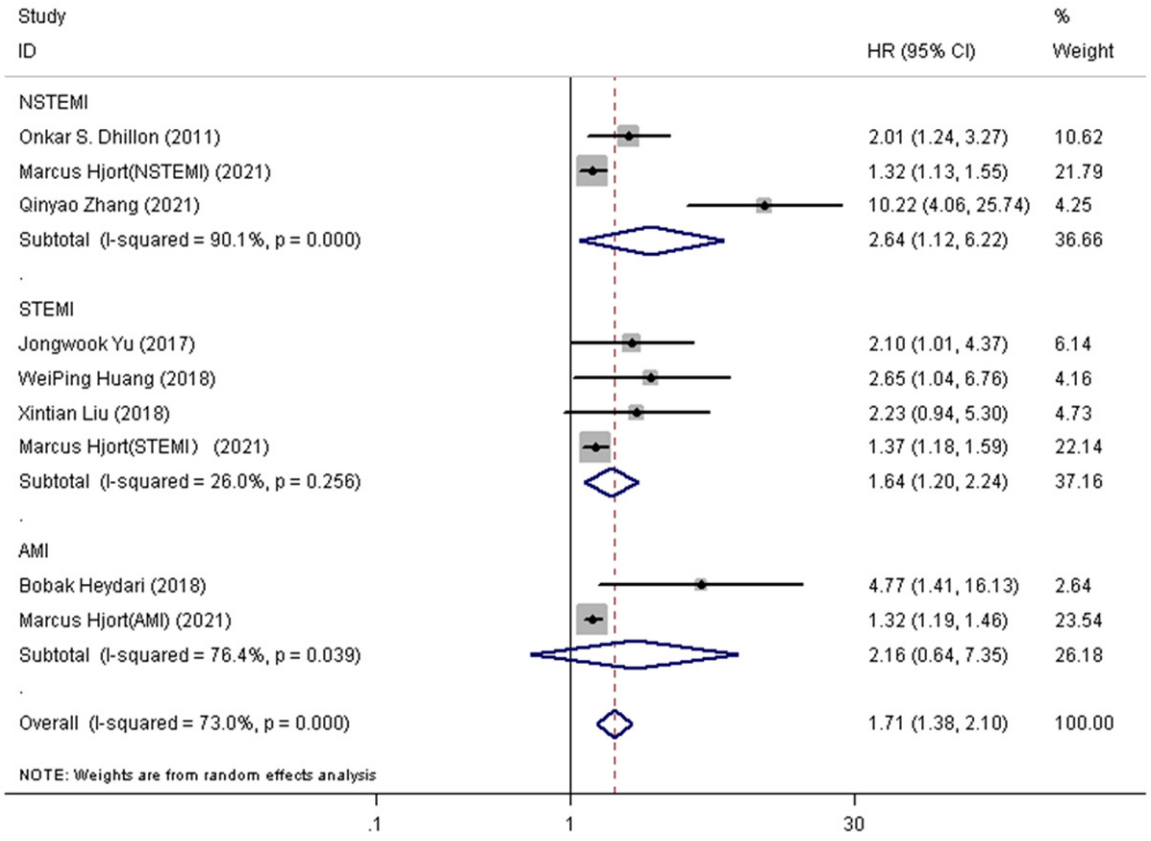

Figure 5. The ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unselected acute myocardial infarction (AMI) subgroups were positively correlated with elevated soluble suppression of tumorigenicity 2 (sST2) and major adverse cardiovascular events (MACEs).

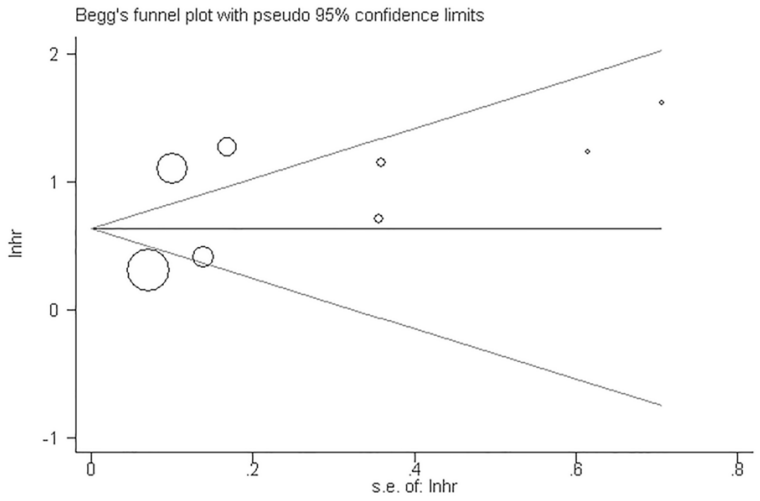

Figure 6. Publication bias.

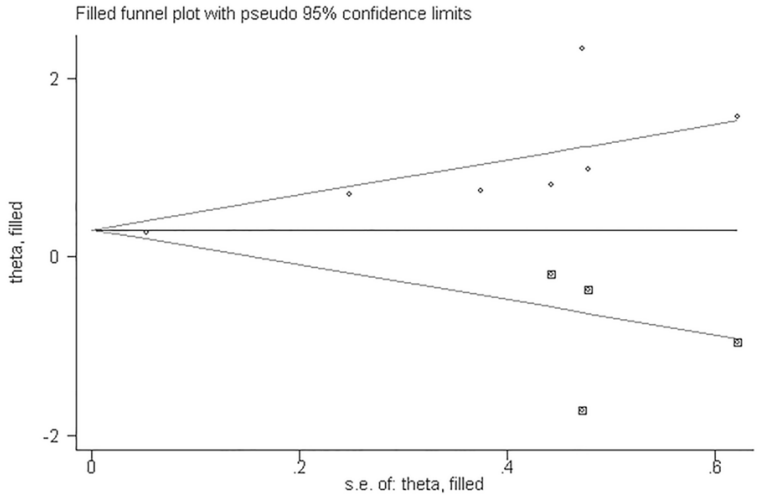

Figure 7. Trim-and-fill method obtained pooled adjusted HR.

egories of STEMI, NSTEMI, and unselected AMI, as illustrated in **Figure 5**.

Assessment of publication bias

Begg's funnel plot and Egger's linear regression test were utilized to access publication bias of included studies. No indications of publication bias were found concerning overall mortality. However, there was evidence of publication bias in the case of MACEs (Pr > |z| = 0.711 according to Begg test and P > |t| = 0.258 according to Egger test; **Figure 6**). Funnel plot of the MACEs subset exhibited an irregular shape, indicating the potential presence of publication bias. The unfilled circles implied that some studies might be missing in the less significant regions of the graph, contributing to the observed asymmetry, which could be partly attributed to publication bias. This suspicion was further reinforced by conducting the Egger test ($P < 0.01$). When applying trim and fill technique, a combined adjusted hazard ratio (under a random-effects model) of 1.474 (95% confidence interval, 0.925-2.350) was obtained, aligning with the main analysis (**Figure 7**).

Sensitivity analysis

To assess the robustness of the results, a sensitivity analysis was carried out due to the substantial heterogeneity observed in meta-analysis of sST2 with all-cause mortality (**Figure 8**) and MACE (**Figure 9**). Importantly, none of the individual studies significantly altered the pooled effect, underscoring the statistical robustness of the findings.

Discussion

Although some studies have sought to elucidate the enduring predictive significance of sST2 levels in individuals experiencing AMI, they didn't obtain a consistent conclusion. Therefore, we performed this meta-analysis to comprehensively evaluate the long-term prognostic relevance of sST2 in AMI patients. In this study, we included 13 studies with 11,387 participants, and the quality assessment showed excellent quality of them.

Studies had reported that there were notable associations between ventricular remodeling, myocardial scarring, and inflammation following AMI and the prognosis of AMI patients [26-28]. ST2, a member of the interleukin (IL)-1 receptor family, is present in both bound (ST2L) and free forms (sST2) within myocardial cells. The binding of sST2 with IL-33 contributes to

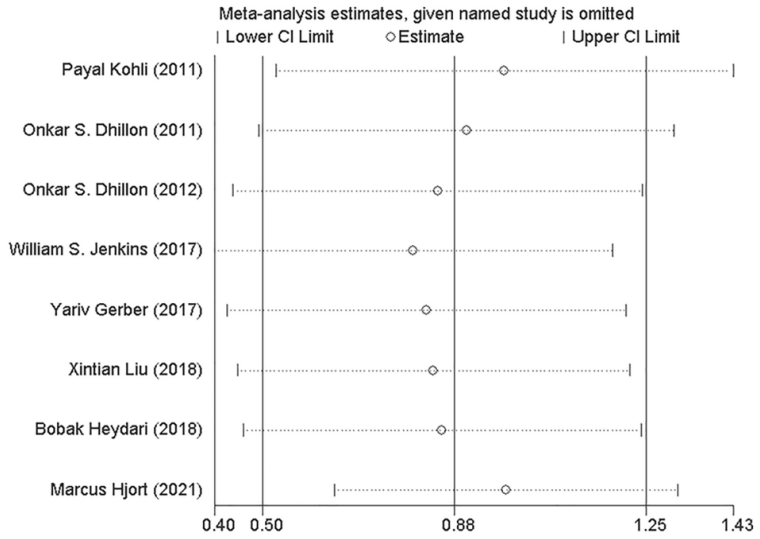

Figure 8. A sensitivity analysis for meta-analysis of soluble suppression of tumorigenicity 2 (sST2) with all-cause mortality.

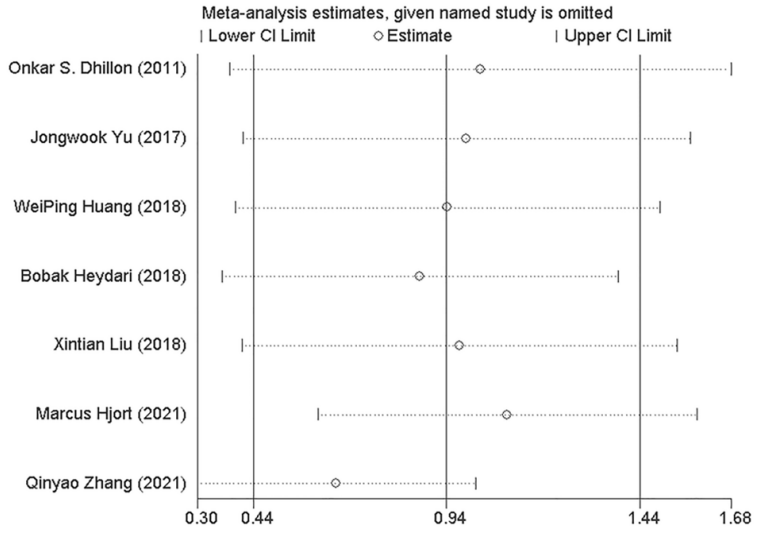

Figure 9. A sensitivity analysis for meta-analysis of soluble suppression of tumorigenicity 2 (sST2) with major adverse cardiovascular events (MACEs).

ventricular remodeling and myocardial fibrosis. This binding attenuates the formation of fibrotic tissue, preventing cardiomyocyte hypertrophy, reducing apoptosis, and enhancing myocardial functionality [29, 30]. Additionally, sST2 plays a role in extracellular matrix, inflammation, independent of IL-33 pathway [31, 32]. In this meta-analysis, we found elevated sST2 level was positively associated with an increased risk of all-cause mortality and MACEs in AMI patients. In the subgroup analysis, we also found there were favorable associations between elevated sST2 level and all-cause mortality and MACEs in subcategories of NSTEMI, STEMI, and unselected AMI. These findings suggested the strong correlation between sST2 and MACEs after AMI and underscore its possible effectiveness as a predictive biomarker [33-35].

Crucially, sST2 offers specific advantages compared to other biomarkers associated with fibrosis, myocardial damage because of its limited impact on glomerular filtration rate. Consequently, the stability of sST2 renders it a valuable tool for risk stratification and prognostic assessment [36]. According to laboratory studies, sST2 level increased at 2 hours after coronary artery ligation, peaked at 9 hours, and gradually returned to baseline levels by 15 hours; highest sST2 level appeared at 12 hours after the onset of AMI and returned to baseline by the 14th day [37]. Importantly, the initial sST2 level at the commencement of AMI surpasses the previously mentioned time-related values in its capacity to forecast cardiovascular incidents and survival outcomes. Therefore, this meta-analysis focused on studies investigating the initial sST2 level during the onset of AMI [38].

Nonetheless, this study has certain limitations. Firstly, there was significant heterogeneity in HR for all-cause mortality and MACEs among the included study. Despite conducting sensitivity and subgroup analyses, the sources of this variability remained uncertain. Contributing factors may include age, gender, and the specified sST2 cut-off value. Secondly, as this analysis is based on published literature, there is a potential for the presence of publication bias, particularly evident in HRs for MACEs (P =

0.086). This phenomenon might be attributed to a preference for publishing positive outcomes. Additionally, the restriction to studies published in English may have influenced the observed publication bias. Furthermore, the varying interpretations of sST2 threshold values used in different facilities underscore the necessity of implementing a standardized and unified sST2 threshold. Therefore, further research with unified sST2 thresholds is needed to verify our findings.

Conclusion

In summary, this meta-analysis has highlighted the potential of elevated sST2 as a robust long-term predictive element in individuals experiencing AMI. Nevertheless, the need for rigorously designed experiments with larger sample sizes is paramount to validate these findings.

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Material. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	yes
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	yes
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	yes
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	yes
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	yes
Informationsources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify thedate when each source was last searched or consulted.	yes
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	yes
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each recordand each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	yes
Data collectionprocess	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked indepen-dently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in theprocess.	yes
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in eachstudy were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	yes
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any as-sumptions made about any missing or unclear information.	yes
Study risk of biasassessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	yes
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	yes
Synthesismethods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	yes
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or dataconver-sions.	yes
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	yes
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe themodel(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	yes
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	yes
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	yes
Reporting biasassessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	yes
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	yes
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included inthe review, ideally using a flow diagram.	yes
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	yes
Study characteristics	17	Cite each included study and present its characteristics.	yes
Risk of bias instudies	18	Present assessments of risk of bias for each included study.	yes

Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision(e.g. confidence/credible interval), ideally using structured tables or plots.	yes
Results ofsyntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	yes
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g.confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	yes
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	yes
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	yes
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	yes
Certainty ofevidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	yes
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	yes
	23b	Discuss any limitations of the evidence included in the review.	yes
	23c	Discuss any limitations of the review processes used.	yes
	23d	Discuss implications of the results for practice, policy, and future research.	yes
OTHER INFORMATION			
Registration andprotocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	not registered
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	not registered
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	no
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	yes
Competinginterests	26	Declare any competing interests of review authors.	no
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from includedstudies; data used for all analyses; analytic code; any other materials used in the review.	no

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.