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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Short title：Sex differences in STEMI

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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Objectives

To assess the effect of sex differences on short- and long-term mortality among patients with ST-segment elevation myocardial infarction (STEMI) by performing a meta-analysis of contemporary available evidence in this topic.

Methods

PubMed, Embase and Cochrane Library were searched for relevant studies reporting sex specific outcomes among patients with STEMI. Only study conducted in last ten years were included. The primary outcome was all-cause death at short- and long-term follow-up. Risk ratio (RR) 95% CIs were measured using the Mantel-Haenszel method. The random-effect model was used for analysis. All statistical analyses were performed using STATA version 15.0.

Results

A total of fifteen studies involving 128,585 patients (31,706 women and 96879 patients) were included. In the unadjusted analyses, women were at a higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<.001, I^2=77%) but not long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P<.001, I^2=77.5%). When adjusted effect estimates from individual studies were used in meta-analysis, the association between women and higher risk of

short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P=0.103, I^2=39.6%). And adjusted long-term mortality was also similar between women and men (RR, 0.11; 95%CI, 0.42-1.80, P=0.008, I^2=74.5%).

Conclusions

An increased short- but not long-term mortality was found in women with STEMI. After adjustment for baseline cardiovascular risk factors and clinical profiles, short-term mortality remains higher in women with STEMI compared to men.

Strengths and limitations of this study

- We assessed the contemporary effect of sex differences on mortality among patients with STEMI by meta-analysis of studies from the last decade.
- We screened a greater number of potentially eligible articles and performed a comprehensive review.
- Each included study was assessed using the Newcastle-Ottawa Scale, and heterogeneity test, bias assessment, and sensitivity analysis were conducted.
- Theres is substantial and nonnegligible heterogeneity in our meta-analysis

Contemporary sex differences in short- and long-term mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Introduction

Acute myocardial infarction remains one of leading causes of mortality in both men and women worldwide despite improvement of acute cardiac care.[1] Numerous studies have reported that women have a higher risk of in-hospital and long-term adverse outcomes following ST-segment elevation myocardial infarction (STEMI) compared with men.[2] Confounders including advanced age and more frequent comorbidities, such as hypertension and diabetes mellitus[3, 4], might contribute to excess mortality in women. Moreover, previous studies show lower rates of guideline directed medical therapy and revascularization are also associated with poorer prognosis for women with STEMI.[5]

Sex discrepancies in management and outcomes after STEMI have been increasingly reported in the literature and raised public awareness.[6] Major progress in therapy for myocardial infarction and primary and secondary preventive interventions has been made to reduce cardiovascular mortality for women.[1, 7] And there have been marked reductions in cardiovascular disease mortality in women with acute myocardial infarction in the past two decades.[1] Conflicting results are noted in recent studies on sex differences following STEMI. It is unclear whether the sex differences still exist, in view of substantial improvements in prognosis of cardiovascular disease over the past decade.

In order to assess the contemporary effect of sex differences on short- and long-term

mortality among patients with STEMI, we performed a systematic review and meta-analysis of all available evidence from last decade reporting sex-specific outcomes after STEMI.

Methods

The present systematic review and meta-analysis was performed following the principle of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

Literature search

We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library from January 1, 2010 to August 1, 2020 to identify studies from the last decade that described sex differences in in short- or long-term mortality among patients with STEMI. We queried MeSH and the abstract text for the following three search terms: gender part (including "gender", "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular mortality" or "short term mortality"); myocardial infarction part (including "myocardial infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or "primary angioplasty") to identify relevant studies. There was no language

restriction.

Study selection

According to the aim of our analyses, studies were included in this systematic review if data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality stratified by sex in patients with STEMI were reported. Two reviewers identified studies eligible for further review by performing an initial screen of titles or abstracts of the search results. Subsequently, a second screen of full texts eligibility was performed by another two reviewers. Studies had to fulfil the following criteria to be included in the present analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and ii) studies providing enough details to obtain numbers of events or incidence rates according to sex; and iii) enrollment starting earlier than a decade ago. Editorials, letters included only if sufficient information was available in abstracts or associated tables or figures. Any disagreement was reviewed by a third reviewer and resolved by consensus.

Data extraction

Detailed data from selected studies were extracted independently by two reviewers using a standardized form independently. Data about study and participants characteristics, including year of study, sample size, time of enrollment, geographical location, endpoints of study, and follow-up duration, were collected. Any discrepancies were reviewed by a third reviewer and resolved by consensus. The quality of included studies was evaluated by Newcastle-Ottawa scale using prespecified items comprised of patients' selection

(representativeness and selection of patients, ascertainment of exposure), comparability of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy of follow-up).[9] A quality score (0–9) was generated according to a maximum of 1 score for each item.

Patient and public involvement

Due to the nature of the systematic review and meta-analysis, this study did not involve patients and the public in the design, or conduct, or reporting or dissemination plans.

Statistical analysis

The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent the effect of sex differences on mortality after STEMI. And data were combined using random-effects model of DerSimonian and Laird with inverse variance weighting. Random-effect model was used due to substantial clinical and statistical heterogeneity. Following analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality using raw number of death and total participants at risk for death specific to each sex, ii) adjusted RRs for short- and long-term all-cause mortality using adjusted RRs described in included studies.

We assess heterogeneity across studies with Cochran's Q test and I2 test, with P<0.1 or I2 >50% considered significant. To assess the potential effect of publication bias, we inspected funnel plots for asymmetry and used the Egger's regression asymmetry test in which P<0.10 was considered to indicate significant publication bias. Sensitivity analyses

was conducted by excluding one study at a time and comparing the results with the complete one. In addition, we also performed sensitivity analyses by restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and restricting to studies with sample size bigger than 1000 participants. All statistical analyses were performed using STATA version 15.0 (Stata Corp, College Station, TX).

Results

Literature search

Study selection details were outlined in Figure 1. The literature search identified 2,611 potentially relevant articles. After screening based on title and abstract review, 116 full-text were assessed for eligibility, with 96 papers excluded due to not meeting inclusion criteria. Another 5 papers reviewed in detail were excluded after due to data from the same cohorts. A total of 15 studies were finally included in the present systematic review and meta-analysis.[10-24]

Study characteristics

Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than 10,000 patients with STEMI. See Table 1 for further information of included studies. Except for 1 study, which was a prespecified gender analysis of randomized controlled trial, the remaining 14 were observational studies. Among the 10 included studies which reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension, and

prior myocardial infarction/PCI, while some adjusted for renal insufficiency, cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset.

Patient characteristics

A total of 128,585 patients with STEMI (31,706 women and 95,610 man) were involved in the 15 included studies. Women tended to be older and had higher prevalence of diabetes mellitus in all included studies. And in most studies, other important comorbidities, including hypertension and hyperlipidemia, were more frequent in women. Greater proportions of men were smokers and had prior PCI or myocardial infarction. In addition, some studies reported that door-to-balloon time and symptom onset to balloon time were longer in women than men. Part of patient baseline characteristics were summarized in Table 2.

Short-term all-cause mortality

Thirteen studies reported sex-specific unadjusted short-term mortality of patients with STEMI. There were 2,873 of 31,409 (9.1%) cases of all-cause mortality in women compared with 4,380 of 95,610 (4.6%) in men. Women were at a significantly higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<.001, I^2=77%) compared with men (Figure 2 A). Nine studies involving 119,379 patients reported adjusted short-term mortality specific to sex. In adjusted analysis, the association between women and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P=0.103, I^2=39.6%) (Figure 2 B). However, the strength of association calculated with adjusted RRs from these

9 studies was attenuated. Results of assessment of study quality using Newcastle-Ottawa scale were shown in eTable 1 in the Supplementary Material.

Long-term all-cause mortality

Six studies involved 18,018 patients with STEMI (4,191 women and 13,827 men) and followed up for more than 1 year, and reported all-cause mortality for women and men. The incidence of long-term all-cause mortality was 13.9% (n=584) in women and 8.7% (n=1202) in men. In unadjusted analysis, no significant sex difference was found in long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P<.001, I^2=77.5%) (Figure 3 A). And the adjusted analysis of the pooled results from four studies, also showed a similar risk of mortality at long-term follow-up in women compared with men (RR, 1.11; 95%CI, 0.42-1.80, P=0.008, I^2=74.5%) (Figure 3 B).

Sensitivity analyses and publication bias

Sensitivity analysis by excluding one study at a time (See eFigure 1 in the Supplementary Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75; 95%CI, 1.54-1.99, P<.001, I^2=82.9%) both indicated that none of the studies affected the results of short-term mortality in this meta-analysis significantly. In analysis for long-term mortality, sensitivity analysis showed a possibly higher influence on the result attribute to the study of Tai et al (See eFigure 2 in the Supplementary Material). After removing this study from meta-analysis, the association of women with increased long-term mortality became significant (RR, 1.50; 95%CI, 1.23-1.83, P=0.148, I^2=40.9%). We found no

evidence of publication bias across studies based on visual inspection of funnel plots (See eFigure 3 in the Supplementary Material) and the results from Egger's tests for short-term mortality (P=0.462) and for long-term mortality (P=0.053).

Discussion:

Our systematic review and meta-analysis of contemporary literature on sex differences among patients with STEMI demonstrate that women have a higher risk of short- but not long-term mortality compared with men with STEMI. Furthermore, after adjustment for baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term mortality are attenuated but remain significant, while women have the similar long-term mortality with men.

It is widely accepted that there are significant differences in outcomes of women and men with acute myocardial infarction. In our study, after adjusted for participants' baseline cardiovascular risk factors and clinical profiles, the strength of association between gender and short-term mortality was substantially attenuated, which suggested that poorer baseline cardiovascular risk profile partially explained the impact of sex differences on mortality. Multiple studies have shown that women with STEMI present at older age and have a higher burden of comorbidities, contributing to the sex differences in mortality after STEMI.[25] All studies included in our meta-analysis demonstrate that female patients are older and with more diabetes mellitus as well as hypertension. In addition, some sex-

specific studies found that certain risk factors and comorbidities were more potent in women.[26] Diabetes mellitus , hypertension and smoking status are more strongly associated with increased risk of cardiac events in women compared with men.[25, 27]

Notably, that these differences mentioned above still could not completely explain the gap in mortality between sexes. It has been proved that women with acute myocardial infarction were less likely to be treated with guideline directed medical therapy and less likely to receive primary reperfusion therapy including primary percutaneous coronary intervention or fibrinolysis.[28] Regarding medical therapy, numerous studies conducted around the world consistently demonstrate female survivors are receiving less optimal medical therapy after acute myocardial infarction during hospitalization or at discharge.[29, 30] Though there might be no differences in treatment adherence between men and women, some studies report significant sex disparities in initiation of appropriate pharmacotherapy after myocardial infarction.[31] Results from these observational studies show women are receiving less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme inhibitors in all age groups, especially young women, and suggest that clinicians and patients may benefit from better education and awareness of undertreatment of younger women.[31, 32]

Lower rates of revascularization are observed among women with STEMI compared with men in several studies despite proven benefit of this therapy.[33] Moreover, the sex differences might be driven by delays in presentation to hospital and women with STEMI

were more likely to experience longer delays than men. Although a great improvement in emergency medical services and timely revascularization over the past decades, recent studies show that women with STEMI still present later and have a longer ischemic time than men. Previous studies have shown consistently that women have longer door-to balloon times and longer door-to needle times.[34, 35] In addition, women are also more likely to exhibit longer pre-hospital delays in seeking medical care after the development of symptoms suggestive of myocardial infarction. Although there have been significant reductions in patient and system delay in the last decade, women continue to have longer presentation and treatment times.[36] Sex differences also exist in clinical presentation of STEMI. Although chest pain was the most common ACS symptom in both sexes, women were more likely to present without chest pain than men.[37, 38] Lower rates of typical chest pain reported among women with STEMI may also influence provider decision-making to pursue less aggressive care including invasive revascularization.

Complications including bleeding, heart failure and mechanical complications are more likely to develop in women with acute myocardial infarction and increase the risk of mortality.[14, 39, 40] Bleeding secondary to antithrombotic therapies and invasive procedures is more frequent in women.[41] Three included studies reported incidence of bleeding following STEMI and they all found that women were at higher risk of bleeding.[10, 13, 18] One study included in our analysis examined the relationships among sex, acute heart failure, and related outcomes after STEMI.[14] Its results demonstrate that women are at higher risk to develop de novo heart failure after STEMI and women with de novo

heart failure have worse survival compared with man. However, we could not compare the incidence of these complications due to the lack of sufficient data. Mechanical complications requiring surgical intervention are also much more common in women after acute myocardial infarction and associated with high mortality rates.[42]

Several limitations of this meta-analysis should be considered. First, the included studies are all observational studies except one post hoc analysis of randomized controlled trial. Hence, there may be residual confounding bias inherent in the observational study design in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the same confounders and not all studies reported adjusted RRs. Third, there was substantial heterogeneity in our meta-analysis, which could partly be attributed to the wide variability in the sample sizes, locations, and treatment regimens across included studies. Fourth, the analysis of long-term mortality, especially the adjusted analysis, included far fewer studies compared with analysis of short-term mortality. Hence, there might be significant bias in the results about long-term mortality.

In conclusion, our meta-analysis, pooling data from contemporary literature, shows that women with STENI have a higher risk of short-term mortality but not long-term mortality. The effect of sex differences on mortality in patients with STEMI remain significant after adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that public awareness of increased risk and further improvements in management in women with STEMI are necessary.

Contribution statement

Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis, Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data acquisition, Data analysis/interpretation. Jinan Li, Yang Li, Jianfeng Zheng and Runlin Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.

Conflict of interest

The authors declare that there is no conflict of interest.

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Ethics approval

The institutional central committee at Fuwai Hospital approved that the study protocol and inform consent was not required for a systematic review and meta-analysis.

Data sharing statement

As this is a systematic review and meta-analysis, the data used in the study have already been published by the authors of the included studies. Further information can be obtained

from the corresponding author

Table 1 Characteristics of included studies.

First Author	*Year*	*Region*	*Multicenter*	*Time of enrollment*	*Number of STEMI patients enrolled*	*Female*	*Endpoint*	*Follow-up duration*
Venetsanos	2017	13 countries	Yes	Sep, 2011-Oct, 2013	1,862	369 (20.0)	Major adverse cardiovascular events and definite stent thrombosis	30 d
Ali	2018	Germany	No	2013-2017	312	101 (32.4)	All-cause in-hospital mortality	NA
Langabeer	2018	US	Yes	Jan, 2010-Dec, 2015	9,674	2,569 (26.6)	In-hospital mortality	NA
Tang	2018	China	No	Jan, 2013-Dec,	1,238	210 (1.9)	Major adverse cardiac and	730 ± 30 d

				2013				cerebrovascular events	
Cenko	2019	12 European countries	Yes	Jan, 2018	2010-Jul,	10,443	3,112 (29.8)	30-day all-cause mortality	30 d
Hao	2019	China	Yes	Nov, 2018	2014-Jun,	50,203	11,016 (21,9)	In-hospital mortality	NA
Hannan	2019	US	Yes	Jan, 2015	2013-Dec,	23,809	7,791 (32.7)	In hospital/30-day mortality	30 d
Maznyczka	2019	UK	No	July, 2012	2011-Nov,	324	87 (26.9)	All-cause death/ first heart failure hospitalisation	5 years
Stehli	2019	Australia	Yes	2013-2016		6431	1,317 (20.5)	In hospital/30-day major adverse events, and major bleeding	30 d

Burgess	2020	Australia	No	Dec, 2010-Apr, 2014	589	123 (21)	Cardiac death and myocardial infarction	2 years
Dharma	2020	Indonesia	No	Feb, 2011-Aug, 2019	6557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherlands	Yes	2015-2016	787	229 (29)	All-cause mortality	1 year
Siabani	2020	Iran	No	Jun, 2016-May, 2018	1484	311(21)	In-hospital mortality	NA
Tai	2020	China	No	Jan, 2013-Dec, 2017	182	56 (30.8)	In hospital/1-year mortality	1 year
Tizón	2020	Spain	Yes	2010-2016	14,690	3486 (23.7)	30-day/1-year all-cause mortality	1 year

Table 2 Baseline characteristics of participants in included studies.

First Author	*Year*	*Age, mean (SD), years*		*Diabetes, %*		*Hypertension, %*		*Hyperlipidemia, %*		*Smoking, %*		*Prior MI, %*		*Prior PCI, %*	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Venetsanos	2017	69 (13.0)	59 (11.0)	13.0	13.7	51.5	40.5	31.7	35.9	NA	NA	6.5	9.0	4.3	8.3
Ali	2018	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Langabeer	2018	62.5 (13.6)	60.2 (12.5)	29.6	27.8	NA	NA	49.3	52.0	37.0	38.9	16.9	18.4	NA	NA
Tang	2018	64.5	54.4	31.4	25.1	67.1	53.3	59.5	60.3	15.7	77.3	4.8	6.8	28.6	22.8

	(9.3)	(10.7)												
Cenko	2019	66.1 (11.7)	59.7 (11.7)	29.7	20.9	74.6	61.4	43.3	42.3	32.5	50.7	9.7	11.5	9.8	10.4
Hao	2019	69.0 (10.6)	61.1 (12.4)	48.1	39.4	74.1	62.9	85.4	83.3	8.2	53.0	NA	NA	NA	NA
Hannan	2019	70.72 (14.73)	62.11 (12.82)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	11.1	13.8
Mazny czka	2019	61.2 (12.2)	58.6(11.2)	9.2	11.0	36.8	30.8	32.2	27.8	65.5	58.6	5.7	8.4	2.3	6.8
Stehli	2019	66.5 (13.2)	60.8 (12.2)	18.6	15.1	NA	NA	NA	NA	NA	NA	NA	NA	7.9	11.3
Burgess	2020	62.7 (52.7-	58.2 (50.6-	31.7	18.9	68.3	52.1	67.5	52.3	52.0	54.1	7.3	8.8	NA	NA

		73.2)	65.7)												
Dharma	2020	60 (10)	55 (10)	43.4	27.5	69.6	51.3	32.2	31.6	11.7	71.9	NA	NA	NA	NA
Kerkmanx	2020	68 (14)	61 (12)	17.6	12.5	45.7	33.6	25.9	21.0	41.1	49.3	13.6	13.7	14.4	14.2
Siabani	2020	65.8 (11.3)	59.0 (12.4)	37.7	16.2	63.7	35.4	36.7	18.5	13.2	55.9	NA	NA	NA	NA
Tai	2020	78 (76–81)	78 (76–80)	35.2	26.5	79.5	72.8	NA	NA	5.4	56.5	NA	NA	13.5	18.1
Tizón	2020	69.9 (13.7)	60.9 (12.6)	24.2	17.2	34.2	24.3	25.2	21.2	13.6	24.2	NA	NA	NA	NA

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Figure 1 Flowchart of selection of studies included in meta-analysis.

Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 1 Flowchart of selection of studies included in meta-analysis.

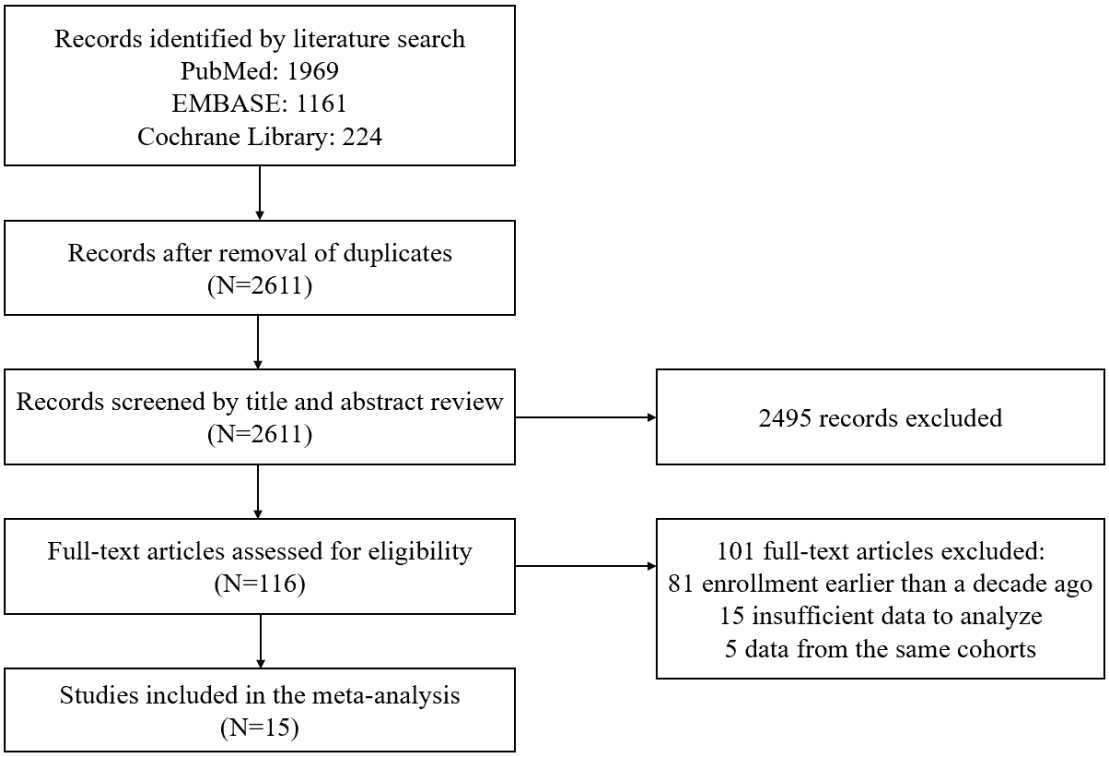
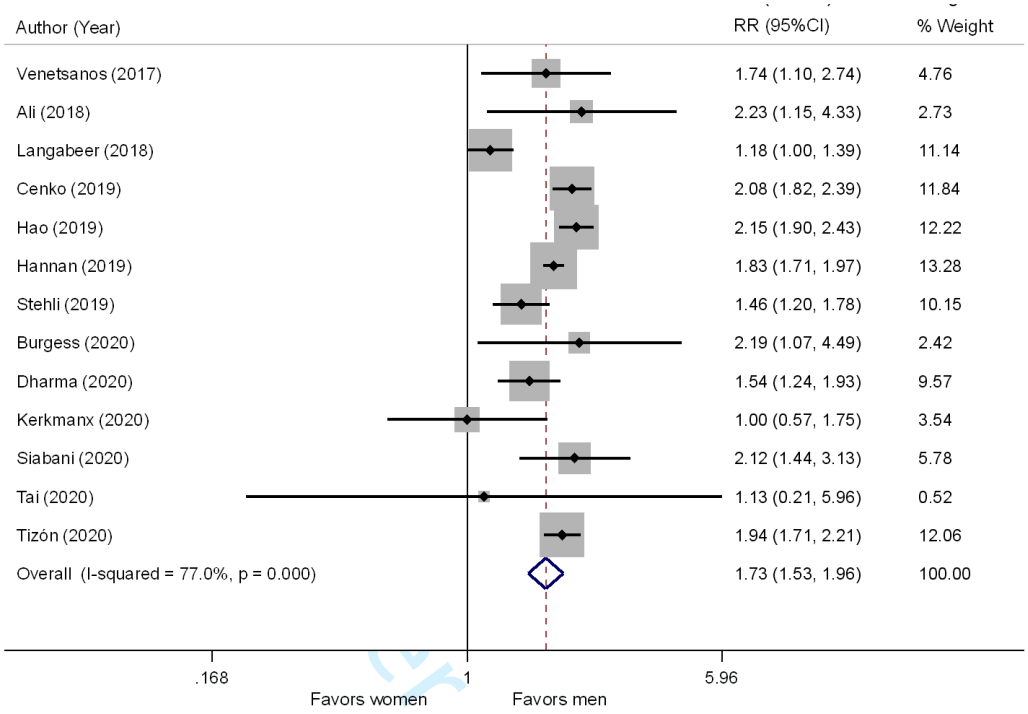
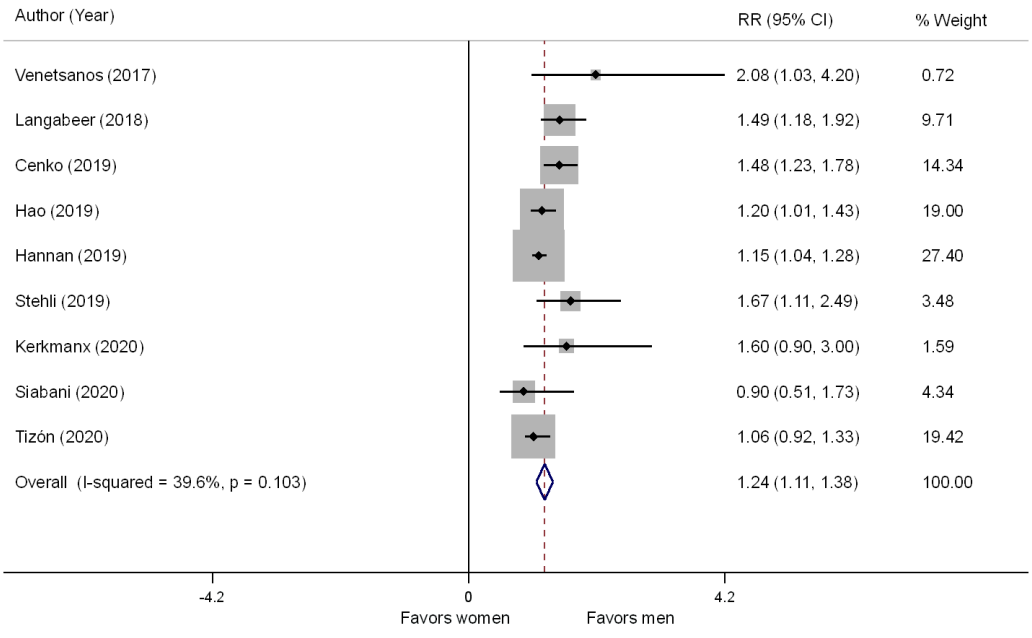


Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



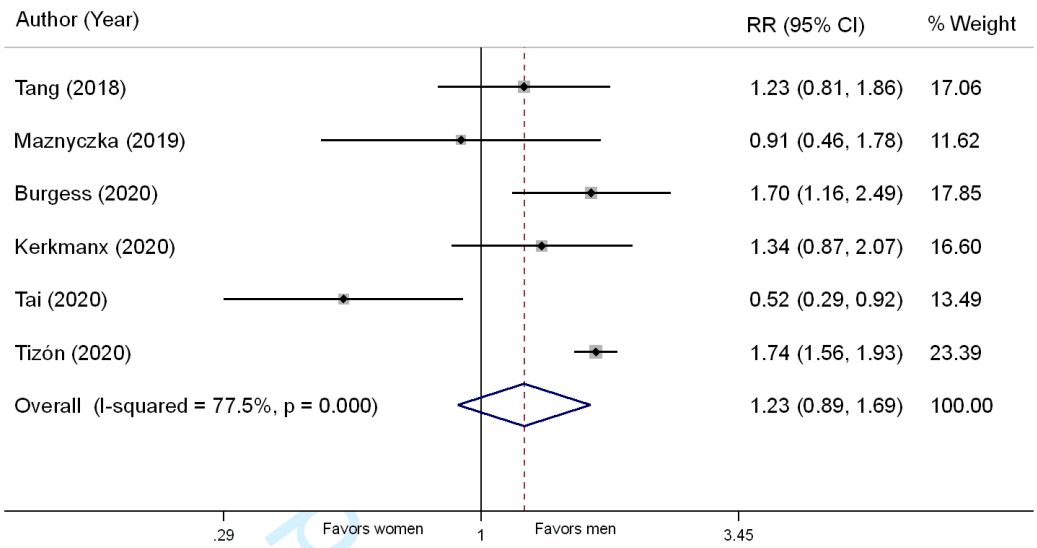
B



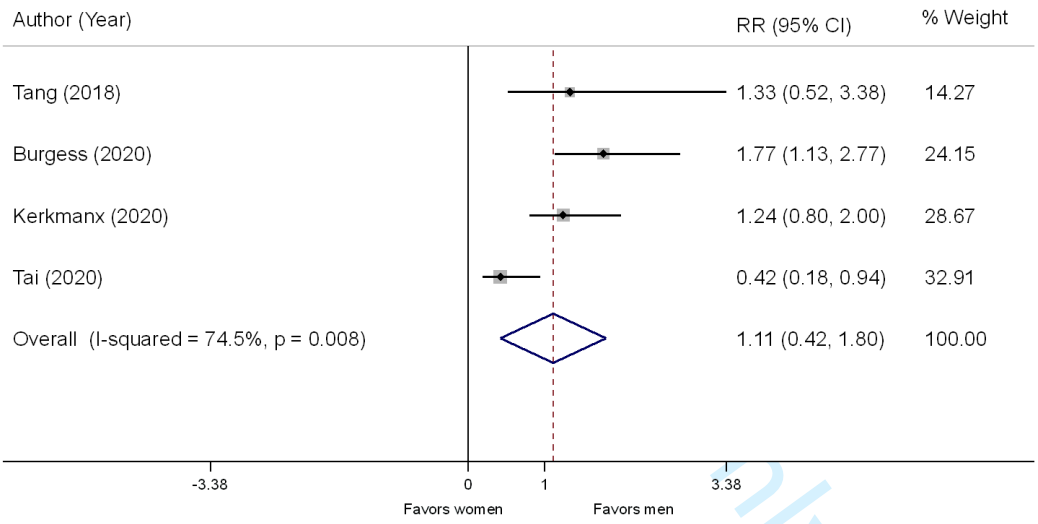
Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



B



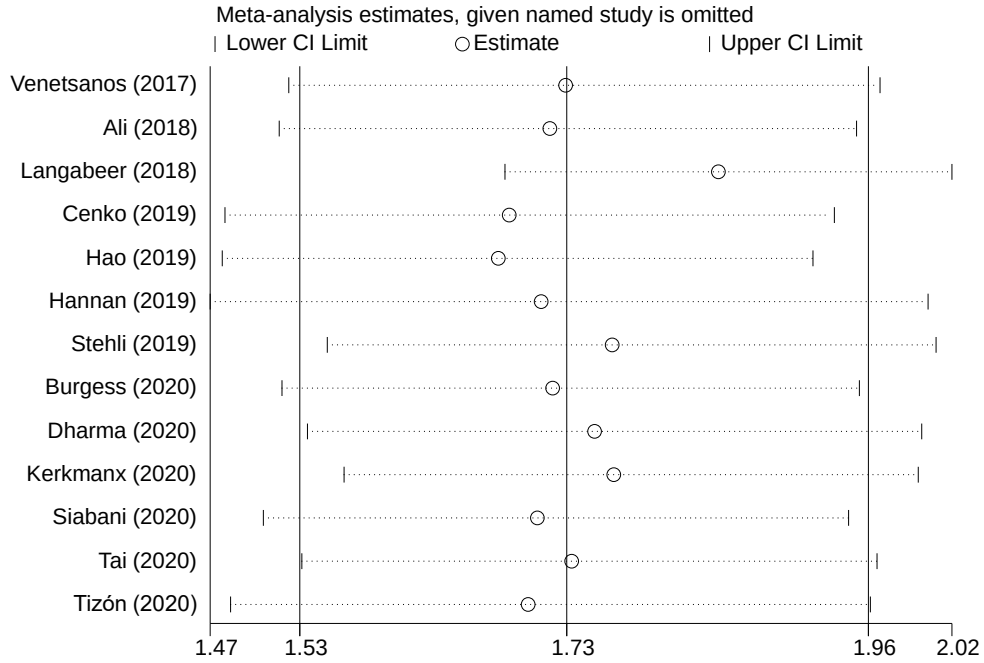
Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

eTable 1 Table 3 Assessment of study quality using Newcastle-Ottawa scale.

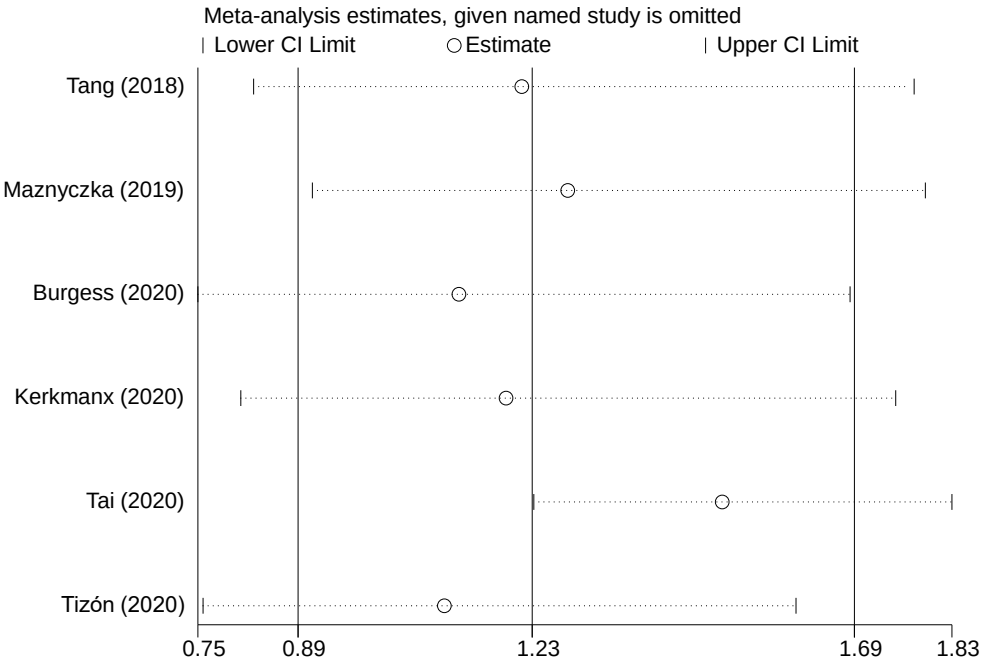
First Author	*Year*	*Selection*				*Comparability*	*Outcome*			*Total points*
		Representativeness of the exposed cohor	Selection of the no exposed cohort	Ascertainment of exposure to implants	Outcome of interest not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up	
Venetsanos	2017	*	*	*	*	**	*	\	*	8
Ali	2018	\	\	*	*	\	*	\	*	4
Langabeer	2018	*	*	*	*	*	*	\	*	7
Tang	2018	\	\	*	*	**	*	*	*	7
Cenko	2019	*	*	*	*	**	*	\	*	8
Hao	2019	*	*	*	*	**	*	\	*	8
Hannan	2019	*	*	*	*	**	*	\	*	8
Maznyczk	2019	\	\	*	*	\	*	*	*	5

a									
Stehli	2019	*	*	*	*	**	*	\	*	8
Burgess	2020	\	\	*	*	**	*	*	*	7
Dharma	2020	\	\	*	*	*	*	*	*	6
Kerkmanx	2020	*	*	*	*	\	*	*	*	7
Siabani	2020	\	\	*	*	*	*	\	*	5
Tai	2020	\	\	*	*	**	*	*	*	7
Tizón	2020	*	*	*	*	**	*	*	*	9

eFigure 1 Meta-influence analysis for unadjusted short-term mortality

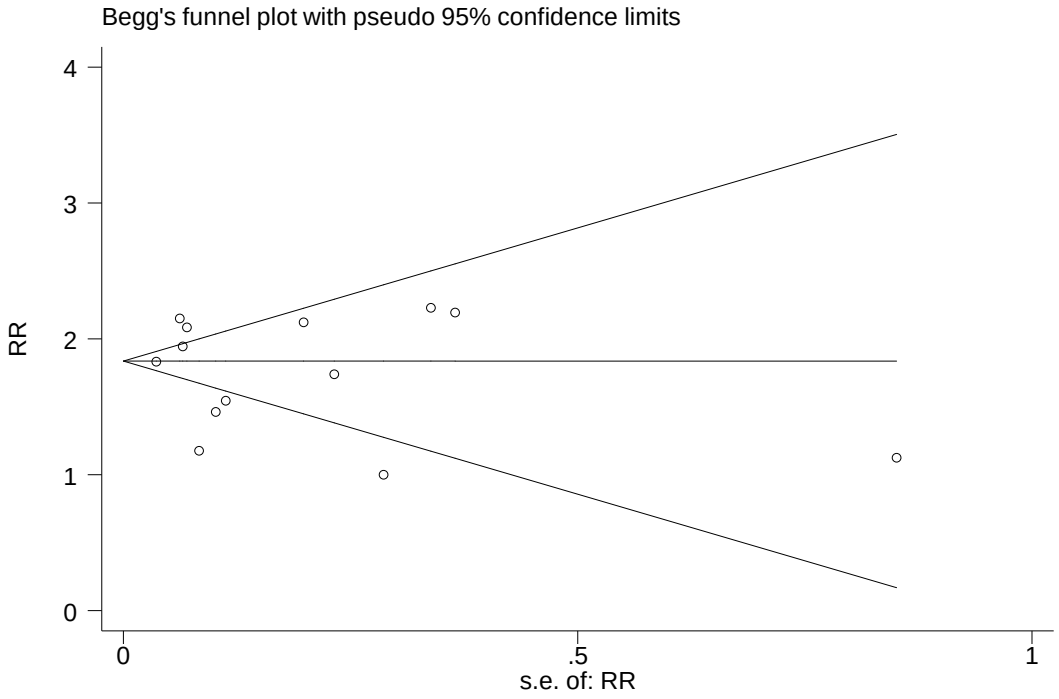


eFigure 2 Meta-influence analysis for unadjusted long-term mortality

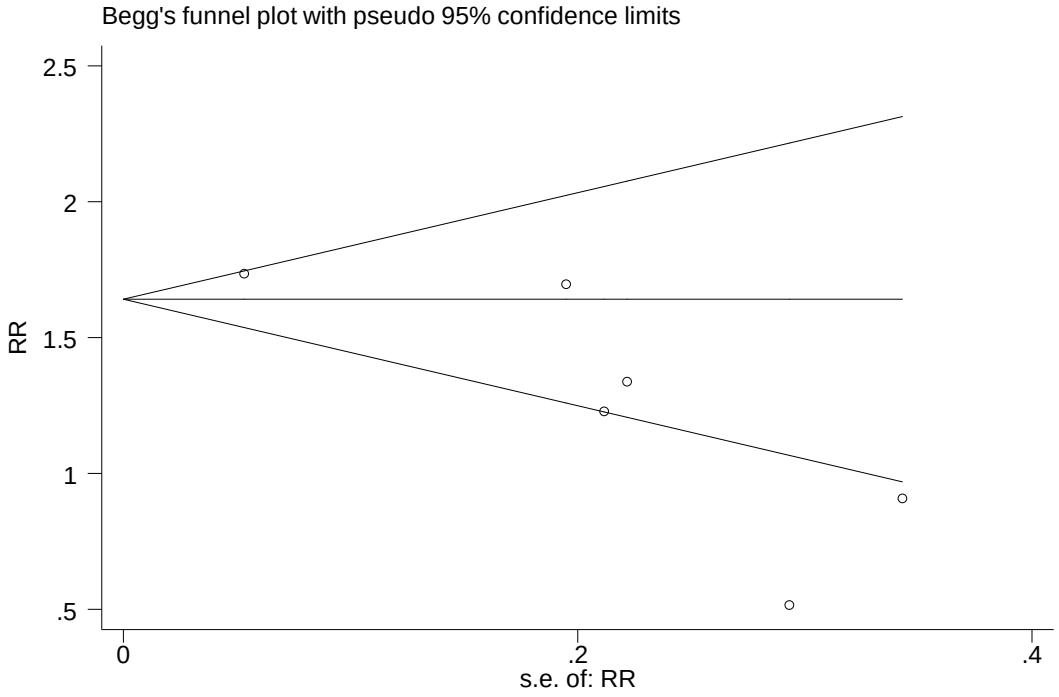


eFigure 3 Funnel plots for publication bias for unadjusted short-term (A) and long-term (B) mortality

A


Begg's funnel plot with pseudo 95% confidence limits
RR
4
3
2
1
0
0
.5
1
s.e. of: RR

B


Begg's funnel plot with pseudo 95% confidence limits
RR
2.5
2
1.5
1
.5
0
.2
.4
s.e. of: RR

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
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 record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
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 each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	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.	Page 5
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.	Page 5
Synthesis methods	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)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
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 in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 7
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.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 6
	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.	Page 6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 7
	23b	Discuss any limitations of the evidence included in the review.	Page 8-9
	23c	Discuss any limitations of the review processes used.	Page 8-9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 7-8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
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 included studies; data used for all analyses; analytic code; any other materials used in the review.	

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

BMJ Open

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Emergency medicine
Keywords:	EPIDEMIOLOGY, Coronary heart disease < CARDIOLOGY, Myocardial infarction < CARDIOLOGY

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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Short title：Sex differences in STEMI

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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Objectives: To assess the effect of sex differences on short- and long-term mortality among patients with ST-segment elevation myocardial infarction (STEMI).

Design: Systematic review and meta-analysis of contemporary available evidence.

Setting: PubMed, Embase and Cochrane Library were searched for relevant studies reporting sex specific outcomes among patients with STEMI published between January 1, 2010 to August 1, 2020. Risk ratio (RR) 95% 95% confidence intervals (CIs) were measured using DerSimonian and Laird random-effects model. Sensitivity analyses were performed and publication bias was also checked. All statistical analyses were performed using STATA version 15.0.

Participants: Studies providing data about short- or long-term mortality stratified by sex in patients with STEMI were included. Only study conducted in last ten years were included.

Primary and secondary outcome measures: The primary outcome was all-cause death at short-(in-hospital or 30 days) and long-term (at least 12 months) follow-up.

Results

A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879 [75.3%] male) were included. In the unadjusted analyses, female were at a higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) but not long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%). When adjusted effect estimates from individual studies were used in meta-analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%). And adjusted long-term mortality was also similar between female and male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%).

Conclusions

An increased short- but not long-term mortality was found in female with STEMI. After adjustment for baseline cardiovascular risk factors and clinical profiles, short-term mortality remains higher in female with STEMI compared to male, indicating the need for further improvements in management in female patients.

Strengths and limitations of this study

- We assessed the contemporary effect of sex differences on mortality among patients with STEMI by meta-analysis of studies from the last decade.
- A greater number of potentially eligible articles were screened and the large sample size ensures adequate statistical power to detect even a small effect of interest.
- Sensitivity analyses by excluding one study at a time and restricting to studies with high quality or with large sample size got consistent results.
- Substantial and nonnegligible heterogeneity still exist in our meta-analysis and might result in potential bias.
- Residual confounding bias could not be totally excluded due to the observational study design of most included studies.

Contemporary sex differences in short- and long-term mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Introduction

Acute myocardial infarction remains one of leading causes of mortality in both men and women worldwide despite improvement of acute cardiac care.[1] Numerous studies have reported that women have a higher risk of in-hospital and long-term adverse outcomes following ST-segment elevation myocardial infarction (STEMI) compared with men.[2] Confounders including advanced age and more frequent comorbidities, such as hypertension and diabetes mellitus[3 4], might contribute to excess mortality in women. Moreover, previous studies show lower rates of guideline directed medical therapy and revascularization are also associated with poorer prognosis for women with STEMI.[5]

Sex discrepancies in management and outcomes after STEMI have been increasingly reported in the literature and raised public awareness.[6] Major progress in therapy for myocardial infarction and primary and secondary preventive interventions has been made to reduce cardiovascular mortality for women.[1 7] And there have been marked reductions in cardiovascular disease mortality in women with acute myocardial infarction in the past two decades.[1] Conflicting results are noted in recent studies on sex differences following STEMI. It is unclear whether the sex differences still exist, in view of substantial improvements in prognosis of cardiovascular disease over the past decade.

In order to assess the contemporary effect of sex differences on short- and long-term

mortality among patients with STEMI, we performed a systematic review and meta-analysis of all available evidence from last decade reporting sex-specific outcomes after STEMI.

Methods

The present systematic review and meta-analysis was performed following the principle of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

Literature search

We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library from January 1, 2010 to August 1, 2020 to identify studies from the last decade that described sex differences in in short- or long-term mortality among patients with STEMI. Both observational studies and randomized clinical trials were eligible. We queried MeSH and the abstract text for the following three search terms: gender part (including "gender", "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular mortality" or "short term mortality"); myocardial infarction part (including "myocardial infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or

"primary angioplasty") to identify relevant studies. There was no language restriction or age limit.

Study selection

According to the aim of our analyses, studies were included in this systematic review if data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality stratified by sex in patients with STEMI were reported. Two reviewers identified studies eligible for further review by performing an initial screen of titles or abstracts of the search results. Subsequently, a second screen of full texts eligibility was performed by another two reviewers. Studies had to fulfil the following criteria to be included in the present analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and ii) studies providing enough details to obtain numbers of events or incidence rates according to sex; and iii) enrollment starting earlier than a decade ago. Editorials, letters, conference proceedings and abstracts were considered to be eligible only if sufficient information was available in abstracts or associated tables or figures. We excluded studies if they were review articles or case reports, or if they involved pregnant participants, critically ill patients, or provided insufficient data to allow for risk estimates to be calculated. Any disagreement was reviewed by a third reviewer and resolved by consensus.

Data extraction

Detailed data from selected studies were extracted independently by two reviewers using a standardized form independently. Data about study and participants characteristics,

including year of study, sample size, time of enrollment, geographical location, endpoints of study, and follow-up duration, were collected. Any discrepancies were reviewed by a third reviewer and resolved by consensus. The quality of included studies was evaluated by Newcastle-Ottawa scale using prespecified items comprised of patients' selection (representativeness and selection of patients, ascertainment of exposure), comparability of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy of follow-up).[9] A quality score (0–9 points) was generated according to a maximum of 1 point for each item.

Patient and public involvement

Due to the nature of the systematic review and meta-analysis, this study did not involve patients and the public in the design, or conduct, or reporting or dissemination plans.

Statistical analysis

The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent the effect of sex differences on mortality after STEMI. And data were combined using random-effects model of DerSimonian and Laird with inverse variance weighting. Random-effect model was used due to substantial clinical and statistical heterogeneity. Following analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality using raw number of death and total participants at risk for death specific to each sex, ii) adjusted RRs for short- and long-term all-cause mortality using adjusted RRs if they were described in those included studies.

We assess heterogeneity across studies with Cochran's Q test and I2 test, with P<0.1 or I2 >50% considered significant. We also performed meta-regression to identify the potential sources of heterogeneity in the included studies. Furthermore, stratified analysis was conducted as well by dividing the included studies into different subgroups based on the Newcastle-Ottawa scale scores (>7 points or ≤7 points) to assess the potential sources of heterogeneity. To assess the potential effect of publication bias, we inspected funnel plots for asymmetry and used the Egger's regression asymmetry test in which P<0.05 was considered to indicate significant publication bias.

Sensitivity analyses was conducted by excluding one study at a time and comparing the results with the complete one. In addition, we also performed sensitivity analyses by restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and restricting to studies with sample size bigger than 1000 participants. All statistical analyses were performed using STATA version 15.0 (Stata Corp, College Station, TX). Differences were considered statistically significant at P < .05 (2-sided).

Results

Literature search

Study selection details were outlined in Figure 1. The literature search identified 2,611 potentially relevant articles. After screening based on title and abstract review, 2495 records were excluded. A total of 116 full-text were finally assessed for eligibility, with 96 papers excluded due to enrollment starting earlier than a decade ago or no sufficient

gender specific data to analyze. Another 5 papers reviewed in detail were excluded after due to data from the same cohorts. A total of 15 studies were finally included in the present systematic review and meta-analysis.[10-24]

Study characteristics

Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than 10,000 patients with STEMI. See Table 1 for further information of included studies. Baseline characteristics of participants were missing in some included studies, but all included studies provided sufficient data for analysis of sex differences in clinical outcomes. Except for 1 study, which was a prespecified gender analysis of randomized controlled trial, the remaining 14 were observational studies. Among the 10 included studies which reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension, and prior myocardial infarction/PCI, while some adjusted for renal insufficiency, cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset. Variables that were adjusted in the adjusted analyses from the included studies were presented in eTable 1 of the Supplementary Material. Results of assessment of study quality using Newcastle-Ottawa scale were shown in eTable 2 in the Supplementary Material.

Patient characteristics

A total of 128,585 patients with STEMI (31,706 [24.7%] female and 96,879 [75.3%] male) were involved in the 15 included studies. Female tended to be older and had higher

prevalence of diabetes mellitus in all included studies. And in most studies, other important comorbidities, including hypertension and hyperlipidemia, were more frequent in female. Greater proportions of male were smokers and had prior PCI or myocardial infarction. Besides, some studies reported that door-to-balloon time and symptom onset to balloon time were longer in female than male. Part of patient baseline characteristics were summarized in Table 2.

Short-term all-cause mortality

Thirteen studies reported sex-specific unadjusted short-term mortality of patients with STEMI. There were 2,873 of 31,409 (9.1%) cases of all-cause mortality in female compared with 4,380 of 95,610 (4.6%) in male. Female were at a significantly higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) compared with male (Figure 2 A). Nine studies involving 119,379 patients reported adjusted short-term mortality specific to sex. In adjusted analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%) (Figure 2 B). However, the strength of association calculated with adjusted RRs from these 9 studies was attenuated. Subgroup analysis demonstrated that the results of studies with Newcastle-Ottawa scale >7 points (RR, 1.90; 95%CI, 1.73-2.09, P=0.018, I2=63.4%) and studies with ≤7 points (RR, 1.52; 95%CI, 1.20-1.93, P=0.026, I2=58.1%) were consistent in unadjusted short-term mortality (See eFigure 1 in the Supplementary Material).

Long-term all-cause mortality

Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and followed up for more than 1 year, and reported all-cause mortality for female and male. The incidence of long-term all-cause mortality was 13.9% (n=584) in female and 8.7% (n=1202) in male. In unadjusted analysis, no significant sex difference was found in long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%) (Figure 3 A). And the adjusted analysis of the pooled results from four studies, also showed a similar risk of mortality at long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%) (Figure 3 B).

Meta-Regression Analysis, sensitivity analyses and publication bias

According to meta-regression analysis, differences in prevalence of diabetes (β coefficient, 0.248; P=0.337), hypertension (β coefficient, -0.255; P=0.538), hyperlipidemia(β coefficient, 0.260; P=0.415), smoking (β coefficient, -0.040; P=0.255), prior MI (β coefficient, -2.725; P=0.126), and prior PCI (β coefficient, 0.109; P=0.896) between sexes were not identified as significant sources of heterogeneity for short-term all-cause mortality. Given that not all included study provided information on confounders stratified by sex, the results of meta-regression analyses should be interpreted with caution.

Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75; 95%CI, 1.54-1.99, P<.001, I^2=82.9%) both indicated that none of the studies affected the results of short-term mortality in this meta-analysis significantly. In analysis for long-term mortality, sensitivity analysis showed a possibly higher influence on the result attribute to

the study of Tai et al (See eFigure 3 in the Supplementary Material). After removing this study from meta-analysis, the association of female with increased long-term mortality became significant (RR, 1.50; 95%CI, 1.23-1.83, P=0.148, I^2=40.9%). We found no evidence of publication bias across studies based on visual inspection of funnel plots (See eFigure 4 in the Supplementary Material) and the results from Egger's tests for short-term mortality (P=0.462) and for long-term mortality (P=0.053).

Discussion:

Our systematic review and meta-analysis of contemporary literature on sex differences among patients with STEMI demonstrate that female have a higher risk of short- but not long-term mortality compared with male with STEMI. Furthermore, after adjustment for baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term mortality are attenuated but remain significant, while female have the similar long-term mortality with male.

Our results are somewhat in accordance with several previously published meta-analysis.[2] [25] A considerable number of studies have consistently suggested that women were at a higher risk of short-term mortality after ACS. However, whether risk of long-term mortality is also higher in women with ACS remains under debate. Some studies indicated that women with STEMI had a higher 1-year rate of death compared to men[26], while the 1-year mortality rate was conversely lower in women than men in some other studies[23] [24]. In our

study, with respect to short-term mortality, the analyses of studies with high or low quality, and big or small sample size yielded similar results. However, in terms of long-term mortality, caution is needed when interpreting our finding of non-significant increased long-term mortality in adjusted analyses, due to the results of sensitivity analysis which showed a significant association between female and increased long-term mortality after removing one study from adjusted analyses.

It is widely accepted that there are significant differences in outcomes of women and men with acute myocardial infarction. In our study, after adjusted for participants' baseline cardiovascular risk factors and clinical profiles, the strength of association between gender and short-term mortality was substantially attenuated, which suggested that poorer baseline cardiovascular risk profile partially explained the impact of sex differences on mortality. Multiple studies have shown that women with STEMI present at older age and have a higher burden of comorbidities, contributing to the sex differences in mortality after STEMI.[27] All studies included in our meta-analysis demonstrate that female patients are older and with more diabetes mellitus as well as hypertension. In addition, some sex-specific studies found that certain risk factors and comorbidities were more potent in women.[28] Diabetes mellitus , hypertension and smoking status are more strongly associated with increased risk of cardiac events in women compared with men.[27 29]

Notably, that these differences mentioned above still could not completely explain the gap in mortality between sexes. It has been proved that women with acute myocardial infarction

were less likely to be treated with guideline directed medical therapy and less likely to receive primary reperfusion therapy including primary percutaneous coronary intervention or fibrinolysis.[30] Regarding medical therapy, numerous studies conducted around the world consistently demonstrate female survivors are receiving less optimal medical therapy after acute myocardial infarction during hospitalization or at discharge.[31 32] Though there might be no differences in treatment adherence between men and women, some studies report significant sex disparities in initiation of appropriate pharmacotherapy after myocardial infarction.[33] Results from these observational studies have shown women are receiving less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme inhibitors in all age groups, especially young women, and suggested that clinicians and patients may benefit from better education and awareness of undertreatment of younger women.[33 34]

Lower rates of revascularization are observed among women with STEMI compared with men in several studies despite proven benefit of this therapy.[35] Moreover, the sex differences might be driven by delays in presentation to hospital and women with STEMI were more likely to experience longer delays than men. Although a great improvement in emergency medical services and timely revascularization over the past decades, recent studies show that women with STEMI still present later and have a longer ischemic time than men. Previous studies have shown consistently that women have longer door-to balloon times and longer door-to needle times.[36 37] In addition, women are also more likely to exhibit longer pre-hospital delays in seeking medical care after the development of

symptoms suggestive of myocardial infarction. Although there have been significant reductions in patient and system delay in the last decade, women continue to have longer presentation and treatment times.[38] Sex differences also exist in clinical presentation of STEMI. Although chest pain was the most common ACS symptom in both sexes, women were more likely to present without chest pain than men.[39 40] Lower rates of typical chest pain reported among women with STEMI may also influence provider decision-making to pursue less aggressive care including invasive revascularization.

Some included studies of our meta-analysis enrolled STEMI patients in general[14-16], while some others enrolled patients undergoing PCI for STEMI[11 13 18]. The different prognosis of patients receiving reperfusion therapy or no-reperfusion therapy might be a potential source of heterogeneity of our study. Nevertheless, our results are completely consistent with a previous meta-analysis from Pancholy et al., which investigated sex differences in mortality among patients with STEMI treated with primary PCI.[2] Its results demonstrated that, when adjusted RRs were used, the increased risk for 1-year mortality in women was no longer significant and the risk of in-hospital mortality still significantly elevated. It should be noted that more than 50% of patients were treated with PCI in the most study conducted among the general STEMI patients and included by our analysis, even more than 90% in some included studies.[12 24] The increasing rate of primary PCI in recent years might be a reason for the consistency of our fundings and previous studies conducted specifically among STEMI patients undergoing PCI

Complications including bleeding, heart failure and mechanical complications are more likely to develop in women with acute myocardial infarction and increase the risk of mortality.[14 41 42] Bleeding secondary to antithrombotic therapies and invasive procedures is more frequent in women.[43] Three included studies reported incidence of bleeding following STEMI and they all found that women were at higher risk of bleeding.[10 13 18] One study included in our analysis examined the relationships among sex, acute heart failure, and related outcomes after STEMI.[14] Its results demonstrate that women are at higher risk to develop de novo heart failure after STEMI and women with de novo heart failure have worse survival compared with man. However, we could not compare the incidence of these complications due to the lack of sufficient data. Mechanical complications requiring surgical intervention are also much more common in women after acute myocardial infarction and associated with high mortality rates.[44]

Several limitations of this meta-analysis should be considered. First, the included studies are all observational studies except one post hoc analysis of randomized controlled trial. Hence, there may be residual confounding bias inherent in the observational study design in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the same confounders and not all studies reported adjusted RRs. The confounders which were adjusted in the included studies might differ greatly across studies. Third, there was substantial heterogeneity in our meta-analysis, which could partly be attributed to the wide variability in the sample sizes, locations, and treatment regimens across included studies. Additionally, although we calculated adjusted RRs for all-cause mortality, it needed to be

noted that relevant confounders might have differed across studies. Fourth, the analysis of long-term mortality, especially the adjusted analysis, included far fewer studies compared with analysis of short-term mortality. Hence, there might be significant bias in the results about long-term mortality.

In conclusion, our meta-analysis, pooling data from contemporary literature, shows that women with STENI have a higher risk of short-term mortality but not long-term mortality. The effect of sex differences on mortality in patients with STEMI remain significant after adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that public awareness of increased risk and further improvements in management in women with STEMI are necessary.

Other Information:

Contribution statement

Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis, Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data acquisition, Data analysis/interpretation. Jianan Li, Yang Li, Jianfeng Zheng and Runlin Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.

Conflict of interest

The authors declare that there is no conflict of interest.

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Ethics approval

The institutional central committee at Fuwai Hospital approved that the study protocol and inform consent was not required for a systematic review and meta-analysis.

Data sharing statement

As this is a systematic review and meta-analysis, the data used in the study have already been published by the authors of the included studies. All data relevant to the study are included in the article or uploaded as supplementary information.

Table 1 Characteristics of included studies.

First Author	Year	Region	Study design	Data source	Multicenter	Time of enrollment	Number of STEMI patients	Female	Endpoint	Follow-up
Venetsanos	2017	13 countries	Prospective	Clinical registry	Yes	Sep, 2011-Oct, 2013	1,862	369 (20.0)	Major adverse cardiovascular events and definite stent thrombosis	30 d
Ali	2018	Germany	Prospective	Administrative database	No	2013-2017	312	101 (32.4)	All-cause in-hospital mortality	NA
Langabeer	2018	US	Prospective	Clinical registry	Yes	Jan, 2010-Dec, 2015	9,674	2,569 (26.6)	In-hospital mortality	NA
Tang	2018	China	Prospective	Administrative database	No	Jan, 2013-Dec, 2013	1,238	210 (1.9)	Major adverse cardiac and cerebrovascular events	730 ± 30 d

Cenko	2019	12 European countries	Prospective	Clinical registry	Yes	Jan, 2010-Jul, 2018	10,443	3,112 (29.8)	30-day all-cause mortality	30 d
Hao	2019	China	Prospective	Clinical registry	Yes	Nov, 2014-Jun, 2018	50,203	11,016 (21,9)	In-hospital mortality	NA
Hannan	2019	US	Retrospective	Administrative database	Yes	Jan, 2013-Dec, 2015	23,809	7,791 (32.7)	In hospital/30-day mortality	30 d
Maznyczka	2019	UK	Retrospective	Clinical registry	No	July, 2011-Nov, 2012	324	87 (26.9)	All-cause death/ first heart failure hospitalization	5 years
Stehli	2019	Australia	Prospective	Clinical registry	Yes	2013-2016	6,431	1,317 (20.5)	In hospital/30-day major adverse events, and major bleeding	30 d
Burgess	2020	Australia	Prospective	Administrativ	No	Dec, 2010-	589	123 (21)	Cardiac death and	2 years

				e database		Apr, 2014			myocardial infarction	
Dharma	2020	Indonesia	Retrospective	Administrative database	No	Feb, 2011-Aug, 2019	6,557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherlands	Retrospective	Administrative database	Yes	2015-2016	787	229 (29)	All-cause mortality	1 year
Siabani	2020	Iran	Prospective	Clinical registry	No	Jun, 2016-May, 2018	1,484	311(21)	In-hospital mortality	NA
Tai	2020	China	Retrospective	Administrative database	No	Jan, 2013-Dec, 2017	182	56 (30.8)	In hospital/1-year mortality	1 year
Tizón	2020	Spain	Prospective	Clinical registry	Yes	2010-2016	14,690	3,486 (23.7)	30-day/1-year all-cause mortality	1 year

Table 2 Baseline characteristics of participants in included studies.

First	**Year**	**Age, mean (SD),**	**Diabete**		**Hypertensio**		**Hyperlipidemi**		**Smokin**		**Prior**		**Prior**	

Author		years		s, n (%)		n, n (%)		a, n (%)		g, n (%)		MI, n (%)		PCI, n (%)	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Venetsanos	2017	69 (13.0)	59 (11.0)	48 (13.0)	205 (13.7)	190 (51.5)	605 (40.5)	117 (31.7)	536 (35.9)	NA	NA	24 (6.5)	135 (9.0)	16 (4.3)	124 (8.3)
Ali	2018	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Langabeer	2018	62.5 (13.6)	60.2 (12.5)	759 (29.6)	1,975 (27.8)	NA	NA	1,265 (49.3)	3,693 (52.0)	951 (37.0)	2,763 (38.9)	435 (16.9)	1,304 (18.4)	NA	NA
Tang	2018	64.5 (9.3)	54.4 (10.7)	66 (31.4)	311 (25.1)	141 (67.1)	659 (53.3)	125 (59.5)	749 (60.3)	33 (15.7)	957 (77.3)	10 (4.8)	83 (6.7)	60 (28.6)	282 (22.8)
Cenko	2019	66.1	59.7	925	1,531	2,322 (74.6)	4,502	1,353 (43.3)	3,100	1,010	3,714	301	842	306	762

		(11.7)	(11.7)	(29.7)	(20.9)		(61.4)		(42.3)	(32.5)	(50.7)	(9.7)	(11.5)	(9.8)	(10.4)
Hao	2019	69.0 (10.6)	61.1 (12.4)	10,141 (48.1)	24,082 (39.4)	15,607 (74.1)	38,426 (62.9)	17,996 (85.4)	50,944 (83.3)	1,719 (8.2)	32,377 (53.0)	NA	NA	NA	NA
Hannan	2019	70.72 (14.73)	62.11 (12.82)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	868 (11.1)	2206 (13.8)
Maznyczka	2019	61.2 (12.2)	58.6(11.2)	8 (9.2)	26 (11.0)	32 (36.8)	73 (30.8)	28 (32.2)	66 (27.8)	57 (65.5)	139 (58.6)	5 (5.7)	20 (8.4)	2 (2.3)	16 (6.8)
Stehli	2019	66.5 (13.2)	60.8 (12.2)	245 (18.6)	770 (15.1)	NA	NA	NA	NA	NA	NA	NA	NA	104 (7.9)	577 (11.3)

Burgess	2020	62.7 (52.7-73.2)	58.2 (50.6-65.7)	39 (31.7)	88 (18.9)	84 (68.3)	243 (52.1)	83 (67.5)	253 (52.3)	64 (52.0)	252 (54.1)	9 (7.3)	41 (8.8)	NA	NA
Dharma	2020	60 (10)	55 (10)	403 (43.4)	1548 (27.5)	647 (69.6)	2,889 (51.3)	299 (32.2)	1,779 (31.6)	109 (11.7)	4,049 (71.9)	NA	NA	NA	NA
Kerkmanx	2020	68 (14)	61 (12)	39 (17.6)	66 (12.5)	101 (45.7)	178 (33.6)	56 (25.9)	110 (21.0)	88 (41.1)	258 (49.3)	30 (13.6)	79 (13.7)	33 (14.4)	77 (14.2)
Siabani	2020	65.8 (11.3)	59.0 (12.4)	114 (37.7)	187 (16.2)	195 (63.7)	410 (35.4)	110 (36.7)	208 (18.5)	41 (13.2)	655 (55.9)	NA	NA	NA	NA
Tai	2020	78 (76–81)	78 (76–80)	96 (35.2)	116 (26.5)	217 (79.5)	319 (72.8)	NA	NA	14 (5.4)	239 (56.5)	NA	NA	36 (13.5)	78 (18.1)

Tizón	2020	69.9 (13.7)	60.9 (12.6)	844 (24.2)	1,927 (17.2)	1,192 (34.2)	2,722 (24.3)	878 (25.2)	2,375 (21.2)	474 (13.6)	2,711 (24.2)	NA	NA	NA	NA

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Figure 1 Flowchart of selection of studies included in meta-analysis.

Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 1 Flowchart of selection of studies included in meta-analysis.

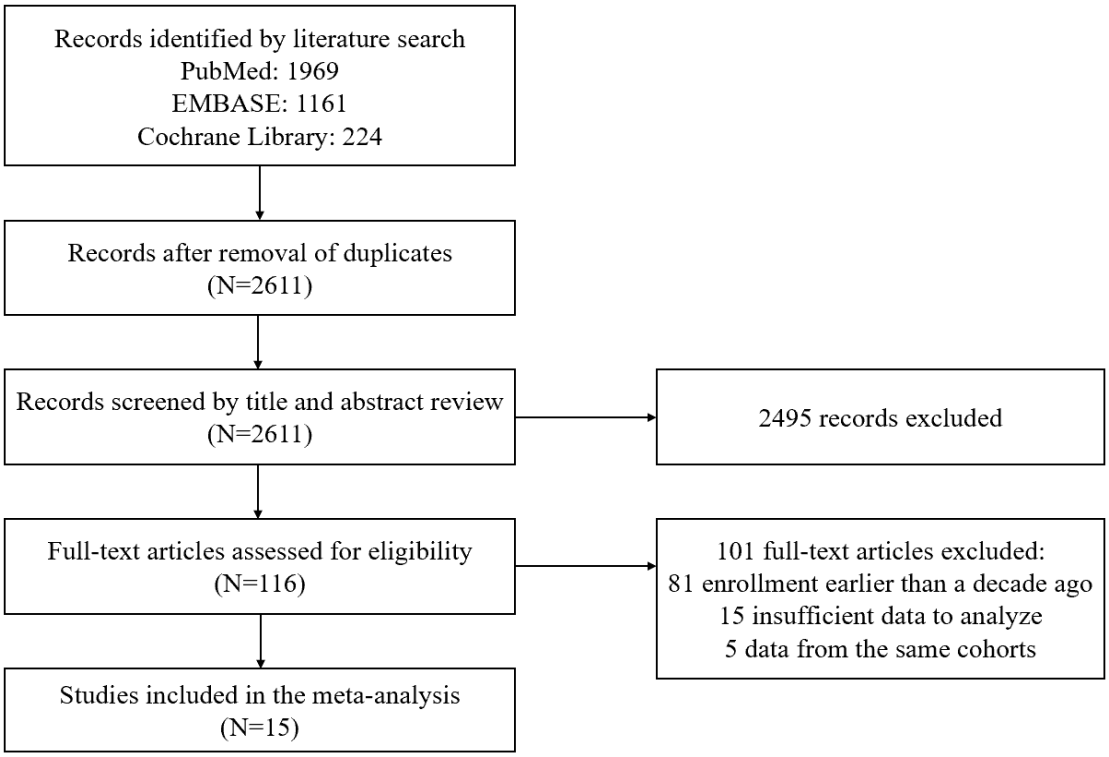
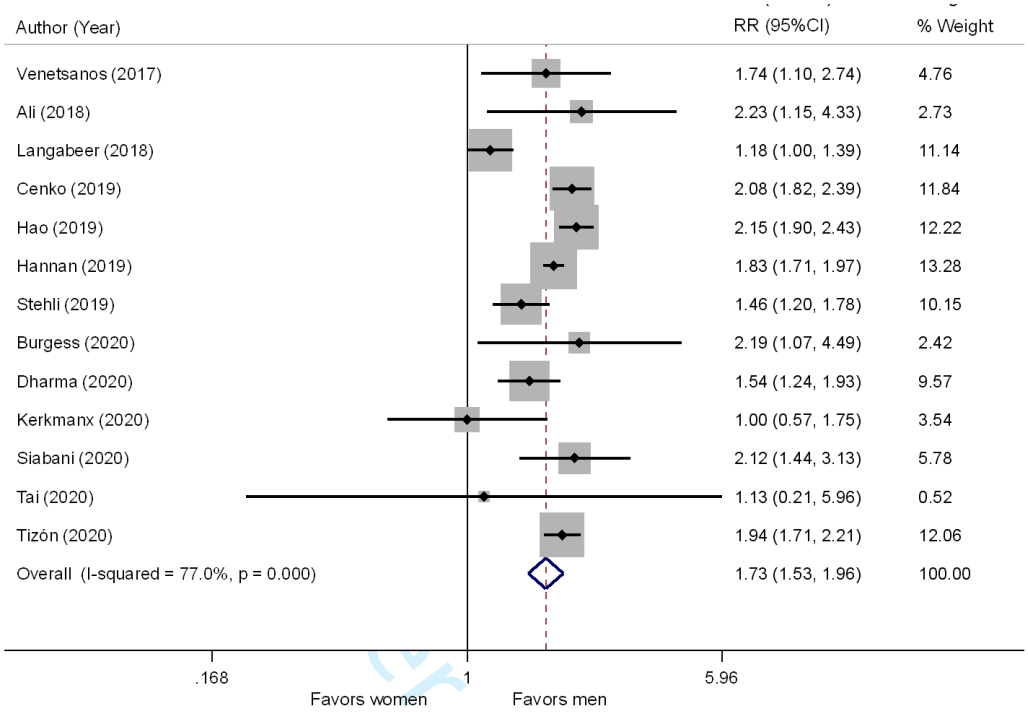
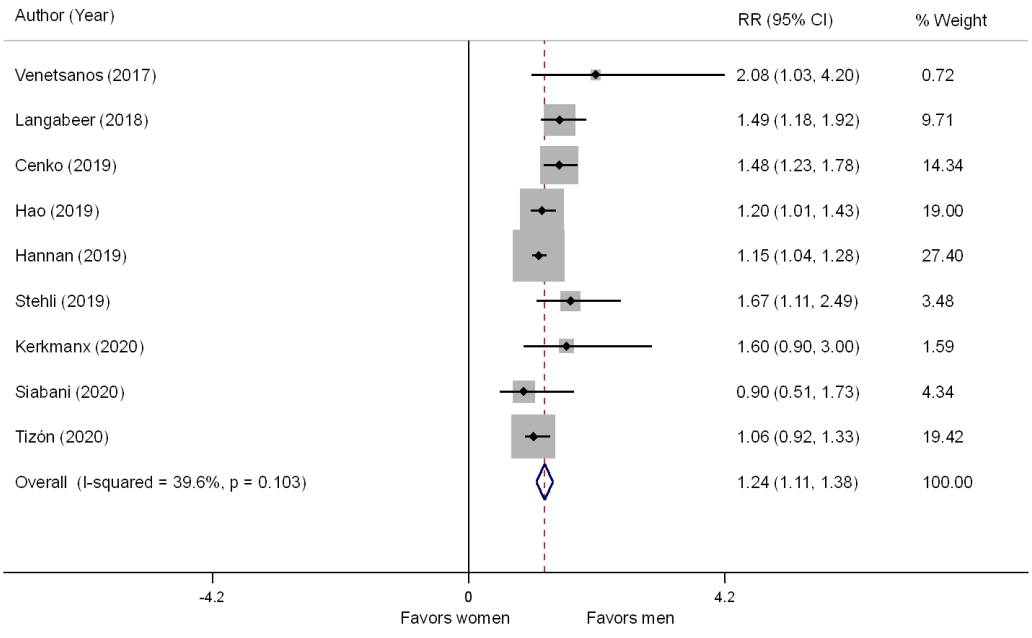


Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



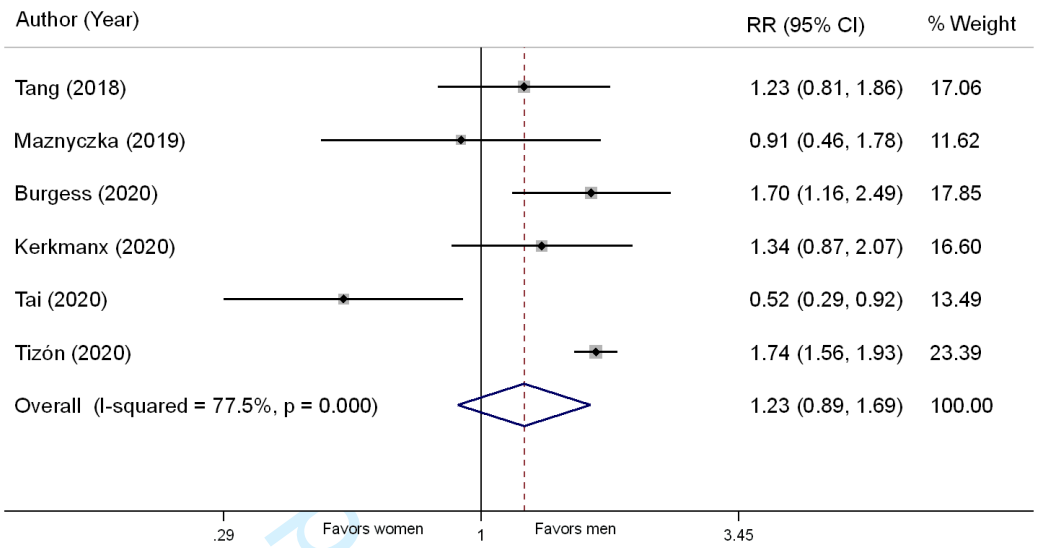
B



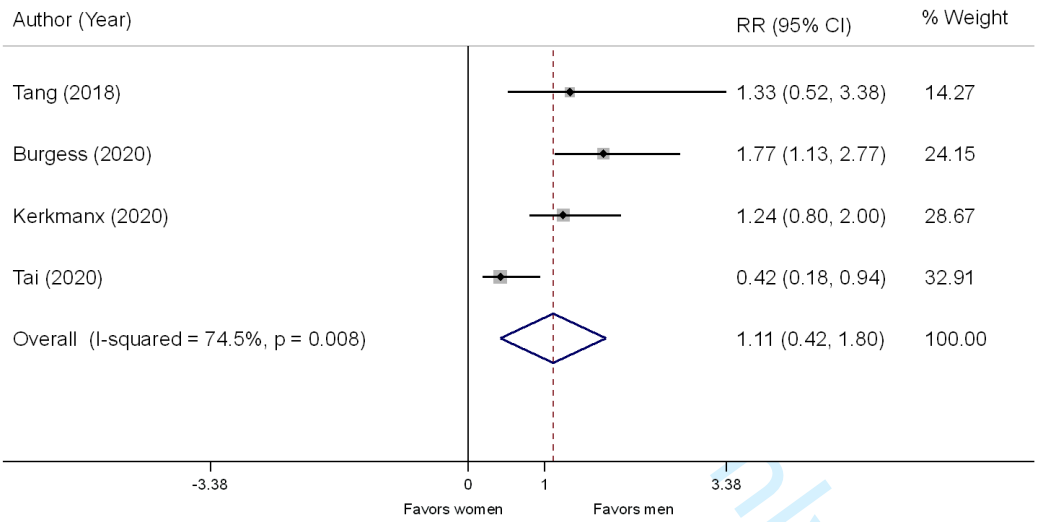
Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



B



Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

eTable 1 Variables adjusted in the adjusted analyses from the included studies.

First Author	Year	Adjusted Variables
Venetsanos	2017	age, weight, prior MI, prior PCI, patient's history of diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-PCI ECG, admission Killip class, baseline hemoglobin, eGFR, access site, use of Glycoprotein IIIb/IIa inhibitor, bivalirudin and unfractionated heparin, location of MI and revascularization
Langabeer	2018	age, smoking, diabetes, prior CVD, prior stroke, heart failure, shock, length of stay, teaching, insurance, total ischemic time, door to balloon
Tang	2018	age, BMI, LVEF, serum creatinine, use of proton pump inhibitors, use of dual-antiplatelet therapy, previous PCI, diabetes mellitus, hypertension, previous stroke, current smoker, thrombocytopenia, use of femoral approach, use of intra-aortic balloon pump, and multivessel disease
Cenko	2019	age, family history of CAD, diabetes, hypertension, hypercholesterolemia, current smoking, former smoking, prior angina pectoris, prior myocardial infarction, prior PCI, prior CABG, peripheral artery disease, prior stroke, ST-segment elevation in anterior leads (at ECG), systolic blood pressure at baseline, heart rate at baseline, serum creatinine at baseline, Killip Class ⩾2
Hao	2019	Age, medical insurance status, acute heart failure, cardiogenic shock, cardiac arrest at admission, heart rate and systolic blood pressure, diabetes mellitus, smoking, history of CHD, heart failure, renal failure, and cerebrovascular disease, prehospital statin use, renal insufficiency, and transfer status.
Hannan	2019	age, STEMI location, heart rate, mean arterial pressure, history

		of hospitalization in last year, history of PCI, history of CABG surgery, septicemia/sepsis/systemic inflammatory response /shock, metastatic cancer/acute leukemia, diabetes with acute complications, end stage liver disease, inflammatory bowel disease, coagulation defects and other specified hematological disorders, dementia, polyneuropathy, muscular dystrophy, seizure disorders and convulsions, coma/brain compression/anoxic damage, cardiorespiratory failure and shock, congestive heart failure, specified heart arrhythmias, ischemic or unspecified stroke, hemiplegia/hemiparesis, vascular disease with complications, vascular disease without complications, aspiration and specified bacterial pneumonias, acute renal failure, chronic kidney disease, Stage 5, unspecified renal failure, nephritis, pressure ulcer of skin with partial thickness skin loss*, pressure pre-ulcer skin changes, chronic ulcer of skin except pressure ulcer, lower limb/amputation complications
Maznyczka	2019	NA
Stehli	2019	age, diabetes mellitus, eGFR, previous PCI and/or coronary artery bypass grafting, history of peripheral vascular disease and CVD, LVEF, out-of-hospital and in-hospital cardiac arrest, cardiogenic shock, and occurrence time of symptom onset
Burgess	2020	NA
Dharma	2020	NA
Kerkmanx	2020	NA
Siabani	2020	BMI⩾25, hypertension, diabetes, current smoking, hypercholesterolemia, congestive heart failure, Killip class (at first presentation) ⩾ II, symptom-to-balloon time> 360 min and door-to-balloon time > 90 min

Tai	2020	NA
Tizón	2020	age, diabetes mellitus, recruitment year, time from symptom onset to culprit coronary artery opening, and Killip class

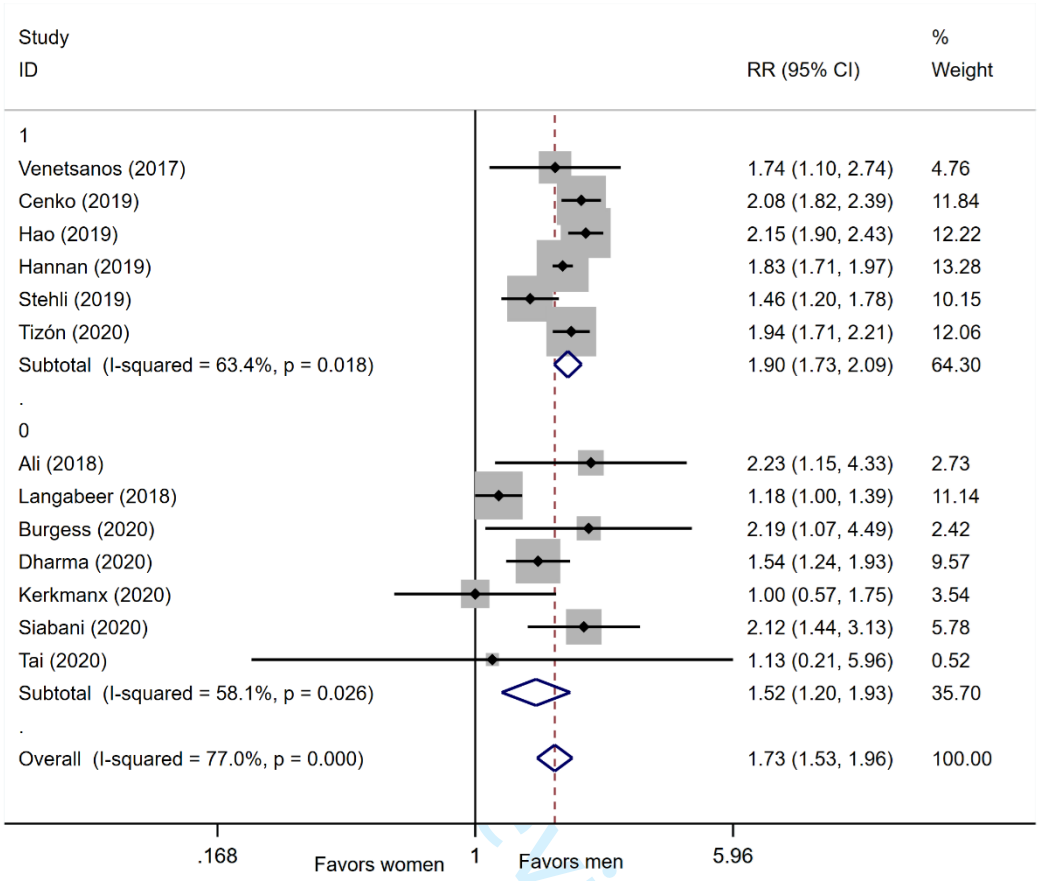
MI: myocardial infarction, PCI: percutaneous coronary intervention, ECG: electrocardiograph, eGFR: estimated glomerular filtration rate, CVD: cardiovascular disease, BMI: body mass index, LVEF: left ventricular ejection fraction, CABG: coronary artery bypass graft, CAD: coronary artery disease,

eTable 2 Assessment of study quality using Newcastle-Ottawa scale.

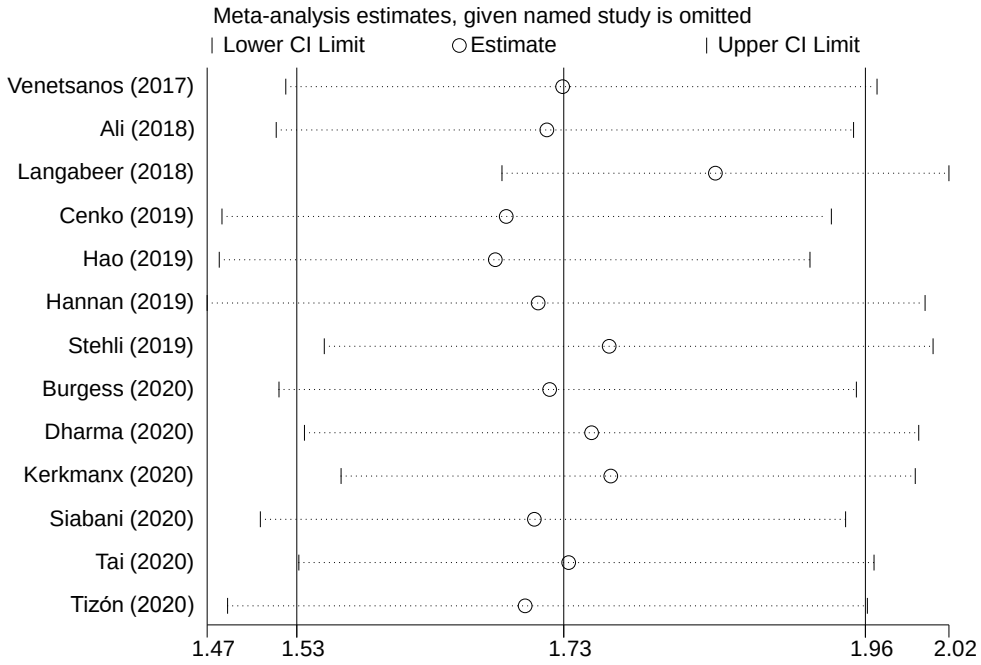
First Author	Year	Selection				Comparability	Outcome			Total points
		Representativeness of the exposed cohor	Selection of the no exposed cohort	Ascertainment of exposure to implants	Outcome of interest not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up	
Venetsanos	2017	*	*	*	*	**	*	\	*	8
Ali	2018	\	\	*	*	\	*	\	*	4
Langabeer	2018	*	*	*	*	*	*	\	*	7
Tang	2018	\	\	*	*	**	*	*	*	7
Cenko	2019	*	*	*	*	**	*	\	*	8
Hao	2019	*	*	*	*	**	*	\	*	8
Hannan	2019	*	*	*	*	**	*	\	*	8
Maznyczka	2019	\	\	*	*	\	*	*	*	5
Stehli	2019	*	*	*	*	**	*	\	*	8

Burgess	2020	\	\	*	*	**	*	*	*	7
Dharma	2020	\	\	*	*	*	*	*	*	6
Kerkmanx	2020	*	*	*	*	\	*	*	*	7
Siabani	2020	\	\	*	*	*	*	\	*	5
Tai	2020	\	\	*	*	**	*	*	*	7
Tizón	2020	*	*	*	*	**	*	*	*	9

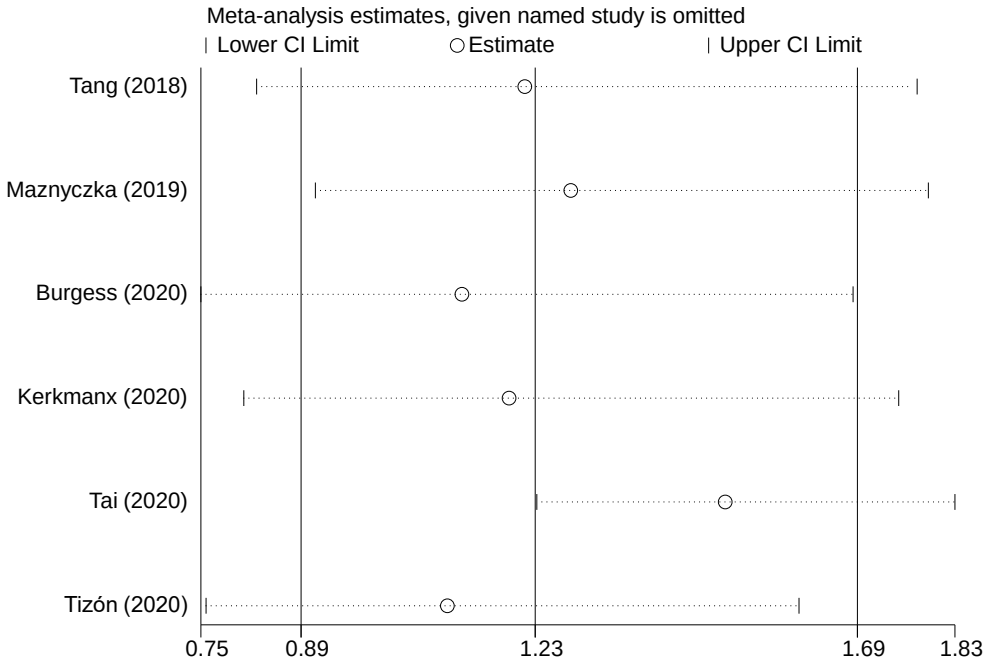
eFigure 1



eFigure 2 Meta-influence analysis for unadjusted short-term mortality

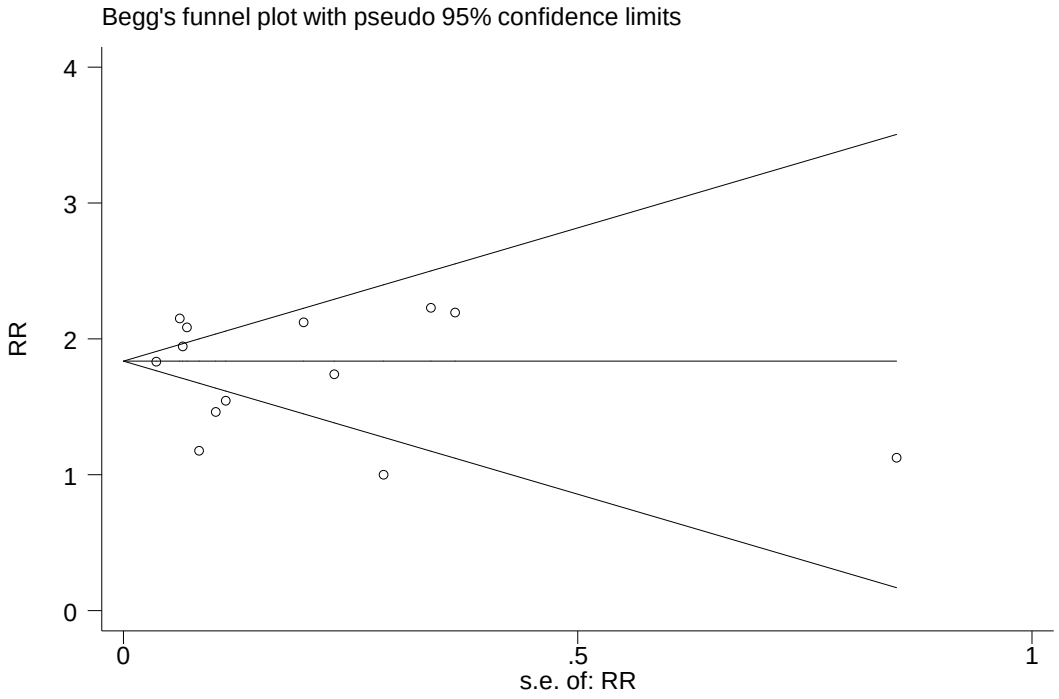


eFigure 3 Meta-influence analysis for unadjusted long-term mortality

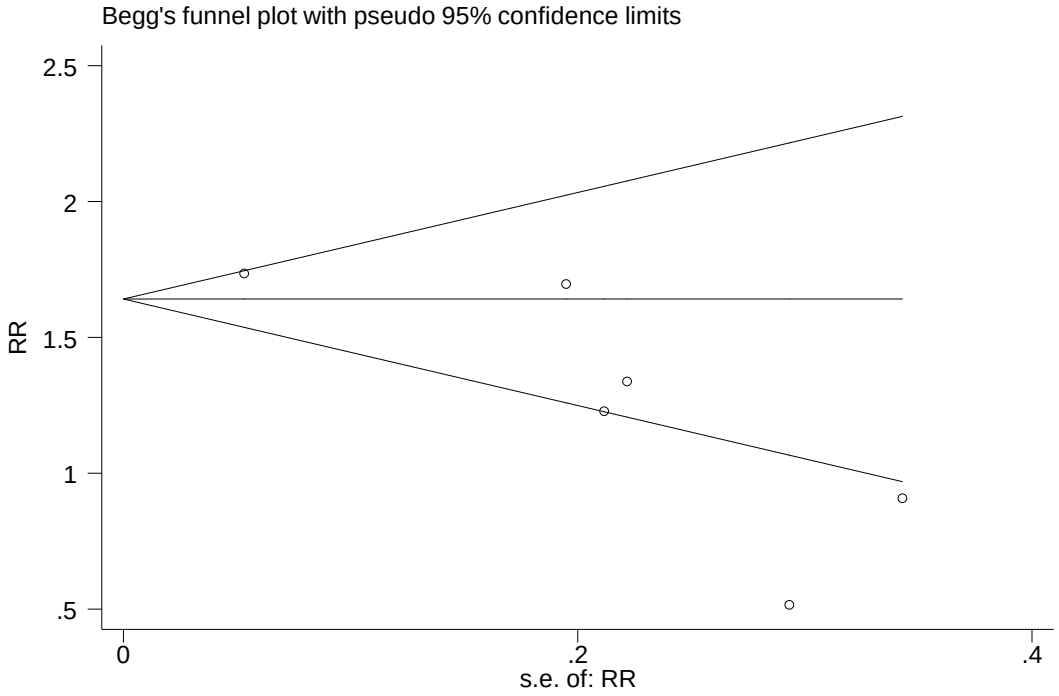


eFigure 4 Funnel plots for publication bias for unadjusted short-term (A) and long-term (B) mortality

A


Begg's funnel plot with pseudo 95% confidence limits
RR
4
3
2
1
0
0
.5
1
s.e. of: RR

B


Begg's funnel plot with pseudo 95% confidence limits
RR
2.5
2
1.5
1
.5
0
.2
.4
s.e. of: RR

Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Short title：Sex differences in STEMI

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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Objectives: To assess the effect of sex differences on short- and long-term mortality among patients with ST-segment elevation myocardial infarction (STEMI).

Design: Systematic review and meta-analysis of contemporary available evidence.

Setting: PubMed, Embase and Cochrane Library were searched for relevant studies reporting sex specific outcomes among patients with STEMI published between January 1, 2010 to August 1, 2020. Risk ratio (RR) 95% 95% confidence intervals (CIs) were measured using DerSimonian and Laird random-effects model. Sensitivity analyses were performed and publication bias was also checked. All statistical analyses were performed using STATA version 15.0.

Participants: Studies providing data about short- or long-term mortality stratified by sex in patients with STEMI were included. Only study conducted in last ten years were included.

Primary and secondary outcome measures: The primary outcome was all-cause death at short-(in-hospital or 30 days) and long-term (at least 12 months) follow-up.

Results

A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879 [75.3%] male) were included. In the unadjusted analyses, female were at a higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) but not long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%). When adjusted effect estimates from individual studies were used in meta-analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%). And adjusted long-term mortality was also similar between female and male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%).

Conclusions

An increased short- but not long-term mortality was found in female with STEMI. After adjustment for baseline cardiovascular risk factors and clinical profiles, short-term mortality remains higher in female with STEMI compared to male, indicating the need for further improvements in management in female patients.

Strengths and limitations of this study

- We assessed the contemporary effect of sex differences on mortality among patients with STEMI by meta-analysis of studies from the last decade.
- A greater number of potentially eligible articles were screened and the large sample size ensures adequate statistical power to detect even a small effect of interest.
- Sensitivity analyses by excluding one study at a time and restricting to studies with high quality or with large sample size got consistent results.
- Substantial and nonnegligible heterogeneity still exist in our meta-analysis and might result in potential bias.
- Residual confounding bias could not be totally excluded due to the observational study design of most included studies.

Contemporary sex differences in short- and long-term mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Introduction

Acute myocardial infarction remains one of leading causes of mortality in both men and women worldwide despite improvement of acute cardiac care.[1] Numerous studies have reported that women have a higher risk of in-hospital and long-term adverse outcomes following ST-segment elevation myocardial infarction (STEMI) compared with men.[2] Confounders including advanced age and more frequent comorbidities, such as hypertension and diabetes mellitus[3 4], might contribute to excess mortality in women. Moreover, previous studies show lower rates of guideline directed medical therapy and revascularization are also associated with poorer prognosis for women with STEMI.[5]

Sex discrepancies in management and outcomes after STEMI have been increasingly reported in the literature and raised public awareness.[6] Major progress in therapy for myocardial infarction and primary and secondary preventive interventions has been made to reduce cardiovascular mortality for women.[1 7] And there have been marked reductions in cardiovascular disease mortality in women with acute myocardial infarction in the past two decades.[1] Conflicting results are noted in recent studies on sex differences following STEMI. It is unclear whether the sex differences still exist, in view of substantial improvements in prognosis of cardiovascular disease over the past decade.

In order to assess the contemporary effect of sex differences on short- and long-term

mortality among patients with STEMI, we performed a systematic review and meta-analysis of all available evidence from last decade reporting sex-specific outcomes after STEMI.

Methods

The present systematic review and meta-analysis was performed following the principle of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

Literature search

We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library from January 1, 2010 to August 1, 2020 to identify studies from the last decade that described sex differences in in short- or long-term mortality among patients with STEMI. Both observational studies and randomized clinical trials were eligible. We queried MeSH and the abstract text for the following three search terms: gender part (including "gender", "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular mortality" or "short term mortality"); myocardial infarction part (including "myocardial infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or

"primary angioplasty") to identify relevant studies. There was no language restriction or age limit.

Study selection

According to the aim of our analyses, studies were included in this systematic review if data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality stratified by sex in patients with STEMI were reported. Two reviewers identified studies eligible for further review by performing an initial screen of titles or abstracts of the search results. Subsequently, a second screen of full texts eligibility was performed by another two reviewers. Studies had to fulfil the following criteria to be included in the present analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and ii) studies providing enough details to obtain numbers of events or incidence rates according to sex; and iii) enrollment starting earlier than a decade ago. Editorials, letters, conference proceedings and abstracts were considered to be eligible only if sufficient information was available in abstracts or associated tables or figures. We excluded studies if they were review articles or case reports, or if they involved pregnant participants, critically ill patients, or provided insufficient data to allow for risk estimates to be calculated. Any disagreement was reviewed by a third reviewer and resolved by consensus.

Data extraction

Detailed data from selected studies were extracted independently by two reviewers using a standardized form independently. Data about study and participants characteristics,

including year of study, sample size, time of enrollment, geographical location, endpoints of study, and follow-up duration, were collected. Any discrepancies were reviewed by a third reviewer and resolved by consensus. The quality of included studies was evaluated by Newcastle-Ottawa scale using prespecified items comprised of patients' selection (representativeness and selection of patients, ascertainment of exposure), comparability of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy of follow-up).[9] A quality score (0–9 points) was generated according to a maximum of 1 point for each item.

Patient and public involvement

Due to the nature of the systematic review and meta-analysis, this study did not involve patients and the public in the design, or conduct, or reporting or dissemination plans.

Statistical analysis

The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent the effect of sex differences on mortality after STEMI. And data were combined using random-effects model of DerSimonian and Laird with inverse variance weighting. Random-effect model was used due to substantial clinical and statistical heterogeneity. Following analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality using raw number of death and total participants at risk for death specific to each sex, ii) adjusted RRs for short- and long-term all-cause mortality using adjusted RRs if they were described in those included studies.

We assess heterogeneity across studies with Cochran's Q test and I2 test, with P<0.1 or I2 >50% considered significant. We also performed meta-regression to identify the potential sources of heterogeneity in the included studies. Furthermore, stratified analysis was conducted as well by dividing the included studies into different subgroups based on the Newcastle-Ottawa scale scores (>7 points or ≤7 points) to assess the potential sources of heterogeneity. To assess the potential effect of publication bias, we inspected funnel plots for asymmetry and used the Egger's regression asymmetry test in which P<0.05 was considered to indicate significant publication bias.

Sensitivity analyses was conducted by excluding one study at a time and comparing the results with the complete one. In addition, we also performed sensitivity analyses by restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and restricting to studies with sample size bigger than 1000 participants. All statistical analyses were performed using STATA version 15.0 (Stata Corp, College Station, TX). Differences were considered statistically significant at P < .05 (2-sided).

Results

Literature search

Study selection details were outlined in Figure 1. The literature search identified 2,611 potentially relevant articles. After screening based on title and abstract review, 2495 records were excluded. A total of 116 full-text were finally assessed for eligibility, with 96 papers excluded due to enrollment starting earlier than a decade ago or no sufficient

gender specific data to analyze. Another 5 papers reviewed in detail were excluded after due to data from the same cohorts. A total of 15 studies were finally included in the present systematic review and meta-analysis.[10-24]

Study characteristics

Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than 10,000 patients with STEMI. See Table 1 for further information of included studies. Baseline characteristics of participants were missing in some included studies, but all included studies provided sufficient data for analysis of sex differences in clinical outcomes. Except for 1 study, which was a prespecified gender analysis of randomized controlled trial, the remaining 14 were observational studies. Among the 10 included studies which reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension, and prior myocardial infarction/PCI, while some adjusted for renal insufficiency, cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset. Variables that were adjusted in the adjusted analyses from the included studies were presented in eTable 1 of the Supplementary Material. Results of assessment of study quality using Newcastle-Ottawa scale were shown in eTable 2 in the Supplementary Material.

Patient characteristics

A total of 128,585 patients with STEMI (31,706 [24.7%] female and 96,879 [75.3%] male) were involved in the 15 included studies. Female tended to be older and had higher

prevalence of diabetes mellitus in all included studies. And in most studies, other important comorbidities, including hypertension and hyperlipidemia, were more frequent in female. Greater proportions of male were smokers and had prior PCI or myocardial infarction. Besides, some studies reported that door-to-balloon time and symptom onset to balloon time were longer in female than male. Part of patient baseline characteristics were summarized in Table 2.

Short-term all-cause mortality

Thirteen studies reported sex-specific unadjusted short-term mortality of patients with STEMI. There were 2,873 of 31,409 (9.1%) cases of all-cause mortality in female compared with 4,380 of 95,610 (4.6%) in male. Female were at a significantly higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) compared with male (Figure 2 A). Nine studies involving 119,379 patients reported adjusted short-term mortality specific to sex. In adjusted analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%) (Figure 2 B). However, the strength of association calculated with adjusted RRs from these 9 studies was attenuated. Subgroup analysis demonstrated that the results of studies with Newcastle-Ottawa scale >7 points (RR, 1.90; 95%CI, 1.73-2.09, P=0.018, I2=63.4%) and studies with ≤7 points (RR, 1.52; 95%CI, 1.20-1.93, P=0.026, I2=58.1%) were consistent in unadjusted short-term mortality (See eFigure 1 in the Supplementary Material).

Long-term all-cause mortality

Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and followed up for more than 1 year, and reported all-cause mortality for female and male. The incidence of long-term all-cause mortality was 13.9% (n=584) in female and 8.7% (n=1202) in male. In unadjusted analysis, no significant sex difference was found in long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%) (Figure 3 A). And the adjusted analysis of the pooled results from four studies, also showed a similar risk of mortality at long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%) (Figure 3 B).

Meta-Regression Analysis, sensitivity analyses and publication bias

According to meta-regression analysis, differences in prevalence of diabetes (β coefficient, 0.248; P=0.337), hypertension (β coefficient, -0.255; P=0.538), hyperlipidemia(β coefficient, 0.260; P=0.415), smoking (β coefficient, -0.040; P=0.255), prior MI (β coefficient, -2.725; P=0.126), and prior PCI (β coefficient, 0.109; P=0.896) between sexes were not identified as significant sources of heterogeneity for short-term all-cause mortality. Given that not all included study provided information on confounders stratified by sex, the results of meta-regression analyses should be interpreted with caution.

Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75; 95%CI, 1.54-1.99, P<.001, I^2=82.9%) both indicated that none of the studies affected the results of short-term mortality in this meta-analysis significantly. In analysis for long-term mortality, sensitivity analysis showed a possibly higher influence on the result attribute to

the study of Tai et al (See eFigure 3 in the Supplementary Material). After removing this study from meta-analysis, the association of female with increased long-term mortality became significant (RR, 1.50; 95%CI, 1.23-1.83, P=0.148, I^2=40.9%). We found no evidence of publication bias across studies based on visual inspection of funnel plots (See eFigure 4 in the Supplementary Material) and the results from Egger's tests for short-term mortality (P=0.462) and for long-term mortality (P=0.053).

Discussion:

Our systematic review and meta-analysis of contemporary literature on sex differences among patients with STEMI demonstrate that female have a higher risk of short- but not long-term mortality compared with male with STEMI. Furthermore, after adjustment for baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term mortality are attenuated but remain significant, while female have the similar long-term mortality with male.

Our results are somewhat in accordance with several previously published meta-analysis.[2] [25] A considerable number of studies have consistently suggested that women were at a higher risk of short-term mortality after ACS. However, whether risk of long-term mortality is also higher in women with ACS remains under debate. Some studies indicated that women with STEMI had a higher 1-year rate of death compared to men[26], while the 1-year mortality rate was conversely lower in women than men in some other studies[23] [24]. In our

study, with respect to short-term mortality, the analyses of studies with high or low quality, and big or small sample size yielded similar results. However, in terms of long-term mortality, caution is needed when interpreting our finding of non-significant increased long-term mortality in adjusted analyses, due to the results of sensitivity analysis which showed a significant association between female and increased long-term mortality after removing one study from adjusted analyses.

It is widely accepted that there are significant differences in outcomes of women and men with acute myocardial infarction. In our study, after adjusted for participants' baseline cardiovascular risk factors and clinical profiles, the strength of association between gender and short-term mortality was substantially attenuated, which suggested that poorer baseline cardiovascular risk profile partially explained the impact of sex differences on mortality. Multiple studies have shown that women with STEMI present at older age and have a higher burden of comorbidities, contributing to the sex differences in mortality after STEMI.[27] All studies included in our meta-analysis demonstrate that female patients are older and with more diabetes mellitus as well as hypertension. In addition, some sex-specific studies found that certain risk factors and comorbidities were more potent in women.[28] Diabetes mellitus , hypertension and smoking status are more strongly associated with increased risk of cardiac events in women compared with men.[27 29]

Notably, that these differences mentioned above still could not completely explain the gap in mortality between sexes. It has been proved that women with acute myocardial infarction

were less likely to be treated with guideline directed medical therapy and less likely to receive primary reperfusion therapy including primary percutaneous coronary intervention or fibrinolysis.[30] Regarding medical therapy, numerous studies conducted around the world consistently demonstrate female survivors are receiving less optimal medical therapy after acute myocardial infarction during hospitalization or at discharge.[31 32] Though there might be no differences in treatment adherence between men and women, some studies report significant sex disparities in initiation of appropriate pharmacotherapy after myocardial infarction.[33] Results from these observational studies have shown women are receiving less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme inhibitors in all age groups, especially young women, and suggested that clinicians and patients may benefit from better education and awareness of undertreatment of younger women.[33 34]

Lower rates of revascularization are observed among women with STEMI compared with men in several studies despite proven benefit of this therapy.[35] Moreover, the sex differences might be driven by delays in presentation to hospital and women with STEMI were more likely to experience longer delays than men. Although a great improvement in emergency medical services and timely revascularization over the past decades, recent studies show that women with STEMI still present later and have a longer ischemic time than men. Previous studies have shown consistently that women have longer door-to balloon times and longer door-to needle times.[36 37] In addition, women are also more likely to exhibit longer pre-hospital delays in seeking medical care after the development of

symptoms suggestive of myocardial infarction. Although there have been significant reductions in patient and system delay in the last decade, women continue to have longer presentation and treatment times.[38] Sex differences also exist in clinical presentation of STEMI. Although chest pain was the most common ACS symptom in both sexes, women were more likely to present without chest pain than men.[39 40] Lower rates of typical chest pain reported among women with STEMI may also influence provider decision-making to pursue less aggressive care including invasive revascularization.

Some included studies of our meta-analysis enrolled STEMI patients in general[14-16], while some others enrolled patients undergoing PCI for STEMI[11 13 18]. The different prognosis of patients receiving reperfusion therapy or no-reperfusion therapy might be a potential source of heterogeneity of our study. Nevertheless, our results are completely consistent with a previous meta-analysis from Pancholy et al., which investigated sex differences in mortality among patients with STEMI treated with primary PCI.[2] Its results demonstrated that, when adjusted RRs were used, the increased risk for 1-year mortality in women was no longer significant and the risk of in-hospital mortality still significantly elevated. It should be noted that more than 50% of patients were treated with PCI in the most study conducted among the general STEMI patients and included by our analysis, even more than 90% in some included studies.[12 24] The increasing rate of primary PCI in recent years might be a reason for the consistency of our fundings and previous studies conducted specifically among STEMI patients undergoing PCI

Complications including bleeding, heart failure and mechanical complications are more likely to develop in women with acute myocardial infarction and increase the risk of mortality.[14 41 42] Bleeding secondary to antithrombotic therapies and invasive procedures is more frequent in women.[43] Three included studies reported incidence of bleeding following STEMI and they all found that women were at higher risk of bleeding.[10 13 18] One study included in our analysis examined the relationships among sex, acute heart failure, and related outcomes after STEMI.[14] Its results demonstrate that women are at higher risk to develop de novo heart failure after STEMI and women with de novo heart failure have worse survival compared with man. However, we could not compare the incidence of these complications due to the lack of sufficient data. Mechanical complications requiring surgical intervention are also much more common in women after acute myocardial infarction and associated with high mortality rates.[44]

Several limitations of this meta-analysis should be considered. First, the included studies are all observational studies except one post hoc analysis of randomized controlled trial. Hence, there may be residual confounding bias inherent in the observational study design in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the same confounders and not all studies reported adjusted RRs. The confounders which were adjusted in the included studies might differ greatly across studies. Third, there was substantial heterogeneity in our meta-analysis, which could partly be attributed to the wide variability in the sample sizes, locations, and treatment regimens across included studies. Additionally, although we calculated adjusted RRs for all-cause mortality, it needed to be

noted that relevant confounders might have differed across studies. Fourth, the analysis of long-term mortality, especially the adjusted analysis, included far fewer studies compared with analysis of short-term mortality. Hence, there might be significant bias in the results about long-term mortality.

In conclusion, our meta-analysis, pooling data from contemporary literature, shows that women with STENI have a higher risk of short-term mortality but not long-term mortality. The effect of sex differences on mortality in patients with STEMI remain significant after adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that public awareness of increased risk and further improvements in management in women with STEMI are necessary.

Other Information:

Contribution statement

Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis, Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data acquisition, Data analysis/interpretation. Jianan Li, Yang Li, Jianfeng Zheng and Runlin Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.

Conflict of interest

The authors declare that there is no conflict of interest.

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Ethics approval

The institutional central committee at Fuwai Hospital approved that the study protocol and inform consent was not required for a systematic review and meta-analysis.

Data sharing statement

As this is a systematic review and meta-analysis, the data used in the study have already been published by the authors of the included studies. All data relevant to the study are included in the article or uploaded as supplementary information.

Table 1 Characteristics of included studies.

First Author	Year	Region	Study design	Data source	Multicenter	Time of enrollment	Number of STEMI patients	Female	Endpoint	Follow-up
Venetsanos	2017	13 countries	Prospective	Clinical registry	Yes	Sep, 2011-Oct, 2013	1,862	369 (20.0)	Major adverse cardiovascular events and definite stent thrombosis	30 d
Ali	2018	Germany	Prospective	Administrative database	No	2013-2017	312	101 (32.4)	All-cause in-hospital mortality	NA
Langabeer	2018	US	Prospective	Clinical registry	Yes	Jan, 2010-Dec, 2015	9,674	2,569 (26.6)	In-hospital mortality	NA
Tang	2018	China	Prospective	Administrative database	No	Jan, 2013-Dec, 2013	1,238	210 (1.9)	Major adverse cardiac and cerebrovascular events	730 ± 30 d

Cenko	2019	12 European countries	Prospective	Clinical registry	Yes	Jan, 2010-Jul, 2018	10,443	3,112 (29.8)	30-day all-cause mortality	30 d
Hao	2019	China	Prospective	Clinical registry	Yes	Nov, 2014-Jun, 2018	50,203	11,016 (21,9)	In-hospital mortality	NA
Hannan	2019	US	Retrospective	Administrative database	Yes	Jan, 2013-Dec, 2015	23,809	7,791 (32.7)	In hospital/30-day mortality	30 d
Maznyczka	2019	UK	Retrospective	Clinical registry	No	July, 2011-Nov, 2012	324	87 (26.9)	All-cause death/ first heart failure hospitalization	5 years
Stehli	2019	Australia	Prospective	Clinical registry	Yes	2013-2016	6,431	1,317 (20.5)	In hospital/30-day major adverse events, and major bleeding	30 d
Burgess	2020	Australia	Prospective	Administrativ	No	Dec, 2010-	589	123 (21)	Cardiac death and	2 years

				e database		Apr, 2014			myocardial infarction	
Dharma	2020	Indonesia	Retrospective	Administrative database	No	Feb, 2011-Aug, 2019	6,557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherlands	Retrospective	Administrative database	Yes	2015-2016	787	229 (29)	All-cause mortality	1 year
Siabani	2020	Iran	Prospective	Clinical registry	No	Jun, 2016-May, 2018	1,484	311(21)	In-hospital mortality	NA
Tai	2020	China	Retrospective	Administrative database	No	Jan, 2013-Dec, 2017	182	56 (30.8)	In hospital/1-year mortality	1 year
Tizón	2020	Spain	Prospective	Clinical registry	Yes	2010-2016	14,690	3,486 (23.7)	30-day/1-year all-cause mortality	1 year

Table 2 Baseline characteristics of participants in included studies.

First	**Year**	**Age, mean (SD),**	**Diabete**		**Hypertensio**		**Hyperlipidemi**		**Smokin**		**Prior**		**Prior**	

Author		years		s, n (%)		n, n (%)		a, n (%)		g, n (%)		MI, n (%)		PCI, n (%)	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Venetsanos	2017	69 (13.0)	59 (11.0)	48 (13.0)	205 (13.7)	190 (51.5)	605 (40.5)	117 (31.7)	536 (35.9)	NA	NA	24 (6.5)	135 (9.0)	16 (4.3)	124 (8.3)
Ali	2018	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Langabeer	2018	62.5 (13.6)	60.2 (12.5)	759 (29.6)	1,975 (27.8)	NA	NA	1,265 (49.3)	3,693 (52.0)	951 (37.0)	2,763 (38.9)	435 (16.9)	1,304 (18.4)	NA	NA
Tang	2018	64.5 (9.3)	54.4 (10.7)	66 (31.4)	311 (25.1)	141 (67.1)	659 (53.3)	125 (59.5)	749 (60.3)	33 (15.7)	957 (77.3)	10 (4.8)	83 (6.7)	60 (28.6)	282 (22.8)
Cenko	2019	66.1	59.7	925	1,531	2,322 (74.6)	4,502	1,353 (43.3)	3,100	1,010	3,714	301	842	306	762

		(11.7)	(11.7)	(29.7)	(20.9)		(61.4)		(42.3)	(32.5)	(50.7)	(9.7)	(11.5)	(9.8)	(10.4)
Hao	2019	69.0 (10.6)	61.1 (12.4)	10,141 (48.1)	24,082 (39.4)	15,607 (74.1)	38,426 (62.9)	17,996 (85.4)	50,944 (83.3)	1,719 (8.2)	32,377 (53.0)	NA	NA	NA	NA
Hannan	2019	70.72 (14.73)	62.11 (12.82)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	868 (11.1)	2206 (13.8)
Maznyczka	2019	61.2 (12.2)	58.6(11.2)	8 (9.2)	26 (11.0)	32 (36.8)	73 (30.8)	28 (32.2)	66 (27.8)	57 (65.5)	139 (58.6)	5 (5.7)	20 (8.4)	2 (2.3)	16 (6.8)
Stehli	2019	66.5 (13.2)	60.8 (12.2)	245 (18.6)	770 (15.1)	NA	NA	NA	NA	NA	NA	NA	NA	104 (7.9)	577 (11.3)

Burgess	2020	62.7 (52.7-73.2)	58.2 (50.6-65.7)	39 (31.7)	88 (18.9)	84 (68.3)	243 (52.1)	83 (67.5)	253 (52.3)	64 (52.0)	252 (54.1)	9 (7.3)	41 (8.8)	NA	NA
Dharma	2020	60 (10)	55 (10)	403 (43.4)	1548 (27.5)	647 (69.6)	2,889 (51.3)	299 (32.2)	1,779 (31.6)	109 (11.7)	4,049 (71.9)	NA	NA	NA	NA
Kerkmanx	2020	68 (14)	61 (12)	39 (17.6)	66 (12.5)	101 (45.7)	178 (33.6)	56 (25.9)	110 (21.0)	88 (41.1)	258 (49.3)	30 (13.6)	79 (13.7)	33 (14.4)	77 (14.2)
Siabani	2020	65.8 (11.3)	59.0 (12.4)	114 (37.7)	187 (16.2)	195 (63.7)	410 (35.4)	110 (36.7)	208 (18.5)	41 (13.2)	655 (55.9)	NA	NA	NA	NA
Tai	2020	78 (76–81)	78 (76–80)	96 (35.2)	116 (26.5)	217 (79.5)	319 (72.8)	NA	NA	14 (5.4)	239 (56.5)	NA	NA	36 (13.5)	78 (18.1)

Tizón	2020	69.9 (13.7)	60.9 (12.6)	844 (24.2)	1,927 (17.2)	1,192 (34.2)	2,722 (24.3)	878 (25.2)	2,375 (21.2)	474 (13.6)	2,711 (24.2)	NA	NA	NA	NA

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Figure 1 Flowchart of selection of studies included in meta-analysis.

Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
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 record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
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 each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	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.	Page 5
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.	Page 5
Synthesis methods	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)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
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 in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 7
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.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 6
	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.	Page 6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 7
	23b	Discuss any limitations of the evidence included in the review.	Page 8-9
	23c	Discuss any limitations of the review processes used.	Page 8-9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 7-8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
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 included studies; data used for all analyses; analytic code; any other materials used in the review.	

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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Short title：Sex differences in STEMI

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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Objectives: To assess the effect of sex differences on short- and long-term mortality among patients with ST-segment elevation myocardial infarction (STEMI).

Design: Systematic review and meta-analysis of contemporary available evidence.

Setting: PubMed, Embase and Cochrane Library were searched for relevant studies reporting sex specific outcomes among patients with STEMI published between January 1, 2010 to August 1, 2020. Risk ratio (RR) 95% 95% confidence intervals (CIs) were measured using DerSimonian and Laird random-effects model. Sensitivity analyses were performed and publication bias was also checked. All statistical analyses were performed using STATA version 15.0.

Participants: Studies providing data about short- or long-term mortality stratified by sex in patients with STEMI were included. Only study conducted in last ten years were included.

Primary and secondary outcome measures: The primary outcome was all-cause death at short-(in-hospital or 30 days) and long-term (at least 12 months) follow-up.

Results

A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879 [75.3%] male) were included. In the unadjusted analyses, female were at a higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) but not long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%). When adjusted effect estimates from individual studies were used in meta-analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%). And adjusted long-term mortality was also similar between female and male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%).

Conclusions

An increased short- but not long-term mortality was found in female with STEMI. After adjustment for baseline cardiovascular risk factors and clinical profiles, short-term mortality remains higher in female with STEMI compared to male, indicating the need for further improvements in management in female patients.

Strengths and limitations of this study

- We assessed the contemporary effect of sex differences on mortality among patients with STEMI by meta-analysis of studies from the last decade.
- A greater number of potentially eligible articles were screened and the large sample size ensures adequate statistical power to detect even a small effect of interest.
- Sensitivity analyses by excluding one study at a time and restricting to studies with high quality or with large sample size got consistent results.
- Substantial and nonnegligible heterogeneity still exist in our meta-analysis and might result in potential bias.
- Residual confounding bias could not be totally excluded due to the observational study design of most included studies.

Contemporary sex differences in short- and long-term mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Introduction

Acute myocardial infarction remains one of leading causes of mortality in both men and women worldwide despite improvement of acute cardiac care.[1] Numerous studies have reported that women have a higher risk of in-hospital and long-term adverse outcomes following ST-segment elevation myocardial infarction (STEMI) compared with men.[2] Confounders including advanced age and more frequent comorbidities, such as hypertension and diabetes mellitus[3 4], might contribute to excess mortality in women. Moreover, previous studies show lower rates of guideline directed medical therapy and revascularization are also associated with poorer prognosis for women with STEMI.[5]

Sex discrepancies in management and outcomes after STEMI have been increasingly reported in the literature and raised public awareness.[6] Major progress in therapy for myocardial infarction and primary and secondary preventive interventions has been made to reduce cardiovascular mortality for women.[1 7] And there have been marked reductions in cardiovascular disease mortality in women with acute myocardial infarction in the past two decades.[1] Conflicting results are noted in recent studies on sex differences following STEMI. It is unclear whether the sex differences still exist, in view of substantial improvements in prognosis of cardiovascular disease over the past decade.

In order to assess the contemporary effect of sex differences on short- and long-term

mortality among patients with STEMI, we performed a systematic review and meta-analysis of all available evidence from last decade reporting sex-specific outcomes after STEMI.

Methods

The present systematic review and meta-analysis was performed following the principle of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

Literature search

We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library from January 1, 2010 to August 1, 2020 to identify studies from the last decade that described sex differences in in short- or long-term mortality among patients with STEMI. Both observational studies and randomized clinical trials were eligible. We queried MeSH and the abstract text for the following three search terms: gender part (including "gender", "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular mortality" or "short term mortality"); myocardial infarction part (including "myocardial infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or

"primary angioplasty") to identify relevant studies. There was no language restriction or age limit.

Study selection

According to the aim of our analyses, studies were included in this systematic review if data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality stratified by sex in patients with STEMI were reported. Two reviewers identified studies eligible for further review by performing an initial screen of titles or abstracts of the search results. Subsequently, a second screen of full texts eligibility was performed by another two reviewers. Studies had to fulfil the following criteria to be included in the present analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and ii) studies providing enough details to obtain numbers of events or incidence rates according to sex; and iii) enrollment starting earlier than a decade ago. Editorials, letters, conference proceedings and abstracts were considered to be eligible only if sufficient information was available in abstracts or associated tables or figures. We excluded studies if they were review articles or case reports, or if they involved pregnant participants, critically ill patients, or provided insufficient data to allow for risk estimates to be calculated. Any disagreement was reviewed by a third reviewer and resolved by consensus.

Data extraction

Detailed data from selected studies were extracted independently by two reviewers using a standardized form independently. Data about study and participants characteristics,

including year of study, sample size, time of enrollment, geographical location, endpoints of study, and follow-up duration, were collected. Any discrepancies were reviewed by a third reviewer and resolved by consensus. The quality of included studies was evaluated by Newcastle-Ottawa scale using prespecified items comprised of patients' selection (representativeness and selection of patients, ascertainment of exposure), comparability of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy of follow-up).[9] A quality score (0–9 points) was generated according to a maximum of 1 point for each item.

Patient and public involvement

Due to the nature of the systematic review and meta-analysis, this study did not involve patients and the public in the design, or conduct, or reporting or dissemination plans.

Statistical analysis

The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent the effect of sex differences on mortality after STEMI. And data were combined using random-effects model of DerSimonian and Laird with inverse variance weighting. Random-effect model was used due to substantial clinical and statistical heterogeneity. Following analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality using raw number of death and total participants at risk for death specific to each sex, ii) adjusted RRs for short- and long-term all-cause mortality using adjusted RRs if they were described in those included studies. In terms of short-term mortality, the RRs for in-hospital

and 30-day mortality were also calculated respectively.

We assess heterogeneity across studies with Cochran's Q test and I2 test, with P<0.1 or I2 >50% considered significant. We also performed meta-regression to identify the potential sources of heterogeneity in the included studies. The potential sources were differences in diabetes, hypertension, hyperlipidemia, smoking, prior MI, and prior PCI. Furthermore, stratified analysis was conducted as well by dividing the included studies into different subgroups based on the Newcastle-Ottawa scale scores (>7 points or ≤7 points) to assess the potential sources of heterogeneity. To assess the potential effect of publication bias, we inspected funnel plots for asymmetry and used the Egger's regression asymmetry test in which P<0.05 was considered to indicate significant publication bias. Sensitivity analyses was conducted by excluding one study at a time and comparing the results with the complete one. In addition, we also performed sensitivity analyses by restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and restricting to studies with sample size bigger than 1000 participants. All statistical analyses were performed using STATA version 15.0 (Stata Corp, College Station, TX). Differences were considered statistically significant at P < .05 (2-sided).

Results

Literature search

Study selection details were outlined in Figure 1. The literature search identified 2,611 potentially relevant articles. After screening based on title and abstract review, 2495

records were excluded. A total of 116 full-text were finally assessed for eligibility, with 96 papers excluded due to enrollment starting earlier than a decade ago or no sufficient gender specific data to analyze. Another 5 papers reviewed in detail were excluded after due to data from the same cohorts. A total of 15 studies were finally included in the present systematic review and meta-analysis.[10-24]

Study characteristics

Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than 10,000 patients with STEMI. See Table 1 for further information of included studies. Baseline characteristics of participants were missing in some included studies, but all included studies provided sufficient data for analysis of sex differences in clinical outcomes. Except for 1 study, which was a prespecified gender analysis of randomized controlled trial, the remaining 14 were observational studies. Among the 10 included studies which reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension, and prior myocardial infarction/PCI, while some adjusted for renal insufficiency, cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset. Variables that were adjusted in the adjusted analyses from the included studies were presented in eTable 1 of the Supplementary Material. Results of assessment of study quality using Newcastle-Ottawa scale were shown in eTable 2 in the Supplementary Material.

Patient characteristics

A total of 128,585 patients with STEMI (31,706 [24.7%] female and 96,879 [75.3%] male) were involved in the 15 included studies. Female tended to be older and had higher prevalence of diabetes mellitus in all included studies. And in most studies, other important comorbidities, including hypertension and hyperlipidemia, were more frequent in female. Greater proportions of male were smokers and had prior PCI or myocardial infarction. Besides, some studies reported that door-to-balloon time and symptom onset to balloon time were longer in female than male. Part of patient baseline characteristics were summarized in Table 2.

Short-term all-cause mortality

Thirteen studies reported sex-specific unadjusted short-term mortality (7 studies with 30-day mortality and 6 studies with in-hospital mortality) of patients with STEMI. There were 2,873 of 31,409 (9.1%) cases of all-cause mortality in female compared with 4,380 of 95,610 (4.6%) in male. Female were at a significantly higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) compared with male (Figure 2 A). Nine studies involving 119,379 patients reported adjusted short-term mortality specific to sex. In adjusted analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%) (Figure 2 B). However, the strength of association calculated with adjusted RRs from these 9 studies was attenuated.

Subgroup analysis demonstrated that the results of studies with Newcastle-Ottawa scale >7 points (RR, 1.90; 95%CI, 1.73-2.09, P=0.018, I^2=63.4%) and studies with ≤7

points (RR, 1.52; 95%CI, 1.20-1.93, P=0.026, I^2=58.1%) were consistent in unadjusted short-term mortality (See eFigure 1 in the Supplementary Material). The impact of sex on in-hospital (RR, 1.71; 95%CI, 1.27-2.31, P<.001, I^2=86.4%) and 30-day mortality (RR, 1.81; 95%CI, 1.62-2.02, P<.001, I^2=56.6%) were consistent. The meta-analysis performed in studies of patients undergoing PCI for STEMI also showed increased unadjusted mortality (RR, 1.45; 95%CI, 1.05-2.00, P=0.026, I^2=39.5%) in female patients.

Long-term all-cause mortality

Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and followed up for more than 1 year, and reported all-cause mortality for female and male. The incidence of long-term all-cause mortality was 13.9% (n=584) in female and 8.7% (n=1202) in male. In unadjusted analysis, no significant sex difference was found in long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%) (Figure 3 A). The unadjusted long-term mortality was also similar between female and male patients undergoing PCI (RR, 1.28; 95%CI, 0.95-1.73, P=0.108, I^2=0.0%). And the adjusted analysis of the pooled results from four studies, also showed a similar risk of mortality at long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%) (Figure 3 B).

Meta-Regression Analysis, sensitivity analyses and publication bias

According to meta-regression analysis, differences in prevalence of diabetes (β coefficient, 0.248; P=0.337; adjusted R^2=1.31%; I^2=80.86%; τ^2=0.044), hypertension (β coefficient, -

0.255; P=0.538; adjusted R^2=24.22%; I^2=41.04%; τ^2=0.008), hyperlipidemia(β coefficient, 0.260; P=0.415; adjusted R^2=-1.84%; I^2=83.59%; τ^2=0.050), smoking (β coefficient, -0.040; P=0.255; adjusted R^2=17.86%; I^2=79.41%; τ^2=0.045), prior MI (β coefficient, -2.725; P=0.126; adjusted R^2=60.30%; I^2=60.19%; τ^2=0.032), and prior PCI (β coefficient, 0.109; P=0.896; adjusted R^2=-58.31%; I^2=61.73%; τ^2=0.042) between sexes were not identified as significant sources of heterogeneity for short-term all-cause mortality. Given that not all included study provided information on confounders stratified by sex, the results of meta-regression analyses should be interpreted with caution.

Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75; 95%CI, 1.54-1.99, P<.001, I^2=82.9%) both indicated that none of the studies affected the results of short-term mortality in this meta-analysis significantly. In analysis for long-term mortality, sensitivity analysis showed a possibly higher influence on the result attribute to the study of Tai et al (See eFigure 3 in the Supplementary Material). After removing this study from meta-analysis, the association of female with increased long-term mortality became significant (RR, 1.50; 95%CI, 1.23-1.83, P<.001, I^2=40.9%). We found no evidence of publication bias across studies based on visual inspection of funnel plots (See eFigure 4 in the Supplementary Material) and the results from Egger's tests for short-term mortality (P=0.462) and for long-term mortality (P=0.053).

Discussion:

Our systematic review and meta-analysis of contemporary literature on sex differences among patients with STEMI demonstrate that female have a higher risk of short- but not long-term mortality compared with male with STEMI. Furthermore, after adjustment for baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term mortality are attenuated but remain significant, while female have the similar long-term mortality with male.

Our results are somewhat in accordance with several previously published meta-analysis.[2] [25] A considerable number of studies have consistently suggested that women were at a higher risk of short-term mortality after ACS. However, whether risk of long-term mortality is also higher in women with ACS remains under debate. Some studies indicated that women with STEMI had a higher 1-year rate of death compared to men[26], while the 1-year mortality rate was conversely lower in women than men in some other studies[23] [24]. In our study, with respect to short-term mortality, the analyses of studies with high or low quality, and big or small sample size yielded similar results. However, in terms of long-term mortality, caution is needed when interpreting our finding of non-significant increased long-term mortality in adjusted analyses, due to the results of sensitivity analysis which showed a significant association between female and increased long-term mortality after removing one study from adjusted analyses.

It is widely accepted that there are significant differences in outcomes of women and men with acute myocardial infarction. In our study, after adjusted for participants' baseline

cardiovascular risk factors and clinical profiles, the strength of association between gender and short-term mortality was substantially attenuated, which suggested that poorer baseline cardiovascular risk profile partially explained the impact of sex differences on mortality. Multiple studies have shown that women with STEMI present at older age and have a higher burden of comorbidities, contributing to the sex differences in mortality after STEMI.[27] All studies included in our meta-analysis demonstrate that female patients are older and with more diabetes mellitus as well as hypertension. In addition, some sex-specific studies found that certain risk factors and comorbidities were more potent in women.[28] Diabetes mellitus , hypertension and smoking status are more strongly associated with increased risk of cardiac events in women compared with men.[27 29]

Notably, that these differences mentioned above still could not completely explain the gap in mortality between sexes. It has been proved that women with acute myocardial infarction were less likely to be treated with guideline directed medical therapy and less likely to receive primary reperfusion therapy including primary percutaneous coronary intervention or fibrinolysis.[30] Regarding medical therapy, numerous studies conducted around the world consistently demonstrate female survivors are receiving less optimal medical therapy after acute myocardial infarction during hospitalization or at discharge.[31 32] Though there might be no differences in treatment adherence between men and women, some studies report significant sex disparities in initiation of appropriate pharmacotherapy after myocardial infarction.[33] Results from these observational studies have shown women are receiving less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme

inhibitors in all age groups, especially young women, and suggested that clinicians and patients may benefit from better education and awareness of undertreatment of younger women.[33 34]

Lower rates of revascularization are observed among women with STEMI compared with men in several studies despite proven benefit of this therapy.[35] Moreover, the sex differences might be driven by delays in presentation to hospital and women with STEMI were more likely to experience longer delays than men. Although a great improvement in emergency medical services and timely revascularization over the past decades, recent studies show that women with STEMI still present later and have a longer ischemic time than men. Previous studies have shown consistently that women have longer door-to balloon times and longer door-to needle times.[36 37] In addition, women are also more likely to exhibit longer pre-hospital delays in seeking medical care after the development of symptoms suggestive of myocardial infarction. Although there have been significant reductions in patient and system delay in the last decade, women continue to have longer presentation and treatment times.[38] Sex differences also exist in clinical presentation of STEMI. Although chest pain was the most common ACS symptom in both sexes, women were more likely to present without chest pain than men.[39 40] Lower rates of typical chest pain reported among women with STEMI may also influence provider decision-making to pursue less aggressive care including invasive revascularization.

Some included studies of our meta-analysis enrolled STEMI patients in general[14-16], while

some others enrolled patients undergoing PCI for STEMI[11 13 18]. The different prognosis of patients receiving reperfusion therapy or no-reperfusion therapy might be a potential source of heterogeneity of our study. Nevertheless, our results are completely consistent with a previous meta-analysis from Pancholy et al., which investigated sex differences in mortality among patients with STEMI treated with primary PCI.[2] Its results demonstrated that, when adjusted RRs were used, the increased risk for 1-year mortality in women was no longer significant and the risk of in-hospital mortality still significantly elevated. It should be noted that more than 50% of patients were treated with PCI in the most study conducted among the general STEMI patients and included by our analysis, even more than 90% in some included studies.[12 24] The increasing rate of primary PCI in recent years might be a reason for the consistency of our fundings and previous studies conducted specifically among STEMI patients undergoing PCI

Complications including bleeding, heart failure and mechanical complications are more likely to develop in women with acute myocardial infarction and increase the risk of mortality.[14 41 42] Bleeding secondary to antithrombotic therapies and invasive procedures is more frequent in women.[43] Three included studies reported incidence of bleeding following STEMI and they all found that women were at higher risk of bleeding.[10 13 18] One study included in our analysis examined the relationships among sex, acute heart failure, and related outcomes after STEMI.[14] Its results demonstrate that women are at higher risk to develop de novo heart failure after STEMI and women with de novo heart failure have worse survival compared with man. However, we could not compare the incidence of these

complications due to the lack of sufficient data. Mechanical complications requiring surgical intervention are also much more common in women after acute myocardial infarction and associated with high mortality rates.[44]

Several limitations of this meta-analysis should be considered. First, the included studies are all observational studies except one post hoc analysis of randomized controlled trial. Hence, there may be residual confounding bias inherent in the observational study design in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the same confounders and not all studies reported adjusted RRs. The confounders which were adjusted in the included studies might differ greatly across studies. Third, there was substantial heterogeneity in our meta-analysis, which could partly be attributed to the wide variability in the sample sizes, locations, and treatment regimens across included studies. Additionally, although we calculated adjusted RRs for all-cause mortality, it needed to be noted that relevant confounders might have differed across studies. Fourth, the analysis of long-term mortality, especially the adjusted analysis, included far fewer studies compared with analysis of short-term mortality. Hence, there might be significant bias in the results about long-term mortality.

In conclusion, our meta-analysis, pooling data from contemporary literature, shows that women with STENI have a higher risk of short-term mortality but not long-term mortality. The effect of sex differences on mortality in patients with STEMI remain significant after adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that

public awareness of increased risk and further improvements in management in women with STEMI are necessary.

Other Information:

Contribution statement

Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis, Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data acquisition, Data analysis/interpretation. Jianan Li, Yang Li, Jianfeng Zheng and Runlin Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.

Conflict of interest

The authors declare that there is no conflict of interest.

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Ethics approval

The institutional central committee at Fuwai Hospital approved that the study protocol and inform consent was not required for a systematic review and meta-analysis.

Data sharing statement

As this is a systematic review and meta-analysis, the data used in the study have already been published by the authors of the included studies. All data relevant to the study are included in the article or uploaded as supplementary information.

Table 1 Characteristics of included studies.

First Author	Year	Region	Study design	Data source	Multicenter	Time of enrollment	Number of STEMI patients	Female	Endpoint	Follow-up
Venetsanos	2017	13 countries	Prospective	Clinical registry	Yes	Sep, 2011-Oct, 2013	1,862	369 (20.0)	Major adverse cardiovascular events and definite stent thrombosis	30 d
Ali	2018	Germany	Prospective	Administrative database	No	2013-2017	312	101 (32.4)	All-cause in-hospital mortality	NA
Langabeer	2018	US	Prospective	Clinical registry	Yes	Jan, 2010-Dec, 2015	9,674	2,569 (26.6)	In-hospital mortality	NA
Tang	2018	China	Prospective	Administrative database	No	Jan, 2013-Dec, 2013	1,238	210 (1.9)	Major adverse cardiac and cerebrovascular events	730 ± 30 d

Cenko	2019	12 European countries	Prospective	Clinical registry	Yes	Jan, 2010-Jul, 2018	10,443	3,112 (29.8)	30-day all-cause mortality	30 d
Hao	2019	China	Prospective	Clinical registry	Yes	Nov, 2014-Jun, 2018	50,203	11,016 (21,9)	In-hospital mortality	NA
Hannan	2019	US	Retrospective	Administrative database	Yes	Jan, 2013-Dec, 2015	23,809	7,791 (32.7)	In hospital/30-day mortality	30 d
Maznyczka	2019	UK	Retrospective	Clinical registry	No	July, 2011-Nov, 2012	324	87 (26.9)	All-cause death/ first heart failure hospitalization	5 years
Stehli	2019	Australia	Prospective	Clinical registry	Yes	2013-2016	6,431	1,317 (20.5)	In hospital/30-day major adverse events, and major bleeding	30 d
Burgess	2020	Australia	Prospective	Administrativ	No	Dec, 2010-	589	123 (21)	Cardiac death and	2 years

				e database		Apr, 2014			myocardial infarction	
Dharma	2020	Indonesia	Retrospective	Administrative database	No	Feb, 2011-Aug, 2019	6,557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherlands	Retrospective	Administrative database	Yes	2015-2016	787	229 (29)	All-cause mortality	1 year
Siabani	2020	Iran	Prospective	Clinical registry	No	Jun, 2016-May, 2018	1,484	311(21)	In-hospital mortality	NA
Tai	2020	China	Retrospective	Administrative database	No	Jan, 2013-Dec, 2017	182	56 (30.8)	In hospital/1-year mortality	1 year
Tizón	2020	Spain	Prospective	Clinical registry	Yes	2010-2016	14,690	3,486 (23.7)	30-day/1-year all-cause mortality	1 year

Table 2 Baseline characteristics of participants in included studies.

First	**Year**	**Age, mean (SD),**	**Diabete**		**Hypertensio**		**Hyperlipidemi**		**Smokin**		**Prior**		**Prior**	

Author		years		s, n (%)		n, n (%)		a, n (%)		g, n (%)		MI, n (%)		PCI, n (%)	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Venetsanos	2017	69 (13.0)	59 (11.0)	48 (13.0)	205 (13.7)	190 (51.5)	605 (40.5)	117 (31.7)	536 (35.9)	NA	NA	24 (6.5)	135 (9.0)	16 (4.3)	124 (8.3)
Ali	2018	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Langabeer	2018	62.5 (13.6)	60.2 (12.5)	759 (29.6)	1,975 (27.8)	NA	NA	1,265 (49.3)	3,693 (52.0)	951 (37.0)	2,763 (38.9)	435 (16.9)	1,304 (18.4)	NA	NA
Tang	2018	64.5 (9.3)	54.4 (10.7)	66 (31.4)	311 (25.1)	141 (67.1)	659 (53.3)	125 (59.5)	749 (60.3)	33 (15.7)	957 (77.3)	10 (4.8)	83 (6.7)	60 (28.6)	282 (22.8)
Cenko	2019	66.1	59.7	925	1,531	2,322 (74.6)	4,502	1,353 (43.3)	3,100	1,010	3,714	301	842	306	762

		(11.7)	(11.7)	(29.7)	(20.9)		(61.4)		(42.3)	(32.5)	(50.7)	(9.7)	(11.5)	(9.8)	(10.4)
Hao	2019	69.0 (10.6)	61.1 (12.4)	10,141 (48.1)	24,082 (39.4)	15,607 (74.1)	38,426 (62.9)	17,996 (85.4)	50,944 (83.3)	1,719 (8.2)	32,377 (53.0)	NA	NA	NA	NA
Hannan	2019	70.72 (14.73)	62.11 (12.82)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	868 (11.1)	2206 (13.8)
Maznyczka	2019	61.2 (12.2)	58.6(11.2)	8 (9.2)	26 (11.0)	32 (36.8)	73 (30.8)	28 (32.2)	66 (27.8)	57 (65.5)	139 (58.6)	5 (5.7)	20 (8.4)	2 (2.3)	16 (6.8)
Stehli	2019	66.5 (13.2)	60.8 (12.2)	245 (18.6)	770 (15.1)	NA	NA	NA	NA	NA	NA	NA	NA	104 (7.9)	577 (11.3)

Burgess	2020	62.7 (52.7-73.2)	58.2 (50.6-65.7)	39 (31.7)	88 (18.9)	84 (68.3)	243 (52.1)	83 (67.5)	253 (52.3)	64 (52.0)	252 (54.1)	9 (7.3)	41 (8.8)	NA	NA
Dharma	2020	60 (10)	55 (10)	403 (43.4)	1548 (27.5)	647 (69.6)	2,889 (51.3)	299 (32.2)	1,779 (31.6)	109 (11.7)	4,049 (71.9)	NA	NA	NA	NA
Kerkmanx	2020	68 (14)	61 (12)	39 (17.6)	66 (12.5)	101 (45.7)	178 (33.6)	56 (25.9)	110 (21.0)	88 (41.1)	258 (49.3)	30 (13.6)	79 (13.7)	33 (14.4)	77 (14.2)
Siabani	2020	65.8 (11.3)	59.0 (12.4)	114 (37.7)	187 (16.2)	195 (63.7)	410 (35.4)	110 (36.7)	208 (18.5)	41 (13.2)	655 (55.9)	NA	NA	NA	NA
Tai	2020	78 (76–81)	78 (76–80)	96 (35.2)	116 (26.5)	217 (79.5)	319 (72.8)	NA	NA	14 (5.4)	239 (56.5)	NA	NA	36 (13.5)	78 (18.1)

Tizón	2020	69.9 (13.7)	60.9 (12.6)	844 (24.2)	1,927 (17.2)	1,192 (34.2)	2,722 (24.3)	878 (25.2)	2,375 (21.2)	474 (13.6)	2,711 (24.2)	NA	NA	NA	NA

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Figure 1 Flowchart of selection of studies included in meta-analysis.

Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 1 Flowchart of selection of studies included in meta-analysis.

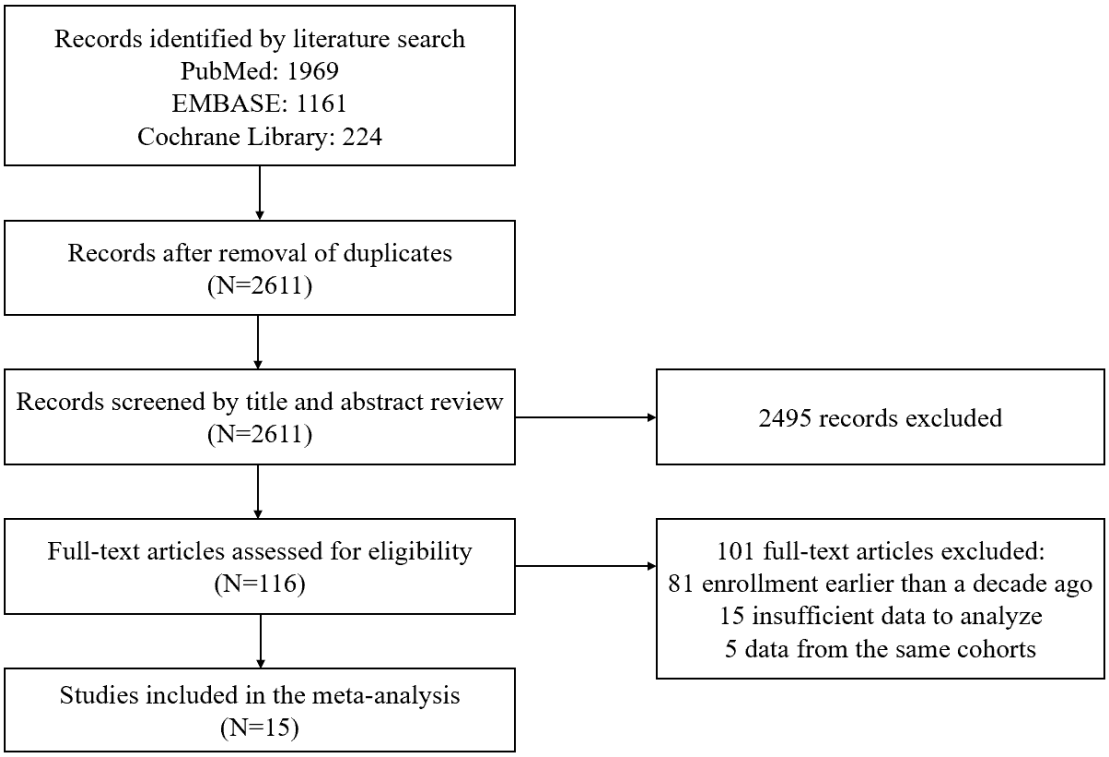
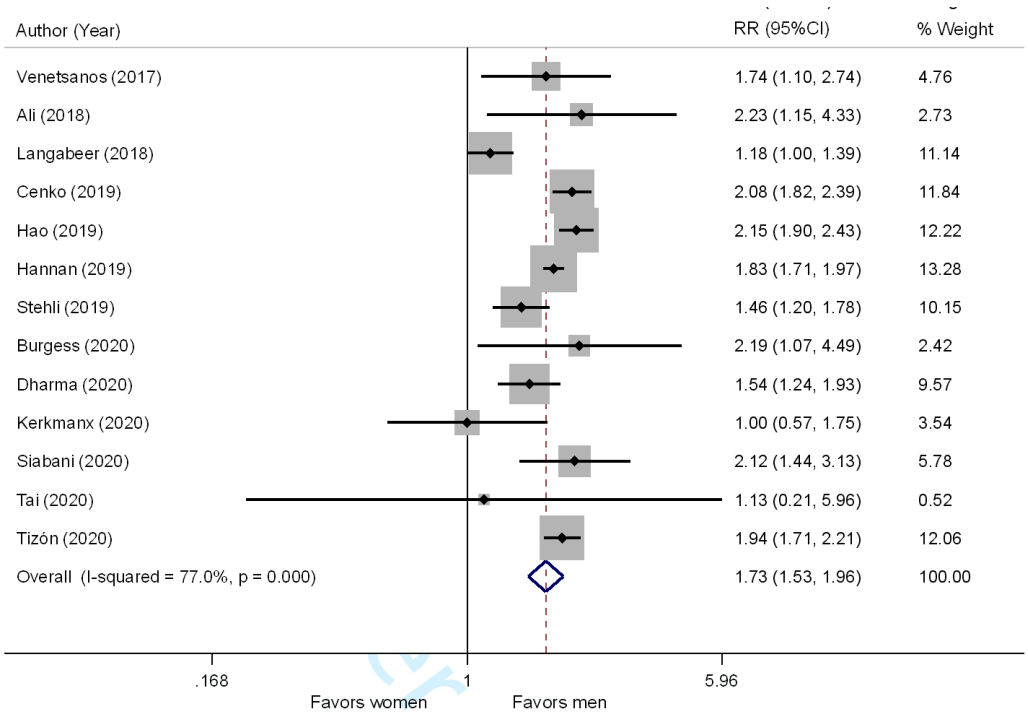
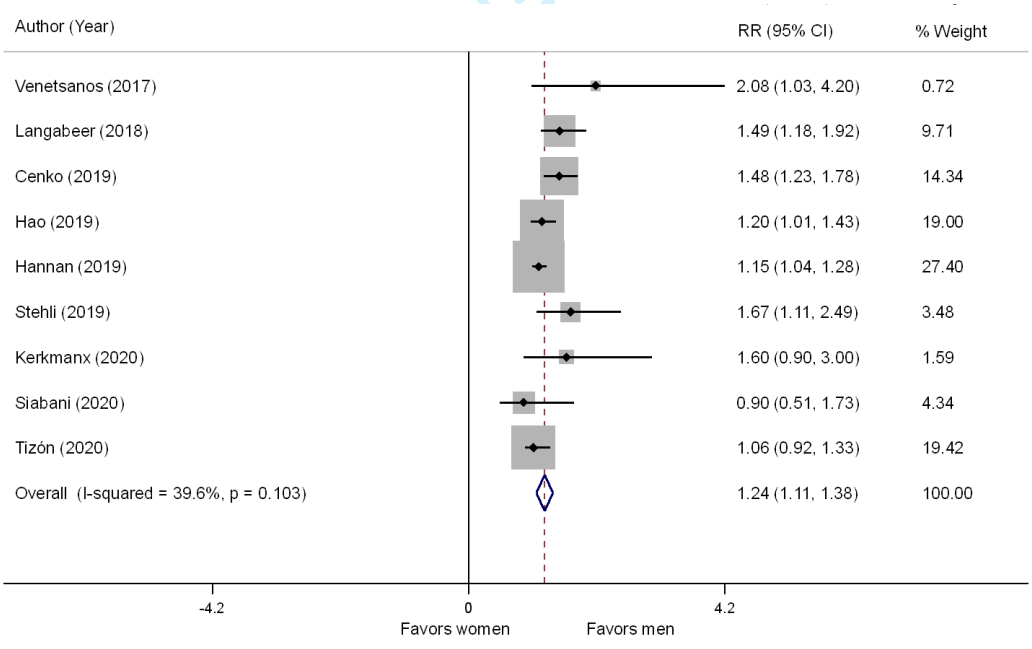


Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



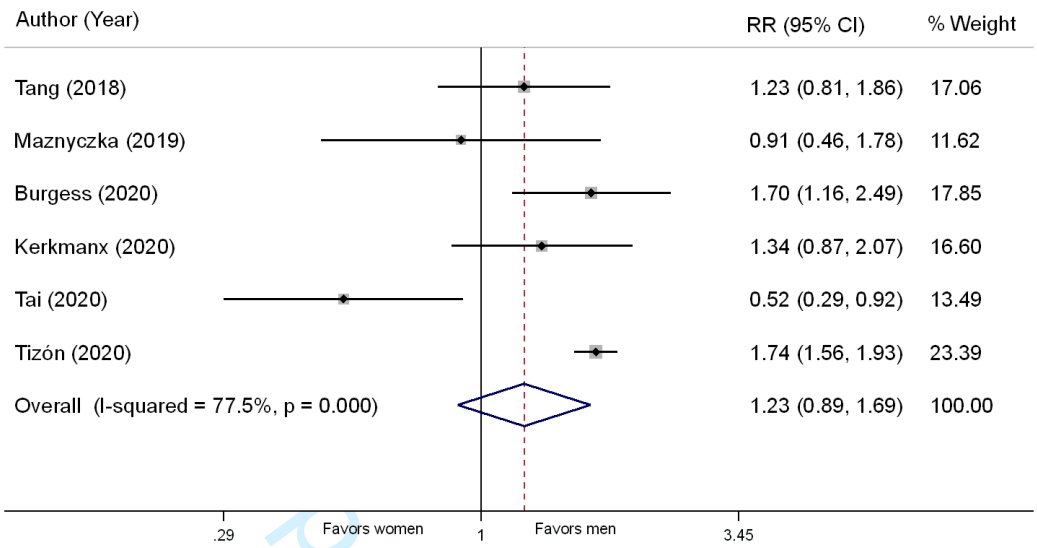
B



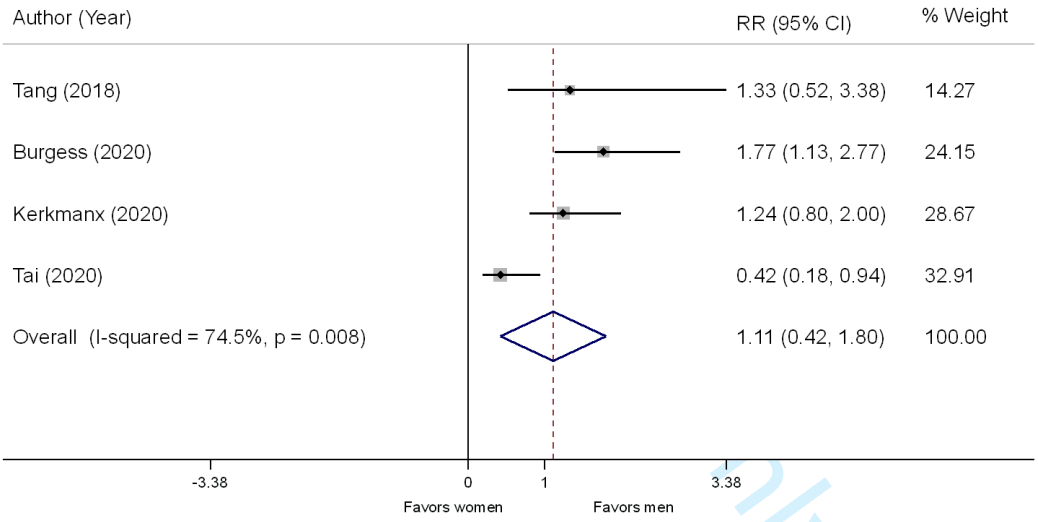
Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



B



Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

eTable 1 Variables adjusted in the adjusted analyses from the included studies.

First Author	Year	Adjusted Variables
Venetsanos	2017	age, weight, prior MI, prior PCI, patient's history of diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-PCI ECG, admission Killip class, baseline hemoglobin, eGFR, access site, use of Glycoprotein IIIb/IIa inhibitor, bivalirudin and unfractionated heparin, location of MI and revascularization
Langabeer	2018	age, smoking, diabetes, prior CVD, prior stroke, heart failure, shock, length of stay, teaching, insurance, total ischemic time, door to balloon
Tang	2018	age, BMI, LVEF, serum creatinine, use of proton pump inhibitors, use of dual-antiplatelet therapy, previous PCI, diabetes mellitus, hypertension, previous stroke, current smoker, thrombocytopenia, use of femoral approach, use of intra-aortic balloon pump, and multivessel disease
Cenko	2019	age, family history of CAD, diabetes, hypertension, hypercholesterolemia, current smoking, former smoking, prior angina pectoris, prior myocardial infarction, prior PCI, prior CABG, peripheral artery disease, prior stroke, ST-segment elevation in anterior leads (at ECG), systolic blood pressure at baseline, heart rate at baseline, serum creatinine at baseline, Killip Class ⩾2
Hao	2019	Age, medical insurance status, acute heart failure, cardiogenic shock, cardiac arrest at admission, heart rate and systolic blood pressure, diabetes mellitus, smoking, history of CHD, heart failure, renal failure, and cerebrovascular disease, prehospital statin use, renal insufficiency, and transfer status.
Hannan	2019	age, STEMI location, heart rate, mean arterial pressure, history

		of hospitalization in last year, history of PCI, history of CABG surgery, septicemia/sepsis/systemic inflammatory response /shock, metastatic cancer/acute leukemia, diabetes with acute complications, end stage liver disease, inflammatory bowel disease, coagulation defects and other specified hematological disorders, dementia, polyneuropathy, muscular dystrophy, seizure disorders and convulsions, coma/brain compression/anoxic damage, cardiorespiratory failure and shock, congestive heart failure, specified heart arrhythmias, ischemic or unspecified stroke, hemiplegia/hemiparesis, vascular disease with complications, vascular disease without complications, aspiration and specified bacterial pneumonias, acute renal failure, chronic kidney disease, Stage 5, unspecified renal failure, nephritis, pressure ulcer of skin with partial thickness skin loss*, pressure pre-ulcer skin changes, chronic ulcer of skin except pressure ulcer, lower limb/amputation complications
Maznyczka	2019	NA
Stehli	2019	age, diabetes mellitus, eGFR, previous PCI and/or coronary artery bypass grafting, history of peripheral vascular disease and CVD, LVEF, out-of-hospital and in-hospital cardiac arrest, cardiogenic shock, and occurrence time of symptom onset
Burgess	2020	NA
Dharma	2020	NA
Kerkmanx	2020	NA
Siabani	2020	BMI⩾25, hypertension, diabetes, current smoking, hypercholesterolemia, congestive heart failure, Killip class (at first presentation) ⩾ II, symptom-to-balloon time> 360 min and door-to-balloon time > 90 min

Tai	2020	NA
Tizón	2020	age, diabetes mellitus, recruitment year, time from symptom onset to culprit coronary artery opening, and Killip class

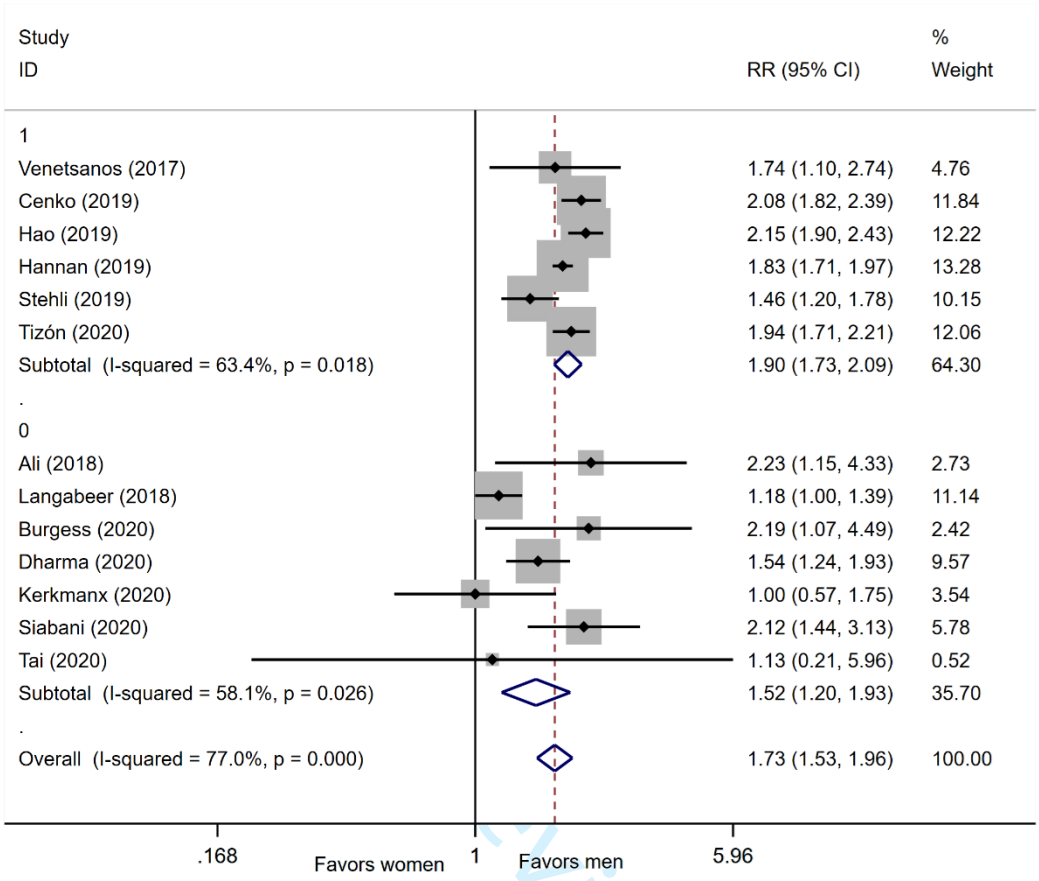
MI: myocardial infarction, PCI: percutaneous coronary intervention, ECG: electrocardiograph, eGFR: estimated glomerular filtration rate, CVD: cardiovascular disease, BMI: body mass index, LVEF: left ventricular ejection fraction, CABG: coronary artery bypass graft, CAD: coronary artery disease,

eTable 2 Assessment of study quality using Newcastle-Ottawa scale.

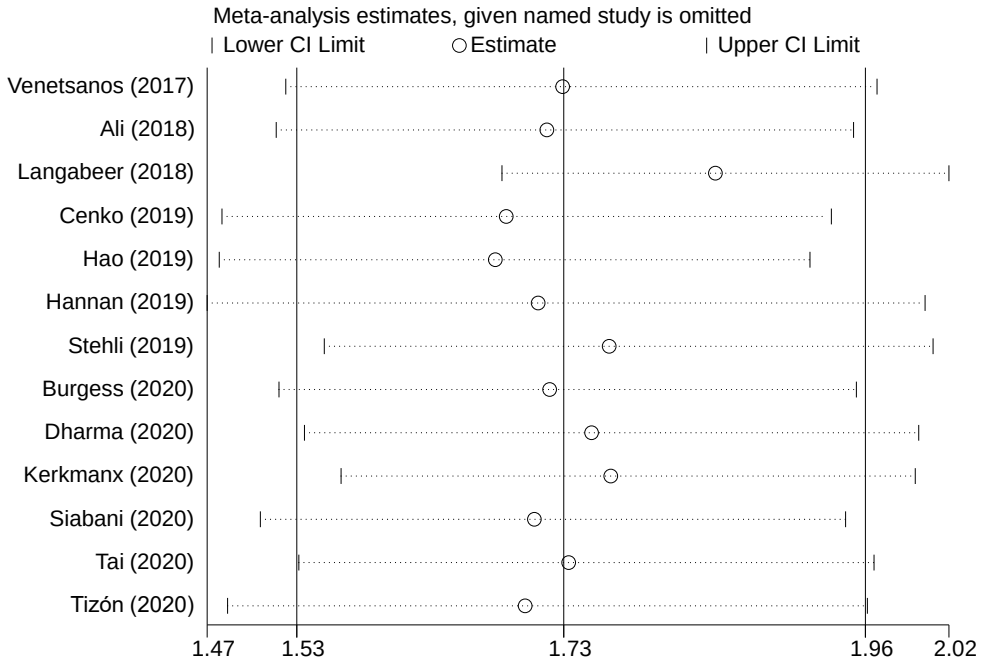
First Author	Year	Selection				Comparability	Outcome			Total points
		Representativeness of the exposed cohor	Selection of the no exposed cohort	Ascertainment of exposure to implants	Outcome of interest not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up	
Venetsanos	2017	*	*	*	*	**	*	\	*	8
Ali	2018	\	\	*	*	\	*	\	*	4
Langabeer	2018	*	*	*	*	*	*	\	*	7
Tang	2018	\	\	*	*	**	*	*	*	7
Cenko	2019	*	*	*	*	**	*	\	*	8
Hao	2019	*	*	*	*	**	*	\	*	8
Hannan	2019	*	*	*	*	**	*	\	*	8
Maznyczka	2019	\	\	*	*	\	*	*	*	5
Stehli	2019	*	*	*	*	**	*	\	*	8

Burgess	2020	\	\	*	*	**	*	*	*	7
Dharma	2020	\	\	*	*	*	*	*	*	6
Kerkmanx	2020	*	*	*	*	\	*	*	*	7
Siabani	2020	\	\	*	*	*	*	\	*	5
Tai	2020	\	\	*	*	**	*	*	*	7
Tizón	2020	*	*	*	*	**	*	*	*	9

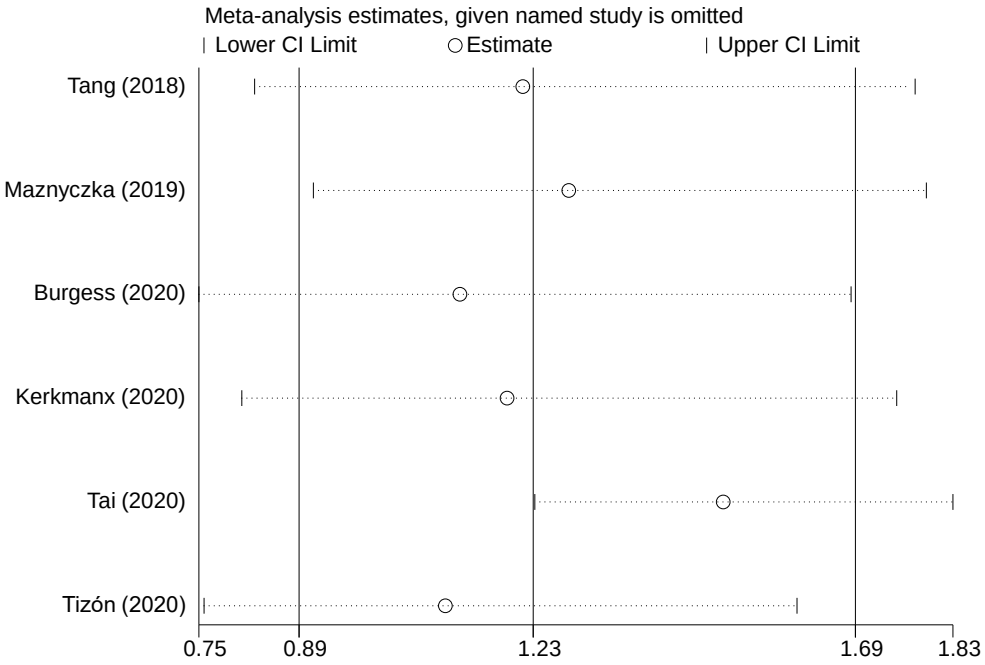
eFigure 1



eFigure 2 Meta-influence analysis for unadjusted short-term mortality

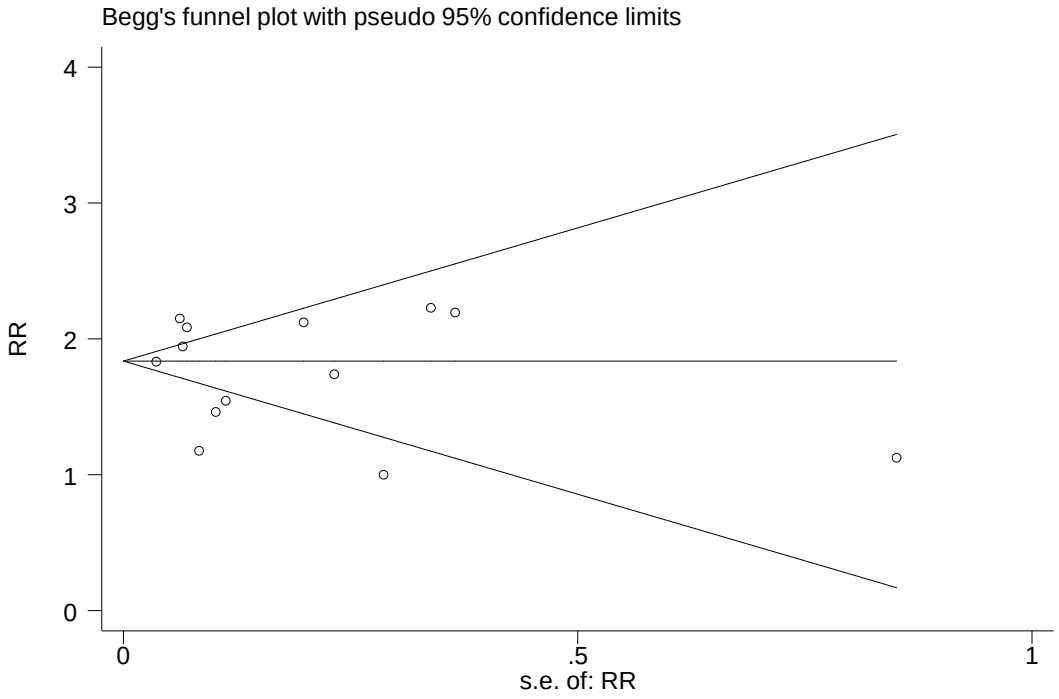


eFigure 3 Meta-influence analysis for unadjusted long-term mortality

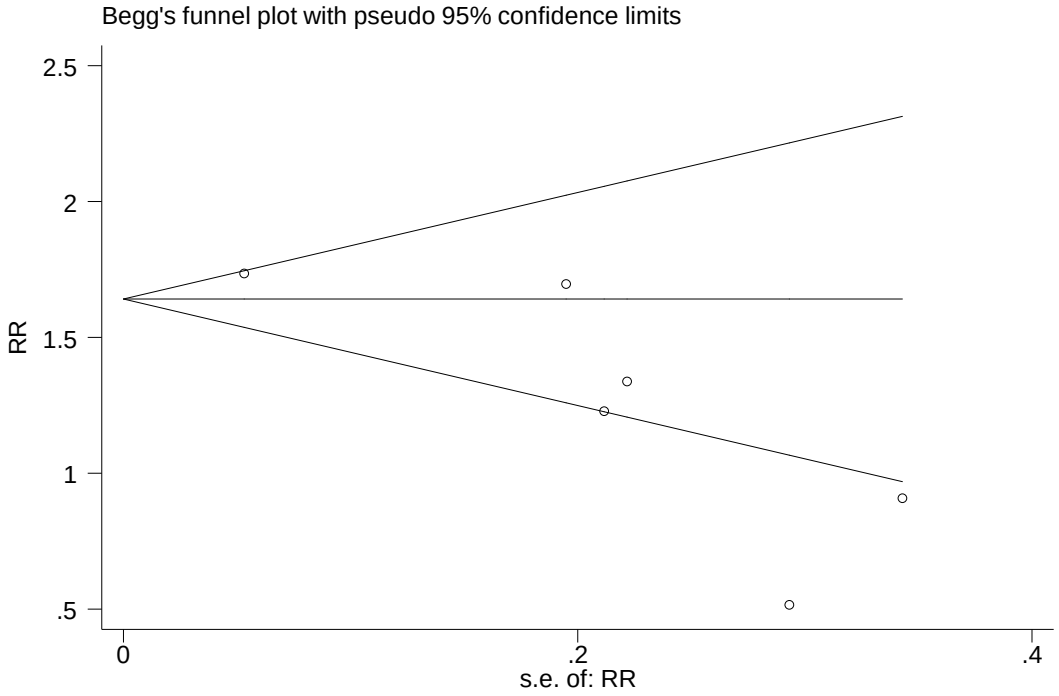


eFigure 4 Funnel plots for publication bias for unadjusted short-term (A) and long-term (B) mortality

A


Begg's funnel plot with pseudo 95% confidence limits
RR
4
3
2
1
0
0
.5
1
s.e. of: RR

B


Begg's funnel plot with pseudo 95% confidence limits
RR
2.5
2
1.5
1
.5
0
.2
.4
s.e. of: RR

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
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 record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
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 each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	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.	Page 5
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.	Page 5
Synthesis methods	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)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
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 in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 7
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.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 6
	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.	Page 6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 7
	23b	Discuss any limitations of the evidence included in the review.	Page 8-9
	23c	Discuss any limitations of the review processes used.	Page 8-9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 7-8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
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 included studies; data used for all analyses; analytic code; any other materials used in the review.	

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

Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Short title：Sex differences in STEMI

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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Objectives: To assess the effect of sex differences on short- and long-term mortality among patients with ST-segment elevation myocardial infarction (STEMI).

Design: Systematic review and meta-analysis of contemporary available evidence.

Setting: PubMed, Embase and Cochrane Library were searched for relevant studies reporting sex specific outcomes among patients with STEMI published between January 1, 2010 to August 1, 2020. Risk ratio (RR) 95% 95% confidence intervals (CIs) were measured using DerSimonian and Laird random-effects model. Sensitivity analyses were performed and publication bias was also checked. All statistical analyses were performed using STATA version 15.0.

Participants: Studies providing data about short- or long-term mortality stratified by sex in patients with STEMI were included. Only study conducted in last ten years were included.

Primary and secondary outcome measures: The primary outcome was all-cause death at short-(in-hospital or 30 days) and long-term (at least 12 months) follow-up.

Results

A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879 [75.3%] male) were included. In the unadjusted analyses, female were at a higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) but not long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%). When adjusted effect estimates from individual studies were used in meta-analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%). And adjusted long-term mortality was also similar between female and male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%).

Conclusions

An increased short- but not long-term mortality was found in female with STEMI. After adjustment for baseline cardiovascular risk factors and clinical profiles, short-term mortality remains higher in female with STEMI compared to male, indicating the need for further improvements in management in female patients.

Strengths and limitations of this study

- We assessed the contemporary effect of sex differences on mortality among patients with STEMI by meta-analysis of studies from the last decade.
- A greater number of potentially eligible articles were screened and the large sample size ensures adequate statistical power to detect even a small effect of interest.
- Sensitivity analyses by excluding one study at a time and restricting to studies with high quality or with large sample size got consistent results.
- Substantial and nonnegligible heterogeneity still exist in our meta-analysis and might result in potential bias.
- Residual confounding bias could not be totally excluded due to the observational study design of most included studies.

Contemporary sex differences in short- and long-term mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Introduction

Acute myocardial infarction remains one of leading causes of mortality in both men and women worldwide despite improvement of acute cardiac care.[1] Numerous studies have reported that women have a higher risk of in-hospital and long-term adverse outcomes following ST-segment elevation myocardial infarction (STEMI) compared with men.[2] Confounders including advanced age and more frequent comorbidities, such as hypertension and diabetes mellitus[3 4], might contribute to excess mortality in women. Moreover, previous studies show lower rates of guideline directed medical therapy and revascularization are also associated with poorer prognosis for women with STEMI.[5]

Sex discrepancies in management and outcomes after STEMI have been increasingly reported in the literature and raised public awareness.[6] Major progress in therapy for myocardial infarction and primary and secondary preventive interventions has been made to reduce cardiovascular mortality for women.[1 7] And there have been marked reductions in cardiovascular disease mortality in women with acute myocardial infarction in the past two decades.[1] Conflicting results are noted in recent studies on sex differences following STEMI. It is unclear whether the sex differences still exist, in view of substantial improvements in prognosis of cardiovascular disease over the past decade.

In order to assess the contemporary effect of sex differences on short- and long-term

mortality among patients with STEMI, we performed a systematic review and meta-analysis of all available evidence from last decade reporting sex-specific outcomes after STEMI.

Methods

The present systematic review and meta-analysis was performed following the principle of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

Literature search

We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library from January 1, 2010 to August 1, 2020 to identify studies from the last decade that described sex differences in in short- or long-term mortality among patients with STEMI. Both observational studies and randomized clinical trials were eligible. We queried MeSH and the abstract text for the following three search terms: gender part (including "gender", "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular mortality" or "short term mortality"); myocardial infarction part (including "myocardial infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or

"primary angioplasty") to identify relevant studies. There was no language restriction or age limit.

Study selection

According to the aim of our analyses, studies were included in this systematic review if data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality stratified by sex in patients with STEMI were reported. Two reviewers identified studies eligible for further review by performing an initial screen of titles or abstracts of the search results. Subsequently, a second screen of full texts eligibility was performed by another two reviewers. Studies had to fulfil the following criteria to be included in the present analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and ii) studies providing enough details to obtain numbers of events or incidence rates according to sex; and iii) enrollment starting earlier than a decade ago. Editorials, letters, conference proceedings and abstracts were considered to be eligible only if sufficient information was available in abstracts or associated tables or figures. We excluded studies if they were review articles or case reports, or if they involved pregnant participants, critically ill patients, or provided insufficient data to allow for risk estimates to be calculated. Any disagreement was reviewed by a third reviewer and resolved by consensus.

Data extraction

Detailed data from selected studies were extracted independently by two reviewers using a standardized form independently. Data about study and participants characteristics,

including year of study, sample size, time of enrollment, geographical location, endpoints of study, and follow-up duration, were collected. Any discrepancies were reviewed by a third reviewer and resolved by consensus. The quality of included studies was evaluated by Newcastle-Ottawa scale using prespecified items comprised of patients' selection (representativeness and selection of patients, ascertainment of exposure), comparability of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy of follow-up).[9] A quality score (0–9 points) was generated according to a maximum of 1 point for each item.

Patient and public involvement

Due to the nature of the systematic review and meta-analysis, this study did not involve patients and the public in the design, or conduct, or reporting or dissemination plans.

Statistical analysis

The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent the effect of sex differences on mortality after STEMI. And data were combined using random-effects model of DerSimonian and Laird with inverse variance weighting. Random-effect model was used due to substantial clinical and statistical heterogeneity. Following analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality using raw number of death and total participants at risk for death specific to each sex, ii) adjusted RRs for short- and long-term all-cause mortality using adjusted RRs if they were described in those included studies. In terms of short-term mortality, the RRs for in-hospital

and 30-day mortality were also calculated respectively.

We assess heterogeneity across studies with Cochran's Q test and I2 test, with P<0.1 or I2 >50% considered significant. We also performed meta-regression to identify the potential sources of heterogeneity in the included studies. The potential sources were differences in diabetes, hypertension, hyperlipidemia, smoking, prior MI, and prior PCI. Furthermore, stratified analysis was conducted as well by dividing the included studies into different subgroups based on the Newcastle-Ottawa scale scores (>7 points or ≤7 points) to assess the potential sources of heterogeneity. To assess the potential effect of publication bias, we inspected funnel plots for asymmetry and used the Egger's regression asymmetry test in which P<0.05 was considered to indicate significant publication bias. Sensitivity analyses was conducted by excluding one study at a time and comparing the results with the complete one. In addition, we also performed sensitivity analyses by restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and restricting to studies with sample size bigger than 1000 participants. All statistical analyses were performed using STATA version 15.0 (Stata Corp, College Station, TX). Differences were considered statistically significant at P < .05 (2-sided).

Results

Literature search

Study selection details were outlined in Figure 1. The literature search identified 2,611 potentially relevant articles. After screening based on title and abstract review, 2495

records were excluded. A total of 116 full-text were finally assessed for eligibility, with 96 papers excluded due to enrollment starting earlier than a decade ago or no sufficient gender specific data to analyze. Another 5 papers reviewed in detail were excluded after due to data from the same cohorts. A total of 15 studies were finally included in the present systematic review and meta-analysis.[10-24]

Study characteristics

Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than 10,000 patients with STEMI. See Table 1 for further information of included studies. Baseline characteristics of participants were missing in some included studies, but all included studies provided sufficient data for analysis of sex differences in clinical outcomes. Except for 1 study, which was a prespecified gender analysis of randomized controlled trial, the remaining 14 were observational studies. Among the 10 included studies which reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension, and prior myocardial infarction/PCI, while some adjusted for renal insufficiency, cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset. Variables that were adjusted in the adjusted analyses from the included studies were presented in eTable 1 of the Supplementary Material. Results of assessment of study quality using Newcastle-Ottawa scale were shown in eTable 2 in the Supplementary Material.

Patient characteristics

A total of 128,585 patients with STEMI (31,706 [24.7%] female and 96,879 [75.3%] male) were involved in the 15 included studies. Female tended to be older and had higher prevalence of diabetes mellitus in all included studies. And in most studies, other important comorbidities, including hypertension and hyperlipidemia, were more frequent in female. Greater proportions of male were smokers and had prior PCI or myocardial infarction. Besides, some studies reported that door-to-balloon time and symptom onset to balloon time were longer in female than male. Part of patient baseline characteristics were summarized in Table 2.

Short-term all-cause mortality

Thirteen studies reported sex-specific unadjusted short-term mortality (7 studies with 30-day mortality and 6 studies with in-hospital mortality) of patients with STEMI. There were 2,873 of 31,409 (9.1%) cases of all-cause mortality in female compared with 4,380 of 95,610 (4.6%) in male. Female were at a significantly higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) compared with male (Figure 2 A). Nine studies involving 119,379 patients reported adjusted short-term mortality specific to sex. In adjusted analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%) (Figure 2 B). However, the strength of association calculated with adjusted RRs from these 9 studies was attenuated.

Subgroup analysis demonstrated that the results of studies with Newcastle-Ottawa scale >7 points (RR, 1.90; 95%CI, 1.73-2.09, P=0.018, I^2=63.4%) and studies with ≤7

points (RR, 1.52; 95%CI, 1.20-1.93, P=0.026, I^2=58.1%) were consistent in unadjusted short-term mortality (See eFigure 1 in the Supplementary Material). The impact of sex on in-hospital (RR, 1.71; 95%CI, 1.27-2.31, P<.001, I^2=86.4%) and 30-day mortality (RR, 1.81; 95%CI, 1.62-2.02, P<.001, I^2=56.6%) were consistent. The meta-analysis performed in studies of patients undergoing PCI for STEMI also showed increased unadjusted mortality (RR, 1.45; 95%CI, 1.05-2.00, P=0.026, I^2=39.5%) in female patients.

Long-term all-cause mortality

Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and followed up for more than 1 year, and reported all-cause mortality for female and male. The incidence of long-term all-cause mortality was 13.9% (n=584) in female and 8.7% (n=1202) in male. In unadjusted analysis, no significant sex difference was found in long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%) (Figure 3 A). The unadjusted long-term mortality was also similar between female and male patients undergoing PCI (RR, 1.28; 95%CI, 0.95-1.73, P=0.108, I^2=0.0%). And the adjusted analysis of the pooled results from four studies, also showed a similar risk of mortality at long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%) (Figure 3 B).

Meta-Regression Analysis, sensitivity analyses and publication bias

According to meta-regression analysis, differences in prevalence of diabetes (β coefficient, 0.248; P=0.337; adjusted R^2=1.31%; I^2=80.86%; τ^2=0.044), hypertension (β coefficient, -

0.255; P=0.538; adjusted R^2=24.22%; I^2=41.04%; τ^2=0.008), hyperlipidemia(β coefficient, 0.260; P=0.415; adjusted R^2=-1.84%; I^2=83.59%; τ^2=0.050), smoking (β coefficient, -0.040; P=0.255; adjusted R^2=17.86%; I^2=79.41%; τ^2=0.045), prior MI (β coefficient, -2.725; P=0.126; adjusted R^2=60.30%; I^2=60.19%; τ^2=0.032), and prior PCI (β coefficient, 0.109; P=0.896; adjusted R^2=-58.31%; I^2=61.73%; τ^2=0.042) between sexes were not identified as significant sources of heterogeneity for short-term all-cause mortality. Given that not all included study provided information on confounders stratified by sex, the results of meta-regression analyses should be interpreted with caution.

Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75; 95%CI, 1.54-1.99, P<.001, I^2=82.9%) both indicated that none of the studies affected the results of short-term mortality in this meta-analysis significantly. In analysis for long-term mortality, sensitivity analysis showed a possibly higher influence on the result attribute to the study of Tai et al (See eFigure 3 in the Supplementary Material). After removing this study from meta-analysis, the association of female with increased long-term mortality became significant (RR, 1.50; 95%CI, 1.23-1.83, P<.001, I^2=40.9%). We found no evidence of publication bias across studies based on visual inspection of funnel plots (See eFigure 4 in the Supplementary Material) and the results from Egger's tests for short-term mortality (P=0.462) and for long-term mortality (P=0.053).

Discussion:

Our systematic review and meta-analysis of contemporary literature on sex differences among patients with STEMI demonstrate that female have a higher risk of short- but not long-term mortality compared with male with STEMI. Furthermore, after adjustment for baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term mortality are attenuated but remain significant, while female have the similar long-term mortality with male.

Our results are somewhat in accordance with several previously published meta-analysis.[2] [25] A considerable number of studies have consistently suggested that women were at a higher risk of short-term mortality after ACS. However, whether risk of long-term mortality is also higher in women with ACS remains under debate. Some studies indicated that women with STEMI had a higher 1-year rate of death compared to men[26], while the 1-year mortality rate was conversely lower in women than men in some other studies[23] [24]. In our study, with respect to short-term mortality, the analyses of studies with high or low quality, and big or small sample size yielded similar results. However, in terms of long-term mortality, caution is needed when interpreting our finding of non-significant increased long-term mortality in adjusted analyses, due to the results of sensitivity analysis which showed a significant association between female and increased long-term mortality after removing one study from adjusted analyses.

It is widely accepted that there are significant differences in outcomes of women and men with acute myocardial infarction. In our study, after adjusted for participants' baseline

cardiovascular risk factors and clinical profiles, the strength of association between gender and short-term mortality was substantially attenuated, which suggested that poorer baseline cardiovascular risk profile partially explained the impact of sex differences on mortality. Multiple studies have shown that women with STEMI present at older age and have a higher burden of comorbidities, contributing to the sex differences in mortality after STEMI.[27] All studies included in our meta-analysis demonstrate that female patients are older and with more diabetes mellitus as well as hypertension. In addition, some sex-specific studies found that certain risk factors and comorbidities were more potent in women.[28] Diabetes mellitus , hypertension and smoking status are more strongly associated with increased risk of cardiac events in women compared with men.[27 29]

Notably, that these differences mentioned above still could not completely explain the gap in mortality between sexes. It has been proved that women with acute myocardial infarction were less likely to be treated with guideline directed medical therapy and less likely to receive primary reperfusion therapy including primary percutaneous coronary intervention or fibrinolysis.[30] Regarding medical therapy, numerous studies conducted around the world consistently demonstrate female survivors are receiving less optimal medical therapy after acute myocardial infarction during hospitalization or at discharge.[31 32] Though there might be no differences in treatment adherence between men and women, some studies report significant sex disparities in initiation of appropriate pharmacotherapy after myocardial infarction.[33] Results from these observational studies have shown women are receiving less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme

inhibitors in all age groups, especially young women, and suggested that clinicians and patients may benefit from better education and awareness of undertreatment of younger women.[33 34]

Lower rates of revascularization are observed among women with STEMI compared with men in several studies despite proven benefit of this therapy.[35] Moreover, the sex differences might be driven by delays in presentation to hospital and women with STEMI were more likely to experience longer delays than men. Although a great improvement in emergency medical services and timely revascularization over the past decades, recent studies show that women with STEMI still present later and have a longer ischemic time than men. Previous studies have shown consistently that women have longer door-to balloon times and longer door-to needle times.[36 37] In addition, women are also more likely to exhibit longer pre-hospital delays in seeking medical care after the development of symptoms suggestive of myocardial infarction. Although there have been significant reductions in patient and system delay in the last decade, women continue to have longer presentation and treatment times.[38] Sex differences also exist in clinical presentation of STEMI. Although chest pain was the most common ACS symptom in both sexes, women were more likely to present without chest pain than men.[39 40] Lower rates of typical chest pain reported among women with STEMI may also influence provider decision-making to pursue less aggressive care including invasive revascularization.

Some included studies of our meta-analysis enrolled STEMI patients in general[14-16], while

some others enrolled patients undergoing PCI for STEMI[11 13 18]. The different prognosis of patients receiving reperfusion therapy or no-reperfusion therapy might be a potential source of heterogeneity of our study. Nevertheless, our results are completely consistent with a previous meta-analysis from Pancholy et al., which investigated sex differences in mortality among patients with STEMI treated with primary PCI.[2] Its results demonstrated that, when adjusted RRs were used, the increased risk for 1-year mortality in women was no longer significant and the risk of in-hospital mortality still significantly elevated. It should be noted that more than 50% of patients were treated with PCI in the most study conducted among the general STEMI patients and included by our analysis, even more than 90% in some included studies.[12 24] The increasing rate of primary PCI in recent years might be a reason for the consistency of our fundings and previous studies conducted specifically among STEMI patients undergoing PCI

Complications including bleeding, heart failure and mechanical complications are more likely to develop in women with acute myocardial infarction and increase the risk of mortality.[14 41 42] Bleeding secondary to antithrombotic therapies and invasive procedures is more frequent in women.[43] Three included studies reported incidence of bleeding following STEMI and they all found that women were at higher risk of bleeding.[10 13 18] One study included in our analysis examined the relationships among sex, acute heart failure, and related outcomes after STEMI.[14] Its results demonstrate that women are at higher risk to develop de novo heart failure after STEMI and women with de novo heart failure have worse survival compared with man. However, we could not compare the incidence of these

complications due to the lack of sufficient data. Mechanical complications requiring surgical intervention are also much more common in women after acute myocardial infarction and associated with high mortality rates.[44]

Several limitations of this meta-analysis should be considered. First, the included studies are all observational studies except one post hoc analysis of randomized controlled trial. Hence, there may be residual confounding bias inherent in the observational study design in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the same confounders and not all studies reported adjusted RRs. The confounders which were adjusted in the included studies might differ greatly across studies. Third, there was substantial heterogeneity in our meta-analysis, which could partly be attributed to the wide variability in the sample sizes, locations, and treatment regimens across included studies. Additionally, although we calculated adjusted RRs for all-cause mortality, it needed to be noted that relevant confounders might have differed across studies. Fourth, the analysis of long-term mortality, especially the adjusted analysis, included far fewer studies compared with analysis of short-term mortality. Hence, there might be significant bias in the results about long-term mortality.

In conclusion, our meta-analysis, pooling data from contemporary literature, shows that women with STENI have a higher risk of short-term mortality but not long-term mortality. The effect of sex differences on mortality in patients with STEMI remain significant after adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that

public awareness of increased risk and further improvements in management in women with STEMI are necessary.

Other Information:

Contribution statement

Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis, Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data acquisition, Data analysis/interpretation. Jianan Li, Yang Li, Jianfeng Zheng and Runlin Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.

Conflict of interest

The authors declare that there is no conflict of interest.

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Ethics approval

The institutional central committee at Fuwai Hospital approved that the study protocol and inform consent was not required for a systematic review and meta-analysis.

Data sharing statement

As this is a systematic review and meta-analysis, the data used in the study have already been published by the authors of the included studies. All data relevant to the study are included in the article or uploaded as supplementary information.

Table 1 Characteristics of included studies.

First Author	Year	Region	Study design	Data source	Multicenter	Time of enrollment	Number of STEMI patients	Female	Endpoint	Follow-up
Venetsanos	2017	13 countries	Prospective	Clinical registry	Yes	Sep, 2011-Oct, 2013	1,862	369 (20.0)	Major adverse cardiovascular events and definite stent thrombosis	30 d
Ali	2018	Germany	Prospective	Administrative database	No	2013-2017	312	101 (32.4)	All-cause in-hospital mortality	NA
Langabeer	2018	US	Prospective	Clinical registry	Yes	Jan, 2010-Dec, 2015	9,674	2,569 (26.6)	In-hospital mortality	NA
Tang	2018	China	Prospective	Administrative database	No	Jan, 2013-Dec, 2013	1,238	210 (1.9)	Major adverse cardiac and cerebrovascular events	730 ± 30 d

Cenko	2019	12 European countries	Prospective	Clinical registry	Yes	Jan, 2010-Jul, 2018	10,443	3,112 (29.8)	30-day all-cause mortality	30 d
Hao	2019	China	Prospective	Clinical registry	Yes	Nov, 2014-Jun, 2018	50,203	11,016 (21,9)	In-hospital mortality	NA
Hannan	2019	US	Retrospective	Administrative database	Yes	Jan, 2013-Dec, 2015	23,809	7,791 (32.7)	In hospital/30-day mortality	30 d
Maznyczka	2019	UK	Retrospective	Clinical registry	No	July, 2011-Nov, 2012	324	87 (26.9)	All-cause death/ first heart failure hospitalization	5 years
Stehli	2019	Australia	Prospective	Clinical registry	Yes	2013-2016	6,431	1,317 (20.5)	In hospital/30-day major adverse events, and major bleeding	30 d
Burgess	2020	Australia	Prospective	Administrativ	No	Dec, 2010-	589	123 (21)	Cardiac death and	2 years

				e database		Apr, 2014			myocardial infarction	
Dharma	2020	Indonesia	Retrospective	Administrative database	No	Feb, 2011-Aug, 2019	6,557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherlands	Retrospective	Administrative database	Yes	2015-2016	787	229 (29)	All-cause mortality	1 year
Siabani	2020	Iran	Prospective	Clinical registry	No	Jun, 2016-May, 2018	1,484	311(21)	In-hospital mortality	NA
Tai	2020	China	Retrospective	Administrative database	No	Jan, 2013-Dec, 2017	182	56 (30.8)	In hospital/1-year mortality	1 year
Tizón	2020	Spain	Prospective	Clinical registry	Yes	2010-2016	14,690	3,486 (23.7)	30-day/1-year all-cause mortality	1 year

Table 2 Baseline characteristics of participants in included studies.

First	**Year**	**Age, mean (SD),**	**Diabete**		**Hypertensio**		**Hyperlipidemi**		**Smokin**		**Prior**		**Prior**	

Author		years		s, n (%)		n, n (%)		a, n (%)		g, n (%)		MI, n (%)		PCI, n (%)	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Venetsanos	2017	69 (13.0)	59 (11.0)	48 (13.0)	205 (13.7)	190 (51.5)	605 (40.5)	117 (31.7)	536 (35.9)	NA	NA	24 (6.5)	135 (9.0)	16 (4.3)	124 (8.3)
Ali	2018	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Langabeer	2018	62.5 (13.6)	60.2 (12.5)	759 (29.6)	1,975 (27.8)	NA	NA	1,265 (49.3)	3,693 (52.0)	951 (37.0)	2,763 (38.9)	435 (16.9)	1,304 (18.4)	NA	NA
Tang	2018	64.5 (9.3)	54.4 (10.7)	66 (31.4)	311 (25.1)	141 (67.1)	659 (53.3)	125 (59.5)	749 (60.3)	33 (15.7)	957 (77.3)	10 (4.8)	83 (6.7)	60 (28.6)	282 (22.8)
Cenko	2019	66.1	59.7	925	1,531	2,322 (74.6)	4,502	1,353 (43.3)	3,100	1,010	3,714	301	842	306	762

		(11.7)	(11.7)	(29.7)	(20.9)		(61.4)		(42.3)	(32.5)	(50.7)	(9.7)	(11.5)	(9.8)	(10.4)
Hao	2019	69.0 (10.6)	61.1 (12.4)	10,141 (48.1)	24,082 (39.4)	15,607 (74.1)	38,426 (62.9)	17,996 (85.4)	50,944 (83.3)	1,719 (8.2)	32,377 (53.0)	NA	NA	NA	NA
Hannan	2019	70.72 (14.73)	62.11 (12.82)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	868 (11.1)	2206 (13.8)
Maznyczka	2019	61.2 (12.2)	58.6(11.2)	8 (9.2)	26 (11.0)	32 (36.8)	73 (30.8)	28 (32.2)	66 (27.8)	57 (65.5)	139 (58.6)	5 (5.7)	20 (8.4)	2 (2.3)	16 (6.8)
Stehli	2019	66.5 (13.2)	60.8 (12.2)	245 (18.6)	770 (15.1)	NA	NA	NA	NA	NA	NA	NA	NA	104 (7.9)	577 (11.3)

Burgess	2020	62.7 (52.7-73.2)	58.2 (50.6-65.7)	39 (31.7)	88 (18.9)	84 (68.3)	243 (52.1)	83 (67.5)	253 (52.3)	64 (52.0)	252 (54.1)	9 (7.3)	41 (8.8)	NA	NA
Dharma	2020	60 (10)	55 (10)	403 (43.4)	1548 (27.5)	647 (69.6)	2,889 (51.3)	299 (32.2)	1,779 (31.6)	109 (11.7)	4,049 (71.9)	NA	NA	NA	NA
Kerkmanx	2020	68 (14)	61 (12)	39 (17.6)	66 (12.5)	101 (45.7)	178 (33.6)	56 (25.9)	110 (21.0)	88 (41.1)	258 (49.3)	30 (13.6)	79 (13.7)	33 (14.4)	77 (14.2)
Siabani	2020	65.8 (11.3)	59.0 (12.4)	114 (37.7)	187 (16.2)	195 (63.7)	410 (35.4)	110 (36.7)	208 (18.5)	41 (13.2)	655 (55.9)	NA	NA	NA	NA
Tai	2020	78 (76–81)	78 (76–80)	96 (35.2)	116 (26.5)	217 (79.5)	319 (72.8)	NA	NA	14 (5.4)	239 (56.5)	NA	NA	36 (13.5)	78 (18.1)

Tizón	2020	69.9 (13.7)	60.9 (12.6)	844 (24.2)	1,927 (17.2)	1,192 (34.2)	2,722 (24.3)	878 (25.2)	2,375 (21.2)	474 (13.6)	2,711 (24.2)	NA	NA	NA	NA

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Figure 1 Flowchart of selection of studies included in meta-analysis.

Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Short title：Sex differences in STEMI

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Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Objectives: To assess the effect of sex differences on short- and long-term mortality among patients with ST-segment elevation myocardial infarction (STEMI).

Design: Systematic review and meta-analysis of contemporary available evidence.

Setting: PubMed, Embase and Cochrane Library were searched for relevant studies reporting sex specific outcomes among patients with STEMI published between January 1, 2010 to August 1, 2020. Risk ratio (RR) 95% 95% confidence intervals (CIs) were measured using DerSimonian and Laird random-effects model. Sensitivity analyses were performed and publication bias was also checked. All statistical analyses were performed using STATA version 15.0.

Participants: Studies providing data about short- or long-term mortality stratified by sex in patients with STEMI were included. Only study conducted in last ten years were included.

Primary and secondary outcome measures: The primary outcome was all-cause death at short- (in-hospital or 30 days) and long-term (at least 12 months) follow-up.

Results

A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879 [75.3%] male) were included. In the unadjusted analyses, female were at a higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) but not long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%). When adjusted effect estimates from individual studies were used in meta-analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%). And adjusted long-term mortality was also similar between female and male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%).

Conclusions

An increased short- but not long-term mortality was found in female with STEMI. After adjustment for baseline cardiovascular risk factors and clinical profiles, short-term mortality remains higher in female with STEMI compared to male, indicating the need for further improvements in management in female patients.

Strengths and limitations of this study

- We assessed the contemporary effect of sex differences on mortality among patients with STEMI by meta-analysis of studies from the last decade.
- A greater number of potentially eligible articles were screened and the large sample size ensures adequate statistical power to detect even a small effect of interest.
- Sensitivity analyses by excluding one study at a time and restricting to studies with high quality or with large sample size got consistent results.
- Substantial and nonnegligible heterogeneity still exist in our meta-analysis and might result in potential bias.
- Residual confounding bias could not be totally excluded due to the observational study design of most included studies.

Contemporary sex differences in mortality among patients with ST-segment elevation myocardial infarction: a systematic review and meta-analysis

Introduction

Acute myocardial infarction remains one of leading causes of mortality in both men and women worldwide despite improvement of acute cardiac care.[1] Numerous studies have reported that women have a higher risk of in-hospital and long-term adverse outcomes following ST-segment elevation myocardial infarction (STEMI) compared with men.[2] Confounders including advanced age and more frequent comorbidities, such as hypertension and diabetes mellitus[3 4], might contribute to excess mortality in women. Moreover, previous studies show lower rates of guideline directed medical therapy and revascularization are also associated with poorer prognosis for women with STEMI.[5]

Sex discrepancies in management and outcomes after STEMI have been increasingly reported in the literature and raised public awareness.[6] Major progress in therapy for myocardial infarction and primary and secondary preventive interventions has been made to reduce cardiovascular mortality for women.[1 7] And there have been marked reductions in cardiovascular disease mortality in women with acute myocardial infarction in the past two decades.[1] Conflicting results are noted in recent studies on sex differences following STEMI. It is unclear whether the sex differences still exist, in view of substantial improvements in prognosis of cardiovascular disease over the past decade.

In order to assess the contemporary effect of sex differences on short- and long-term mortality among patients with STEMI, we performed a systematic review and meta-analysis of all available evidence from last decade reporting sex-specific outcomes after STEMI.

Methods

The present systematic review and meta-analysis was performed following the principle of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

Literature search

We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library from January 1, 2010 to August 1, 2020 to identify studies from the last decade that described sex differences in in short- or long-term mortality among patients with STEMI. Both observational studies and randomized clinical trials were eligible. We queried MeSH and the abstract text for the following three search terms: gender part (including "gender", "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular mortality" or "short term mortality"); myocardial infarction part (including "myocardial infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or "primary angioplasty") to identify relevant studies. There was no language restriction or age limit. The full search strategies were presented in eTable 1 of the Supplementary Material.

Study selection

According to the aim of our analyses, studies were included in this systematic review if data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality stratified by sex in patients with STEMI were reported. Two reviewers identified studies eligible for further review by performing an initial screen of titles or abstracts of the search results. Subsequently, a second screen of full texts eligibility was performed by another two reviewers. Studies had to fulfil the following criteria to be included in the present analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and ii) studies providing enough details to obtain numbers of events or incidence rates according to sex; and iii) enrollment starting not earlier than a decade ago. Editorials, letters, conference proceedings and abstracts were considered to be eligible only if sufficient information was available in abstracts or associated tables or figures. We excluded studies if they were review articles or case reports, or if they involved pregnant participants, critically ill patients, or provided insufficient data to allow for risk estimates to be calculated. Any disagreement was reviewed by a third reviewer and resolved by consensus.

Data extraction

Detailed data from selected studies were extracted independently by two reviewers using a standardized form independently. Data about study and participants characteristics, including year of study, sample size, time of enrollment, geographical location, endpoints of study, and follow-up duration, were collected. Any discrepancies were reviewed by a third reviewer and resolved by consensus. The quality of included studies was evaluated by Newcastle-Ottawa scale using prespecified items comprised of patients' selection (representativeness and selection of patients, ascertainment of exposure), comparability of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy of follow-up).[9] A quality score (0–9 points) was generated according to a maximum of 1 point for each item.

Patient and public involvement

Due to the nature of the systematic review and meta-analysis, this study did not involve patients and the public in the design, or conduct, or reporting or dissemination plans.

Statistical analysis

The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent the effect of sex differences on mortality after STEMI. And data were combined using random-effects model of DerSimonian and Laird with inverse variance weighting. Random-effect model was used due to substantial clinical and statistical heterogeneity. Following analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality using raw number of death and total participants at risk for death specific to each sex, ii) adjusted RRs for short- and long-term all-cause mortality using adjusted RRs if they were described in those included studies. In terms of short-term mortality, the RRs for in-hospital and 30-day mortality were also calculated respectively.

We assess heterogeneity across studies with Cochran's Q test and I2 test, with $P<0.1$ or $I2 >50\%$ considered significant. We also performed meta-regression to identify the potential sources of heterogeneity in the included studies. The potential sources were differences in diabetes, hypertension, hyperlipidemia, smoking, prior MI, and prior PCI. Furthermore, stratified analysis was conducted as well by dividing the included studies into different subgroups based on the Newcastle-Ottawa scale scores (>7 points or ≤7 points) to assess the potential sources of heterogeneity. To assess the potential effect of publication bias, we inspected funnel plots for

asymmetry and used the Egger's regression asymmetry test in which P<0.05 was considered to indicate significant publication bias.

Sensitivity analyses was conducted by excluding one study at a time and comparing the results with the complete one. In addition, we also performed sensitivity analyses by restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and restricting to studies with sample size bigger than 1000 participants. All statistical analyses were performed using STATA version 15.0 (Stata Corp, College Station, TX). Differences were considered statistically significant at P < .05 (2-sided).

Results

Literature search

Study selection details were outlined in Figure 1. The literature search identified 2,611 potentially relevant articles. After screening based on title and abstract review, 2495 records were excluded. A total of 116 full-text were finally assessed for eligibility, with 96 papers excluded due to enrollment starting earlier than a decade ago or no sufficient gender specific data to analyze. Another 5 papers reviewed in detail were excluded after due to data from the same cohorts. A total of 15 studies were finally included in the present systematic review and meta-analysis.[10-24]

Study characteristics

Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than 10,000 patients with STEMI. See Table 1 for further information of included studies. Baseline characteristics of participants were missing in some included studies, but all included studies provided sufficient data for analysis of sex differences in clinical outcomes. Except for 1 study, which was a prespecified gender analysis of randomized controlled trial, the remaining 14 were observational studies. Among the 10 included studies which reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension, and prior myocardial infarction/PCI, while some adjusted for renal insufficiency, cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset. Variables that were adjusted in the adjusted analyses from the included studies were presented in eTable 2 of the Supplementary Material. Results of assessment of study

quality using Newcastle-Ottawa scale were shown in eTable 3 in the Supplementary Material.

Patient characteristics

A total of 128,585 patients with STEMI (31,706 [24.7%] female and 96,879 [75.3%] male) were involved in the 15 included studies. Female tended to be older and had higher prevalence of diabetes mellitus in all included studies. And in most studies, other important comorbidities, including hypertension and hyperlipidemia, were more frequent in female. Greater proportions of male were smokers and had prior PCI or myocardial infarction. Besides, some studies reported that door-to-balloon time and symptom onset to balloon time were longer in female than male. Part of patient baseline characteristics were summarized in Table 2.

Short-term all-cause mortality

Thirteen studies reported sex-specific unadjusted short-term mortality (7 studies with 30-day mortality and 6 studies with in-hospital mortality) of patients with STEMI. There were 2,873 of 31,409 (9.1%) cases of all-cause mortality in female compared with 4,380 of 95,610 (4.6%) in male. Female were at a significantly higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I^2=77%) compared with male (Figure 2 A). Nine studies involving 119,379 patients reported adjusted short-term mortality specific to sex. In adjusted analysis, the association between female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I^2=39.6%) (Figure 2 B). However, the strength of association calculated with adjusted RRs from these 9 studies was attenuated.

Subgroup analysis demonstrated that the results of studies with Newcastle-Ottawa scale >7 points (RR, 1.90; 95%CI, 1.73-2.09, P=0.018, I^2=63.4%) and studies with ≤7 points (RR, 1.52; 95%CI, 1.20-1.93, P=0.026, I^2=58.1%) were consistent in unadjusted short-term mortality (See eFigure 1 in the Supplementary Material). The impact of sex on in-hospital (RR, 1.71; 95%CI, 1.27-2.31, P<.001, I^2=86.4%) and 30-day mortality (RR, 1.81; 95%CI, 1.62-2.02, P<.001, I^2=56.6%) were consistent. The meta-analysis performed in studies of patients undergoing PCI for STEMI also showed increased unadjusted mortality (RR, 1.45; 95%CI, 1.05-2.00, P=0.026, I^2=39.5%) in female patients.

Long-term all-cause mortality

Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and followed up for more than 1 year, and reported all-cause mortality for female and male. The incidence of long-term all-cause mortality was 13.9% (n=584) in female and 8.7% (n=1202) in male. In unadjusted analysis, no significant sex difference was found in long-term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I^2=77.5%) (Figure 3 A). The unadjusted long-term mortality was also similar between female and male patients undergoing PCI (RR, 1.28; 95%CI, 0.95-1.73, P=0.108, I^2=0.0%). And the adjusted analysis of the pooled results from four studies, also showed a similar risk of mortality at long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I^2=74.5%) (Figure 3 B).

Meta-Regression Analysis, sensitivity analyses and publication bias

According to meta-regression analysis, differences in prevalence of diabetes (β coefficient, 0.248; P=0.337; adjusted R^2=1.31%; I^2=80.86%; τ^2=0.044), hypertension (β coefficient, -0.255; P=0.538; adjusted R^2=24.22%; I^2=41.04%; τ^2=0.008), hyperlipidemia(β coefficient, 0.260; P=0.415; adjusted R^2=-1.84%; I^2=83.59%; τ^2=0.050), smoking (β coefficient, -0.040; P=0.255; adjusted R^2=17.86%; I^2=79.41%; τ^2=0.045), prior MI (β coefficient, -2.725; P=0.126; adjusted R^2=60.30%; I^2=60.19%; τ^2=0.032), and prior PCI (β coefficient, 0.109; P=0.896; adjusted R^2=-58.31%; I^2=61.73%; τ^2=0.042) between sexes were not identified as significant sources of heterogeneity for short-term all-cause mortality. Given that not all included study provided information on confounders stratified by sex, the results of meta-regression analyses should be interpreted with caution.

Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75; 95%CI, 1.54-1.99, P<.001, I^2=82.9%) both indicated that none of the studies affected the results of short-term mortality in this meta-analysis significantly. In analysis for long-term mortality, sensitivity analysis showed a possibly higher influence on the result attribute to the study of Tai et al (See eFigure 3 in the Supplementary Material). After removing this study from meta-analysis, the association of female with increased long-term mortality became significant (RR, 1.50; 95%CI, 1.23-1.83, P<.001, I^2=40.9%). We found no evidence of publication bias across studies based on visual inspection of funnel plots (See eFigure 4 in the Supplementary Material) and the results from Egger's tests for

short-term mortality (P=0.462) and for long-term mortality (P=0.053).

Discussion:

Our systematic review and meta-analysis of contemporary literature on sex differences among patients with STEMI demonstrate that female have a higher risk of short- but not long-term mortality compared with male with STEMI. Furthermore, after adjustment for baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term mortality are attenuated but remain significant, while female have the similar long-term mortality with male.

Our results are somewhat in accordance with several previously published meta-analysis.[2 25] A considerable number of studies have consistently suggested that women were at a higher risk of short-term mortality after ACS. However, whether risk of long-term mortality is also higher in women with ACS remains under debate. Some studies indicated that women with STEMI had a higher 1-year rate of death compared to men[26], while the 1-year mortality rate was conversely lower in women than men in some other studies[23 24]. In our study, with respect to short-term mortality, the analyses of studies with high or low quality, and big or small sample size yielded similar results. However, in terms of long-term mortality, caution is needed when interpreting our finding of non-significant increased long-term mortality in adjusted analyses, due to the results of sensitivity analysis which showed a significant association between female and increased long-term mortality after removing one study from adjusted analyses.

It is widely accepted that there are significant differences in outcomes of women and men with acute myocardial infarction. In our study, after adjusted for participants' baseline cardiovascular risk factors and clinical profiles, the strength of association between gender and short-term mortality was substantially attenuated, which suggested that poorer baseline cardiovascular risk profile partially explained the impact of sex differences on mortality. Multiple studies have shown that women with STEMI present at older age and have a higher burden of comorbidities, contributing to the sex differences in mortality after STEMI.[27] All studies included in our meta-analysis demonstrate that female patients are older and with more diabetes mellitus as well as hypertension.

In addition, some sex-specific studies found that certain risk factors and comorbidities were more potent in women.[28] Diabetes mellitus , hypertension and smoking status are more strongly associated with increased risk of cardiac events in women compared with men.[27 29]

Notably, that these differences mentioned above still could not completely explain the gap in mortality between sexes. It has been proved that women with acute myocardial infarction were less likely to be treated with guideline directed medical therapy and less likely to receive primary reperfusion therapy including primary percutaneous coronary intervention or fibrinolysis.[30] Regarding medical therapy, numerous studies conducted around the world consistently demonstrate female survivors are receiving less optimal medical therapy after acute myocardial infarction during hospitalization or at discharge.[31 32] Though there might be no differences in treatment adherence between men and women, some studies report significant sex disparities in initiation of appropriate pharmacotherapy after myocardial infarction.[33] Results from these observational studies have shown women are receiving less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme inhibitors in all age groups, especially young women, and suggested that clinicians and patients may benefit from better education and awareness of undertreatment of younger women.[33 34]

Lower rates of revascularization are observed among women with STEMI compared with men in several studies despite proven benefit of this therapy.[35] Moreover, the sex differences might be driven by delays in presentation to hospital and women with STEMI were more likely to experience longer delays than men. Although a great improvement in emergency medical services and timely revascularization over the past decades, recent studies show that women with STEMI still present later and have a longer ischemic time than men. Previous studies have shown consistently that women have longer door-to balloon times and longer door-to needle times.[36 37] In addition, women are also more likely to exhibit longer pre-hospital delays in seeking medical care after the development of symptoms suggestive of myocardial infarction. Although there have been significant reductions in patient and system delay in the last decade, women continue to have longer presentation and treatment times.[38] Sex differences also exist in clinical presentation of STEMI. Although chest pain was the most common ACS symptom in both sexes, women were more likely

to present without chest pain than men.[39 40] Lower rates of typical chest pain reported among women with STEMI may also influence provider decision-making to pursue less aggressive care including invasive revascularization.

Some included studies of our meta-analysis enrolled STEMI patients in general[14-16], while some others enrolled patients undergoing PCI for STEMI[11 13 18]. The different prognosis of patients receiving reperfusion therapy or no-reperfusion therapy might be a potential source of heterogeneity of our study. Nevertheless, our results are completely consistent with a previous meta-analysis from Pancholy et al., which investigated sex differences in mortality among patients with STEMI treated with primary PCI.[2] Its results demonstrated that, when adjusted RRs were used, the increased risk for 1-year mortality in women was no longer significant and the risk of in-hospital mortality still significantly elevated. It should be noted that more than 50% of patients were treated with PCI in the most study conducted among the general STEMI patients and included by our analysis, even more than 90% in some included studies.[12 24] The increasing rate of primary PCI in recent years might be a reason for the consistency of our findings and previous studies conducted specifically among STEMI patients undergoing PCI.

Complications including bleeding, heart failure and mechanical complications are more likely to develop in women with acute myocardial infarction and increase the risk of mortality.[14 41 42] Bleeding secondary to antithrombotic therapies and invasive procedures is more frequent in women.[43] Three included studies reported incidence of bleeding following STEMI and they all found that women were at higher risk of bleeding.[10 13 18] One study included in our analysis examined the relationships among sex, acute heart failure, and related outcomes after STEMI.[14] Its results demonstrate that women are at higher risk to develop de novo heart failure after STEMI and women with de novo heart failure have worse survival compared with man. However, we could not compare the incidence of these complications due to the lack of sufficient data. Mechanical complications requiring surgical intervention are also much more common in women after acute myocardial infarction and associated with high mortality rates.[44]

Several limitations of this meta-analysis should be considered. First, the included studies are all

observational studies except one post hoc analysis of randomized controlled trial. Hence, there may be residual confounding bias inherent in the observational study design in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the same confounders and not all studies reported adjusted RRs. The confounders which were adjusted in the included studies might differ greatly across studies. Third, there was substantial heterogeneity in our meta-analysis, which could partly be attributed to the wide variability in the sample sizes, locations, and treatment regimens across included studies. Additionally, although we calculated adjusted RRs for all-cause mortality, it needed to be noted that relevant confounders might have differed across studies. Fourth, the analysis of long-term mortality, especially the adjusted analysis, included far fewer studies compared with analysis of short-term mortality. Hence, there might be significant bias in the results about long-term mortality.

In conclusion, our meta-analysis, pooling data from contemporary literature, shows that women with STENI have a higher risk of short-term mortality but not long-term mortality. The effect of sex differences on mortality in patients with STEMI remain significant after adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that public awareness of increased risk and further improvements in management in women with STEMI are necessary.

Other Information:

Contribution statement

Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis, Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data acquisition, Data analysis/interpretation. Jianan Li, Yang Li, Jianfeng Zheng and Runlin Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.

Conflict of interest

The authors declare that there is no conflict of interest.

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Ethics approval

The institutional central committee at Fuwai Hospital approved that the study protocol and inform consent was not required for a systematic review and meta-analysis.

Data sharing statement

As this is a systematic review and meta-analysis, the data used in the study have already been published by the authors of the included studies. All data relevant to the study are included in the article or uploaded as supplementary information.

Table 1 Characteristics of included studies.

First Author	Year	Region	Study design	Data source	Multicenter	Time of enrollment	Number of STEMI patients	Female	Endpoint	Follow-up
Venetsanos	2017	13 countries	Prospective	Clinical registry	Yes	Sep, 2011-Oct, 2013	1,862	369 (20.0)	Major adverse cardiovascular events and definite stent thrombosis	30 d
Ali	2018	Germany	Prospective	Administrative database	No	2013-2017	312	101 (32.4)	All-cause in-hospital mortality	NA
Langabeer	2018	US	Prospective	Clinical registry	Yes	Jan, 2010-Dec, 2015	9,674	2,569 (26.6)	In-hospital mortality	NA
Tang	2018	China	Prospective	Administrative database	No	Jan, 2013-Dec, 2013	1,238	210 (1.9)	Major adverse cardiac and cerebrovascular events	730 ± 30 d
Cenko	2019	12 European countries	Prospective	Clinical registry	Yes	Jan, 2010-Jul, 2018	10,443	3,112 (29.8)	30-day all-cause mortality	30 d
Hao	2019	China	Prospective	Clinical registry	Yes	Nov, 2014-Jun, 2018	50,203	11,016 (21,9)	In-hospital mortality	NA
Hannan	2019	US	Retrospective	Administrative database	Yes	Jan, 2013-Dec, 2015	23,809	7,791 (32.7)	In hospital/30-day mortality	30 d

Maznyczka	2019	UK	Retrospective	Clinical registry	No	July, 2011-Nov, 2012	324	87 (26.9)	All-cause death/ first heart failure hospitalization	5 years
Stehli	2019	Australia	Prospective	Clinical registry	Yes	2013-2016	6,431	1,317 (20.5)	In hospital/30-day major adverse events, and major bleeding	30 d
Burgess	2020	Australia	Prospective	Administrative database	No	Dec, 2010-Apr, 2014	589	123 (21)	Cardiac death and myocardial infarction	2 years
Dharma	2020	Indonesia	Retrospective	Administrative database	No	Feb, 2011-Aug, 2019	6,557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherlands	Retrospective	Administrative database	Yes	2015-2016	787	229 (29)	All-cause mortality	1 year
Siabani	2020	Iran	Prospective	Clinical registry	No	Jun, 2016-May, 2018	1,484	311(21)	In-hospital mortality	NA
Tai	2020	China	Retrospective	Administrative database	No	Jan, 2013-Dec, 2017	182	56 (30.8)	In hospital/1-year mortality	1 year
Tizón	2020	Spain	Prospective	Clinical registry	Yes	2010-2016	14,690	3,486 (23.7)	30-day/1-year all-cause mortality	1 year

Table 2 Baseline characteristics of participants in included studies.

First	**Year**	**Age, mean (SD), years**	**Diabetes**		**Hypertensio**		**Hyperlipidemi**		**Smokin**		**Prior**		**Prior**	

Author		, n (%)		n, n (%)		a, n (%)		g, n (%)		MI, n (%)		PCI, n (%)	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Venetsanos	2017	69 (13.0)	59 (11.0)	48 (13.0)	205 (13.7)	190 (51.5)	605 (40.5)	117 (31.7)	536 (35.9)	NA	NA	24 (6.5)	135 (9.0)	16 (4.3)	124 (8.3)
Ali	2018	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Langabeer	2018	62.5 (13.6)	60.2 (12.5)	759 (29.6)	1,975 (27.8)	NA	NA	1,265 (49.3)	3,693 (52.0)	951 (37.0)	2,763 (38.9)	435 (16.9)	1,304 (18.4)	NA	NA
Tang	2018	64.5 (9.3)	54.4 (10.7)	66 (31.4)	311 (25.1)	141 (67.1)	659 (53.3)	125 (59.5)	749 (60.3)	33 (15.7)	957 (77.3)	10 (4.8)	83 (6.7)	60 (28.6)	282 (22.8)
Cenko	2019	66.1 (11.7)	59.7 (11.7)	925 (29.7)	1,531 (20.9)	2,322 (74.6)	4,502 (61.4)	1,353 (43.3)	3,100 (42.3)	1,010 (32.5)	3,714 (50.7)	301 (9.7)	842 (11.5)	306 (9.8)	762 (10.4)
Hao	2019	69.0 (10.6)	61.1 (12.4)	10,141 (48.1)	24,082 (39.4)	15,607 (74.1)	38,426 (62.9)	17,996 (85.4)	50,944 (83.3)	1,719 (8.2)	32,377 (53.0)	NA	NA	NA	NA
Hannan	2019	70.72 (14.73)	62.11 (12.82)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	868 (11.1)	2206 (13.8)
Maznyczka	2019	61.2 (12.2)	58.6(11.2)	8 (9.2)	26 (11.0)	32 (36.8)	73 (30.8)	28 (32.2)	66 (27.8)	57 (65.5)	139 (58.6)	5 (5.7)	20 (8.4)	2 (2.3)	16 (6.8)

Stehli	2019	66.5 (13.2)	60.8 (12.2)	245 (18.6)	770 (15.1)	NA	NA	NA	NA	NA	NA	NA	NA	104 (7.9)	577 (11.3)
Burgess	2020	62.7 (52.7-73.2)	58.2 (50.6-65.7)	39 (31.7)	88 (18.9)	84 (68.3)	243 (52.1)	83 (67.5)	253 (52.3)	64 (52.0)	252 (54.1)	9 (7.3)	41 (8.8)	NA	NA
Dharma	2020	60 (10)	55 (10)	403 (43.4)	1548 (27.5)	647 (69.6)	2,889 (51.3)	299 (32.2)	1,779 (31.6)	109 (11.7)	4,049 (71.9)	NA	NA	NA	NA
Kerkmanx	2020	68 (14)	61 (12)	39 (17.6)	66 (12.5)	101 (45.7)	178 (33.6)	56 (25.9)	110 (21.0)	88 (41.1)	258 (49.3)	30 (13.6)	79 (13.7)	33 (14.4)	77 (14.2)
Siabani	2020	65.8 (11.3)	59.0 (12.4)	114 (37.7)	187 (16.2)	195 (63.7)	410 (35.4)	110 (36.7)	208 (18.5)	41 (13.2)	655 (55.9)	NA	NA	NA	NA
Tai	2020	78 (76–81)	78 (76–80)	96 (35.2)	116 (26.5)	217 (79.5)	319 (72.8)	NA	NA	14 (5.4)	239 (56.5)	NA	NA	36 (13.5)	78 (18.1)
Tizón	2020	69.9 (13.7)	60.9 (12.6)	844 (24.2)	1,927 (17.2)	1,192 (34.2)	2,722 (24.3)	878 (25.2)	2,375 (21.2)	474 (13.6)	2,711 (24.2)	NA	NA	NA	NA

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Figure 1 Flowchart of selection of studies included in meta-analysis.

Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 1 Flowchart of selection of studies included in meta-analysis.

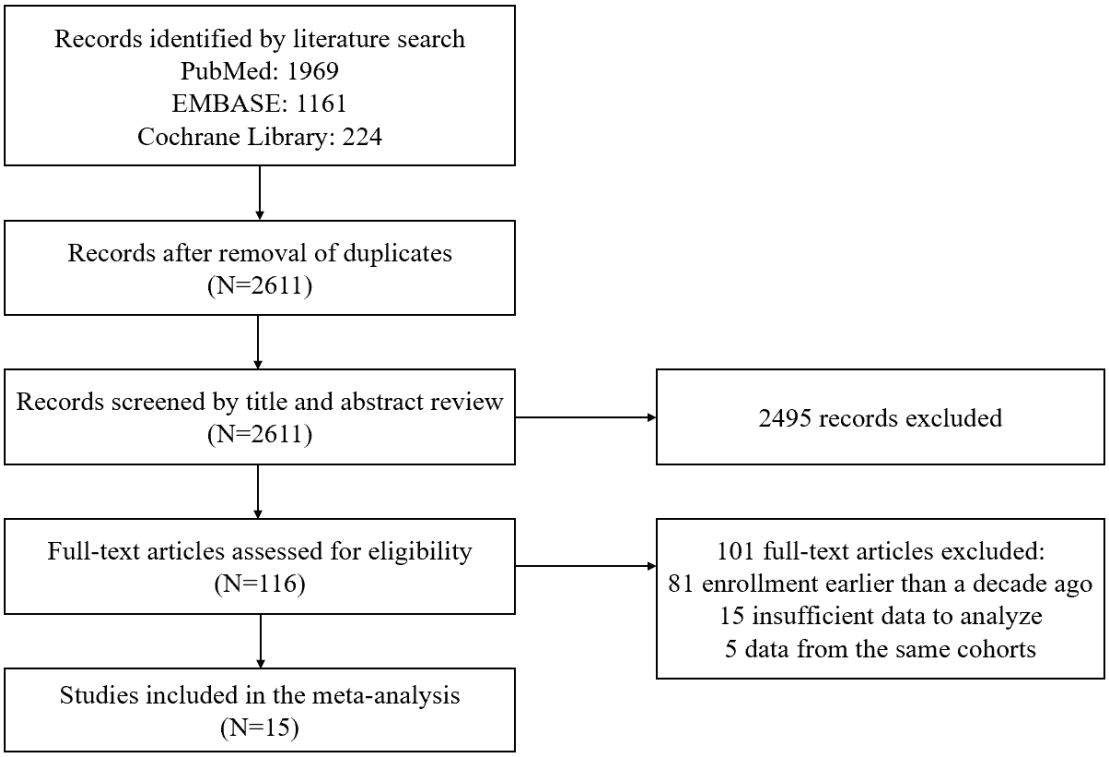
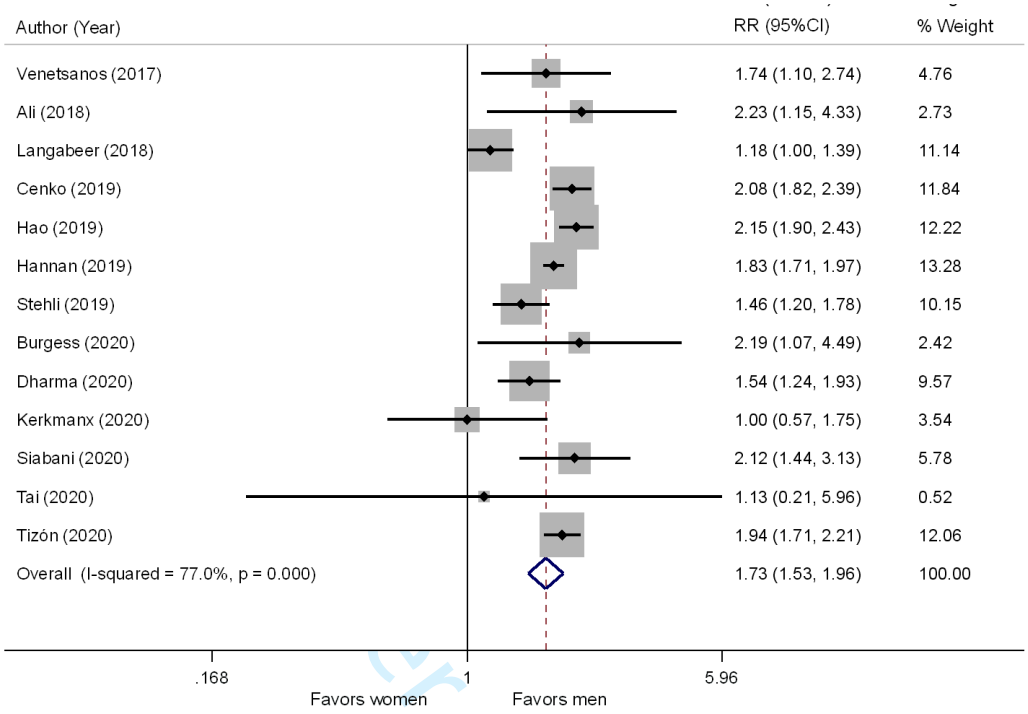
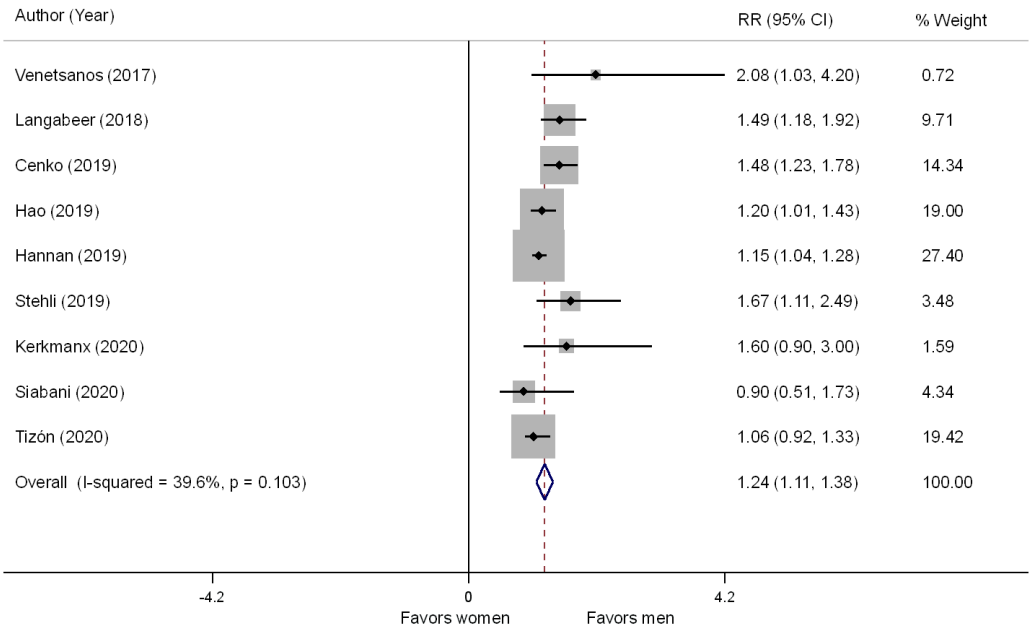


Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



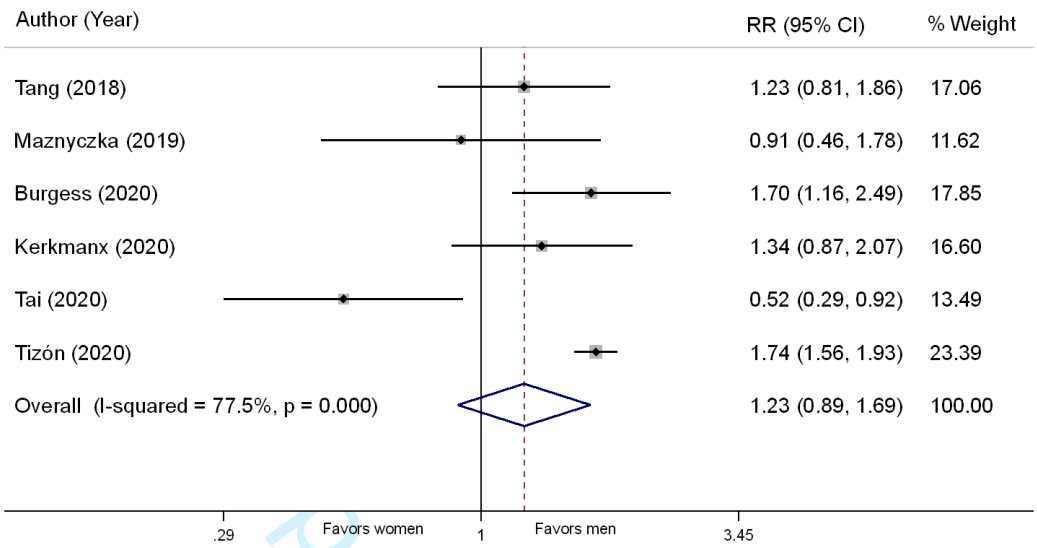
B



Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



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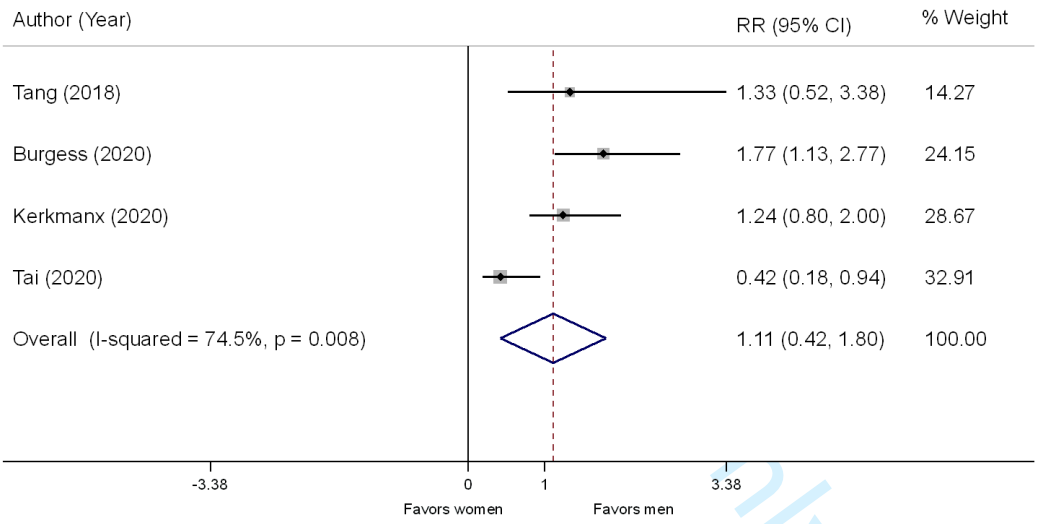


Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

eTable 1 Full search strategies for meta-analysis of studies reporting sex specific outcomes of patients with STEMI.

Database	Search strategy (publications accessible January 1, 2010 to August 1, 2020)
PubMed	("gender"[Title/Abstract] OR "female"[Title/Abstract] OR "male"[Title/Abstract] OR "gender differences"[Title/Abstract] OR "sex differences"[Title/Abstract] OR "sex characteristics"[MeSH Terms]) AND ("death"[MeSH Terms] OR "mortality"[MeSH Terms] OR "hospital mortality"[MeSH Terms] OR "cardiac death"[Title/Abstract] OR "sudden cardiac death"[MeSH Terms] OR "all-cause mortality"[Title/Abstract] OR "long term mortality"[Title/Abstract] OR "one year mortality"[Title/Abstract] OR "cardiovascular mortality"[Title/Abstract] OR "short term mortality"[Title/Abstract]) AND ("myocardial infarction"[MeSH Terms] OR "acute myocardial infarction"[Title/Abstract] OR "ST Elevation Myocardial Infarction"[MeSH Terms] OR "myocardial necrosis"[Title/Abstract] OR "primary percutaneous coronary intervention"[Title/Abstract] OR "primary PCI"[Title/Abstract] OR "primary angioplasty"[Title/Abstract])
EMBASE	(gender.mp OR female.mp OR male.mp OR gender differences.mp OR sex differences.mp OR sex characteristics.mp) AND (death.mp OR mortality.mp OR hospital mortality.mp OR cardiac death.mp OR sudden cardiac death.mp OR all-cause mortality.mp OR long term mortality OR one year mortality.mp OR cardiovascular mortality.mp OR short term mortality) AND (myocardial infarction.mp OR acute myocardial infarction.mp OR ST Elevation Myocardial Infarction.mp OR myocardial necrosis.mp OR primary percutaneous coronary intervention.mp OR primary PCI.mp OR primary angioplasty.mp)
Cochrane Library	[Title and abstract search] (gender OR female OR male OR gender differences OR sex differences OR sex characteristics) AND (death OR mortality OR hospital mortality OR cardiac death OR sudden cardiac death OR all-cause mortality OR long term mortality OR one year mortality OR cardiovascular mortality OR short term mortality) AND (myocardial infarction OR acute myocardial infarction OR ST Elevation Myocardial Infarction OR myocardial necrosis OR primary percutaneous coronary intervention OR primary PCI OR primary angioplasty)

eTable 2 Variables adjusted in the adjusted analyses from the included studies.

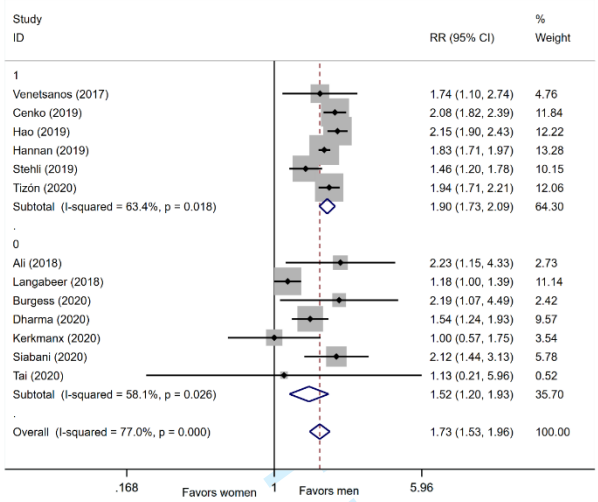
First Author	Year	Adjusted Variables
Venetsanos	2017	age, weight, prior MI, prior PCI, patient's history of diabetes, hypertension, non-hemorrhagic stroke, gastrointestinal bleeding, time from symptom onset to pre-PCI ECG, admission Killip class, baseline hemoglobin, eGFR, access site, use of Glycoprotein IIIb/IIa inhibitor, bivalirudin and unfractionated heparin, location of MI and revascularization
Langabeer	2018	age, smoking, diabetes, prior CVD, prior stroke, heart failure, shock, length of stay, teaching, insurance, total ischemic time, door to balloon
Tang	2018	age, BMI, LVEF, serum creatinine, use of proton pump inhibitors, use of dual-antiplatelet therapy, previous PCI, diabetes mellitus, hypertension, previous stroke, current smoker, thrombocytopenia, use of femoral approach, use of intra-aortic balloon pump, and multivessel disease
Cenko	2019	age, family history of CAD, diabetes, hypertension, hypercholesterolemia, current smoking, former

		smoking, prior angina pectoris, prior myocardial infarction, prior PCI, prior CABG, peripheral artery disease, prior stroke, ST-segment elevation in anterior leads (at ECG), systolic blood pressure at baseline, heart rate at baseline, serum creatinine at baseline, Killip Class ⩾2
Hao	2019	Age, medical insurance status, acute heart failure, cardiogenic shock, cardiac arrest at admission, heart rate and systolic blood pressure, diabetes mellitus, smoking, history of CHD, heart failure, renal failure, and cerebrovascular disease, prehospital statin use, renal insufficiency, and transfer status.
Hannan	2019	age, STEMI location, heart rate, mean arterial pressure, history of hospitalization in last year, history of PCI, history of CABG surgery, septicemia/sepsis/systemic inflammatory response /shock, metastatic cancer/acute leukemia, diabetes with acute complications, end stage liver disease, inflammatory bowel disease, coagulation defects and other specified hematological disorders, dementia, polyneuropathy, muscular dystrophy, seizure disorders and convulsions, coma/brain compression/anoxic damage, cardiorespiratory failure and shock, congestive heart failure, specified heart arrhythmias, ischemic or unspecified stroke, hemiplegia/hemiparesis, vascular disease with complications, vascular disease without complications, aspiration and specified bacterial pneumonias, acute renal failure, chronic kidney disease, Stage 5, unspecified renal failure, nephritis, pressure ulcer of skin with partial thickness skin loss*, pressure pre-ulcer skin changes, chronic ulcer of skin except pressure ulcer, lower limb/amputation complications
Maznyczka	2019	NA
Stehli	2019	age, diabetes mellitus, eGFR, previous PCI and/or coronary artery bypass grafting, history of peripheral vascular disease and CVD, LVEF, out-of-hospital and in-hospital cardiac arrest, cardiogenic shock, and occurrence time of symptom onset
Burgess	2020	NA
Dharma	2020	NA
Kerkmanx	2020	NA
Siabani	2020	BMI⩾25, hypertension, diabetes, current smoking, hypercholesterolemia, congestive heart failure, Killip class (at first presentation) ⩾ II, symptom-to-balloon time> 360 min and door-to-balloon time > 90 min
Tai	2020	NA
Tizón	2020	age, diabetes mellitus, recruitment year, time from symptom onset to culprit coronary artery opening, and Killip class

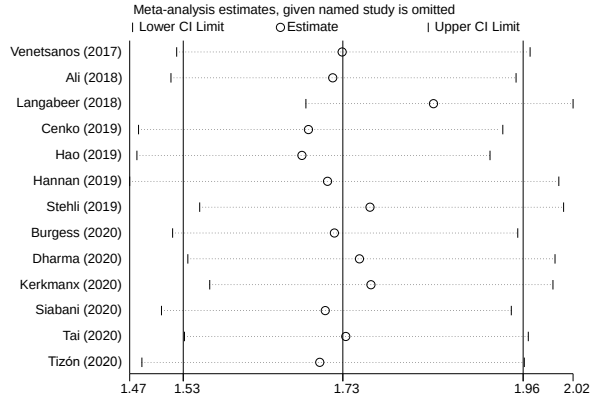
eTable 3 Assessment of study quality using Newcastle-Ottawa scale.

First Author	Year	Selection				Comparability	Outcome			Total points
		Representativeness of the exposed cohor	Selection of the no exposed cohort	Ascertainment of exposure to implants	Outcome of interest not present at start of study		Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up	
Venetsanos	2017	*	*	*	*	**	*	\	*	8
Ali	2018	\	\	*	*	\	*	\	*	4
Langabeer	2018	*	*	*	*	*	*	\	*	7
Tang	2018	\	\	*	*	**	*	*	*	7
Cenko	2019	*	*	*	*	**	*	\	*	8
Hao	2019	*	*	*	*	**	*	\	*	8
Hannan	2019	*	*	*	*	**	*	\	*	8
Maznyczka	2019	\	\	*	*	\	*	*	*	5
Stehli	2019	*	*	*	*	**	*	\	*	8
Burgess	2020	\	\	*	*	**	*	*	*	7
Dharma	2020	\	\	*	*	*	*	*	*	6
Kerkmanx	2020	*	*	*	*	\	*	*	*	7
Siabani	2020	\	\	*	*	*	*	\	*	5
Tai	2020	\	\	*	*	**	*	*	*	7
Tizón	2020	*	*	*	*	**	*	*	*	9

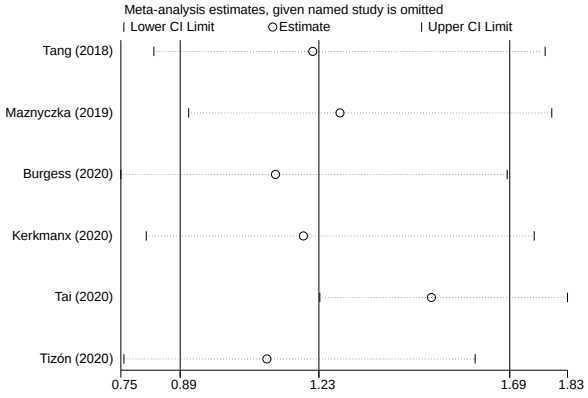
eFigure 1 Forest plots of relative risks of short-term all-cause mortality of studies with Newcastle-Ottawa scale >7 points and with ⩽7 points.



eFigure 2 Meta-influence analysis for unadjusted short-term mortality

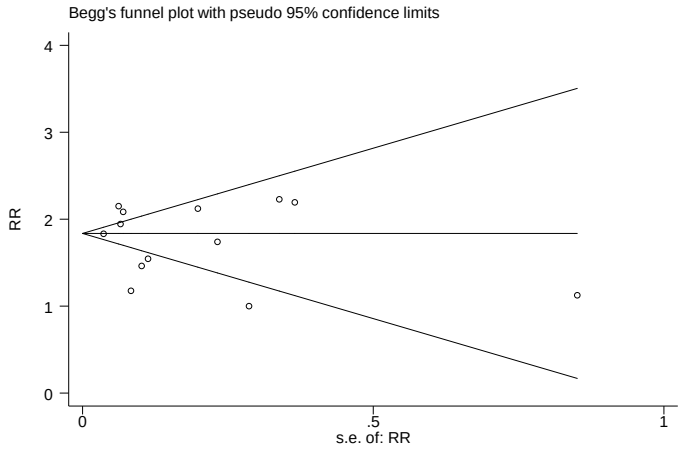


eFigure 3 Meta-influence analysis for unadjusted long-term mortality

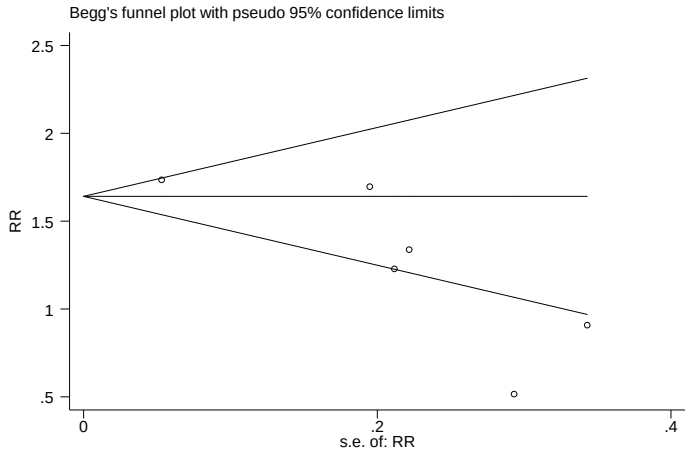


eFigure 4 Funnel plots for publication bias for unadjusted short-term (A) and long-term (B) mortality

A



B



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4
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 record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
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 each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	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.	Page 5
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.	Page 5
Synthesis methods	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)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
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 in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 6
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 7
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.	Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 6
	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.	Page 6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 7
	23b	Discuss any limitations of the evidence included in the review.	Page 8-9
	23c	Discuss any limitations of the review processes used.	Page 8-9
	23d	Discuss implications of the results for practice, policy, and future research.	Page 7-8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
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 included studies; data used for all analyses; analytic code; any other materials used in the review.	

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