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

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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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8
9 **Short title : Sex differences in STEMI**
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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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12 **Objectives**
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14 To assess the effect of sex differences on short- and long-term mortality among patients
15 with ST-segment elevation myocardial infarction (STEMI) by performing a meta-analysis
16 of contemporary available evidence in this topic.
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25 **Methods**
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27 PubMed, Embase and Cochrane Library were searched for relevant studies reporting sex
28 specific outcomes among patients with STEMI. Only study conducted in last ten years were
29 included. The primary outcome was all-cause death at short- and long-term follow-up. Risk
30 ratio (RR) 95% CIs were measured using the Mantel-Haenszel method. The random-effect
31 model was used for analysis. All statistical analyses were performed using STATA version
32 15.0.
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46 **Results**
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48 A total of fifteen studies involving 128,585 patients (31,706 women and 96879 patients)
49 were included. In the unadjusted analyses, women were at a higher risk of short-term
50 mortality (RR, 1.73; 95%CI, 1.53-1.96, P<.001, I²=77%) but not long-term mortality (RR,
51 1.23; 95%CI, 0.89-1.69, P<.001, I²=77.5%). When adjusted effect estimates from individual
52 studies were used in meta-analysis, the association between women and higher risk of
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4 short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, P=0.103, I²=39.6%).
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6 And adjusted long-term mortality was also similar between women and men (RR, 0.11;
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8
9 95%CI, 0.42-1.80, P=0.008, I²=74.5%).
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14 **Conclusions**

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

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4 mortality among patients with STEMI, we performed a systematic review and meta-
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6 analysis of all available evidence from last decade reporting sex-specific outcomes after
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8 STEMI.
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11 12 13 14 **Methods**

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

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

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

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45 Detailed data from selected studies were extracted independently by two reviewers using
46 a standardized form independently. Data about study and participants characteristics,
47 including year of study, sample size, time of enrollment, geographical location, endpoints
48 of study, and follow-up duration, were collected. Any discrepancies were reviewed by a
49 third reviewer and resolved by consensus. The quality of included studies was evaluated
50 by Newcastle-Ottawa scale using prespecified items comprised of patients' selection
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4 (representativeness and selection of patients, ascertainment of exposure), comparability
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6 of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy
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8 of follow-up).[9] A quality score (0–9) was generated according to a maximum of 1 score
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10 for each item.
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14 15 16 17 *Patient and public involvement*

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19 Due to the nature of the systematic review and meta-analysis, this study did not involve
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21 patients and the public in the design, or conduct, or reporting or dissemination plans.
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26 27 *Statistical analysis*

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29 The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent
30
31 the effect of sex differences on mortality after STEMI. And data were combined using
32
33 random-effects model of DerSimonian and Laird with inverse variance weighting. Random-
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35 effect model was used due to substantial clinical and statistical heterogeneity. Following
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37 analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality
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39 using raw number of death and total participants at risk for death specific to each sex, ii)
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41 adjusted RRs for short- and long-term all-cause mortality using adjusted RRs described in
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43 included studies.
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50 We assess heterogeneity across studies with Cochran's Q test and I² test, with P<0.1 or
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52 I² >50% considered significant. To assess the potential effect of publication bias, we
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54 inspected funnel plots for asymmetry and used the Egger's regression asymmetry test in
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56 which P<0.10 was considered to indicate significant publication bias. Sensitivity analyses
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4 was conducted by excluding one study at a time and comparing the results with the
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6 complete one. In addition, we also performed sensitivity analyses by restricting to high-
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8 quality studies with a Newcastle-Ottawa scale of 5 points or more and restricting to studies
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10 with sample size bigger than 1000 participants. All statistical analyses were performed
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12 using STATA version 15.0 (Stata Corp, College Station, TX).
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19 **Results**

20 *Literature search*

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

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49 Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than
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51 10,000 patients with STEMI. See Table 1 for further information of included studies. Except
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53 for 1 study, which was a prespecified gender analysis of randomized controlled trial, the
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55 remaining 14 were observational studies. Among the 10 included studies which reported
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57 adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension, and
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4 prior myocardial infarction/PCI, while some adjusted for renal insufficiency, cardiogenic
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6 shock, cardiac arrest at admission and occurrence time of symptom onset.
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10 11 *Patient characteristics*

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

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40 Thirteen studies reported sex-specific unadjusted short-term mortality of patients with
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42 STEMI. There were 2,873 of 31,409 (9.1%) cases of all-cause mortality in women
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44 compared with 4,380 of 95,610 (4.6%) in men. Women were at a significantly higher risk
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46 of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, $P<.001$, $I^2=77%$) compared with men
47
48 (Figure 2 A). Nine studies involving 119,379 patients reported adjusted short-term mortality
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50 specific to sex. In adjusted analysis, the association between women and higher risk of
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52 short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, $P=0.103$, $I^2=39.6%$)
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54 (Figure 2 B). However, the strength of association calculated with adjusted RRs from these
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4 9 studies was attenuated. Results of assessment of study quality using Newcastle-Ottawa
5
6 scale were shown in eTable 1 in the Supplementary Material.
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10 11 *Long-term all-cause mortality*

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14 Six studies involved 18,018 patients with STEMI (4,191 women and 13,827 men) and
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16 followed up for more than 1 year, and reported all-cause mortality for women and men.
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18 The incidence of long-term all-cause mortality was 13.9% (n=584) in women and 8.7%
19
20 (n=1202) in men. In unadjusted analysis, no significant sex difference was found in long-
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22 term mortality (RR, 1.23; 95%CI, 0.89-1.69, P<.001, I²=77.5%) (Figure 3 A). And the
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24 adjusted analysis of the pooled results from four studies, also showed a similar risk of
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26 mortality at long-term follow-up in women compared with men (RR, 1.11; 95%CI, 0.42-1.80,
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28 P=0.008, I²=74.5%) (Figure 3 B).
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38 *Sensitivity analyses and publication bias*

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40 Sensitivity analysis by excluding one study at a time (See eFigure 1 in the Supplementary
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42 Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75;
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44 95%CI, 1.54-1.99, P<.001, I²=82.9%) both indicated that none of the studies affected the
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46 results of short-term mortality in this meta-analysis significantly. In analysis for long-term
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48 mortality, sensitivity analysis showed a possibly higher influence on the result attribute to
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50 the study of Tai et al (See eFigure 2 in the Supplementary Material). After removing this
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52 study from meta-analysis, the association of women with increased long-term mortality
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54 became significant (RR, 1.50; 95%CI, 1.23-1.83, P=0.148, I²=40.9%). We found no
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4 evidence of publication bias across studies based on visual inspection of funnel plots (See
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6 eFigure 3 in the Supplementary Material) and the results from Egger's tests for short-term
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8 mortality (P=0.462) and for long-term mortality (P=0.053).
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14 **Discussion:**

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19 Our systematic review and meta-analysis of contemporary literature on sex differences
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21 among patients with STEMI demonstrate that women have a higher risk of short- but not
22
23 long-term mortality compared with men with STEMI. Furthermore, after adjustment for
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25 baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term
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27 mortality are attenuated but remain significant, while women have the similar long-term
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29 mortality with men.
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38 It is widely accepted that there are significant differences in outcomes of women and men
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40 with acute myocardial infarction. In our study, after adjusted for participants' baseline
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42 cardiovascular risk factors and clinical profiles, the strength of association between gender
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44 and short-term mortality was substantially attenuated, which suggested that poorer
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46 baseline cardiovascular risk profile partially explained the impact of sex differences on
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48 mortality. Multiple studies have shown that women with STEMI present at older age and
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50 have a higher burden of comorbidities, contributing to the sex differences in mortality after
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52 STEMI.[25] All studies included in our meta-analysis demonstrate that female patients are
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54 older and with more diabetes mellitus as well as hypertension. In addition, some sex-
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4 specific studies found that certain risk factors and comorbidities were more potent in
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6 women.[26] Diabetes mellitus , hypertension and smoking status are more strongly
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8 associated with increased risk of cardiac events in women compared with men.[25, 27]
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14 Notably, that these differences mentioned above still could not completely explain the gap
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16 in mortality between sexes. It has been proved that women with acute myocardial infarction
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18 were less likely to be treated with guideline directed medical therapy and less likely to
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20 receive primary reperfusion therapy including primary percutaneous coronary intervention
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22 or fibrinolysis.[28] Regarding medical therapy, numerous studies conducted around the
23
24 world consistently demonstrate female survivors are receiving less optimal medical therapy
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26 after acute myocardial infarction during hospitalization or at discharge.[29, 30] Though
27
28 there might be no differences in treatment adherence between men and women, some
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30 studies report significant sex disparities in initiation of appropriate pharmacotherapy after
31
32 myocardial infarction.[31] Results from these observational studies show women are
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34 receiving less optimal medical therapy including aspirin, statins, and angiotensin-
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36 converting enzyme inhibitors in all age groups, especially young women, and suggest that
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38 clinicians and patients may benefit from better education and awareness of undertreatment
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40 of younger women.[31, 32]
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53 Lower rates of revascularization are observed among women with STEMI compared with
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55 men in several studies despite proven benefit of this therapy.[33] Moreover, the sex
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57 differences might be driven by delays in presentation to hospital and women with STEMI
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4 were more likely to experience longer delays than men. Although a great improvement in
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6 emergency medical services and timely revascularization over the past decades, recent
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8 studies show that women with STEMI still present later and have a longer ischemic time
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10 than men. Previous studies have shown consistently that women have longer door-to
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12 balloon times and longer door-to needle times.[34, 35] In addition, women are also more
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14 likely to exhibit longer pre-hospital delays in seeking medical care after the development
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16 of symptoms suggestive of myocardial infarction. Although there have been significant
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18 reductions in patient and system delay in the last decade, women continue to have longer
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20 presentation and treatment times.[36] Sex differences also exist in clinical presentation of
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22 STEMI. Although chest pain was the most common ACS symptom in both sexes, women
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24 were more likely to present without chest pain than men.[37, 38] Lower rates of typical
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26 chest pain reported among women with STEMI may also influence provider decision-
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28 making to pursue less aggressive care including invasive revascularization.
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40 Complications including bleeding, heart failure and mechanical complications are more
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42 likely to develop in women with acute myocardial infarction and increase the risk of
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44 mortality.[14, 39, 40] Bleeding secondary to antithrombotic therapies and invasive
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46 procedures is more frequent in women.[41] Three included studies reported incidence of
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48 bleeding following STEMI and they all found that women were at higher risk of bleeding.[10,
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50 13, 18] One study included in our analysis examined the relationships among sex, acute
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52 heart failure, and related outcomes after STEMI.[14] Its results demonstrate that women
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54 are at higher risk to develop de novo heart failure after STEMI and women with de novo
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4 heart failure have worse survival compared with men. However, we could not compare the
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6 incidence of these complications due to the lack of sufficient data. Mechanical
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8 complications requiring surgical intervention are also much more common in women after
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10 acute myocardial infarction and associated with high mortality rates.[42]
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17 Several limitations of this meta-analysis should be considered. First, the included studies
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19 are all observational studies except one post hoc analysis of randomized controlled trial.
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21 Hence, there may be residual confounding bias inherent in the observational study design
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23 in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the
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25 same confounders and not all studies reported adjusted RRs. Third, there was substantial
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27 heterogeneity in our meta-analysis, which could partly be attributed to the wide variability
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29 in the sample sizes, locations, and treatment regimens across included studies. Fourth,
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31 the analysis of long-term mortality, especially the adjusted analysis, included far fewer
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33 studies compared with analysis of short-term mortality. Hence, there might be significant
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35 bias in the results about long-term mortality.
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46 In conclusion, our meta-analysis, pooling data from contemporary literature, shows that
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48 women with STEMI have a higher risk of short-term mortality but not long-term mortality.
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50 The effect of sex differences on mortality in patients with STEMI remain significant after
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52 adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that
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54 public awareness of increased risk and further improvements in management in women
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56 with STEMI are necessary.
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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

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4 from the corresponding author
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Table 1 Characteristics of included studies.

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

					2013			cerebrovascular events	
<i>Cenko</i>	2019	12	Yes	Jan,	2010-Jul,	10,443	3,112	30-day all-cause mortality	30 d
		Europea			2018		(29.8)		
		n							
		countries							
<i>Hao</i>	2019	China	Yes	Nov,	2014-Jun,	50,203	11,016	In-hospital mortality	NA
					2018		(21.9)		
<i>Hannan</i>	2019	US	Yes	Jan,	2013-Dec,	23,809	7,791	In hospital/30-day mortality	30 d
					2015		(32.7)		
<i>Maznyc</i>	2019	UK	No	July,	2011-Nov,	324	87 (26.9)	All-cause death/ first heart failure	5 years
<i>zka</i>					2012			hospitalisation	
<i>Stehli</i>	2019	Australia	Yes		2013-2016	6431	1,317	In hospital/30-day major adverse events, and major bleeding	30 d
							(20.5)		

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<i>Burgess</i>	2020	Australia	No	Dec, 2010-Apr, 2014	589	123 (21)	Cardiac death and myocardial infarction	2 years
<i>Dharma</i>	2020	Indonesia	No	Feb, 2011-Aug, 2019	6557	929 (14.2)	All-cause mortality	30 d and 1 year
<i>Kerkman</i>	2020	Netherlands	Yes	2015-2016	787	229 (29)	All-cause mortality	1 year
<i>Siabani</i>	2020	Iran	No	Jun, 2016-May, 2018	1484	311(21)	In-hospital mortality	NA
<i>Tai</i>	2020	China	No	Jan, 2013-Dec, 2017	182	56 (30.8)	In hospital/1-year mortality	1 year
<i>Tizón</i>	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	
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
Langa	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)												
<i>Cenko</i>	2019	66.1	59.7	29.7	20.9	74.6	61.4	43.3	42.3	32.5	50.7	9.7	11.5	9.8	10.4
		(11.7)	(11.7)												
<i>Hao</i>	2019	69.0	61.1	48.1	39.4	74.1	62.9	85.4	83.3	8.2	53.0	NA	NA	NA	NA
		(10.6)	(12.4)												
<i>Hanna</i>	2019	70.72	62.11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	11.1	13.8
<i>n</i>		(14.73)	(12.82)												
<i>Mazny</i>	2019	61.2	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
<i>czka</i>		(12.2)	2)												
<i>Stehli</i>	2019	66.5	60.8	18.6	15.1	NA	NA	NA	NA	NA	NA	NA	NA	7.9	11.3
		(13.2)	(12.2)												
<i>Burge</i>	2020	62.7	58.2	31.7	18.9	68.3	52.1	67.5	52.3	52.0	54.1	7.3	8.8	NA	NA
<i>ss</i>		(52.7-	(50.6-												

		73.2)	65.7)												
<i>Dhar</i>	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
<i>ma</i>															
<i>Kerkm</i>	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
<i>anx</i>															
<i>Siaba</i>	2020	65.8	59.0	37.7	16.2	63.7	35.4	36.7	18.5	13.2	55.9	NA	NA	NA	NA
<i>ni</i>		(11.3)	(12.4)												
<i>Tai</i>	2020	78 (76–	78 (76–	35.2	26.5	79.5	72.8	NA	NA	5.4	56.5	NA	NA	13.5	18.1
		81)	80)												
<i>Tizón</i>	2020	69.9	60.9	24.2	17.2	34.2	24.3	25.2	21.2	13.6	24.2	NA	NA	NA	NA
		(13.7)	(12.6)												

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4 Figure 1 Flowchart of selection of studies included in meta-analysis.
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9 Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and
10 men with ST-segment elevation myocardial infarction.
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14 Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of
15 women compared with men with ST-segment elevation myocardial infarction using
16 random-effects model.
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25 Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and
26 men with ST-segment elevation myocardial infarction.
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30 Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of
31 women compared with men with ST-segment elevation myocardial infarction using
32 random-effects model.
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Figure 1 Flowchart of selection of studies included in meta-analysis.

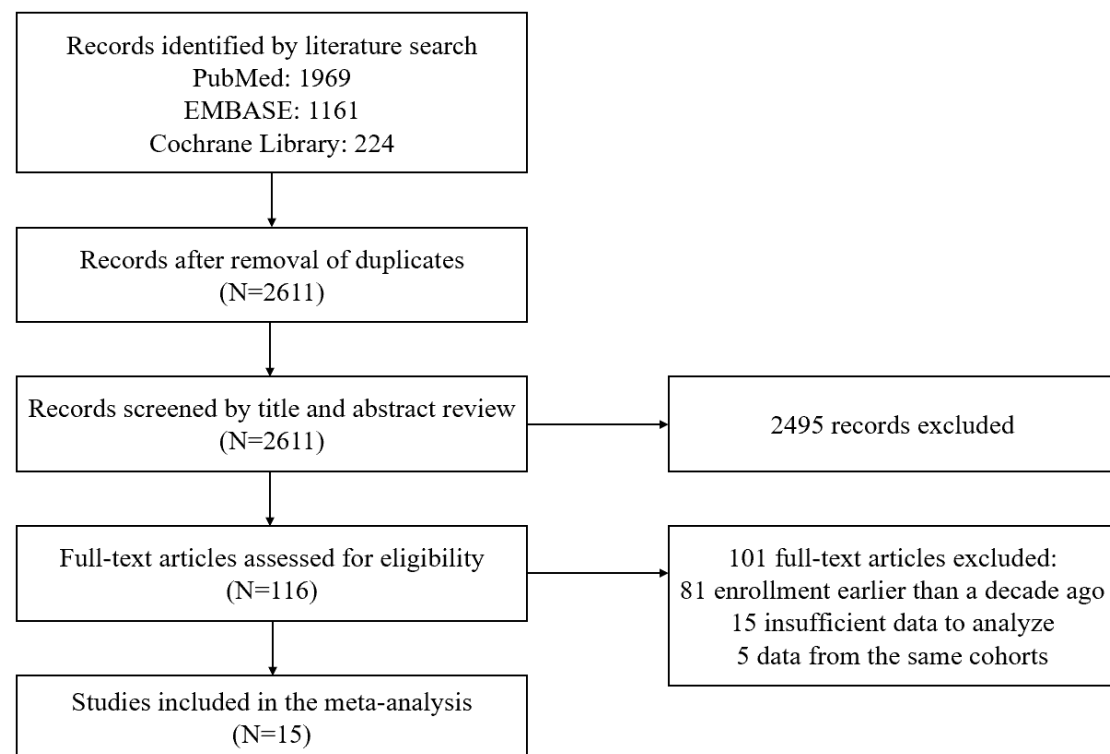
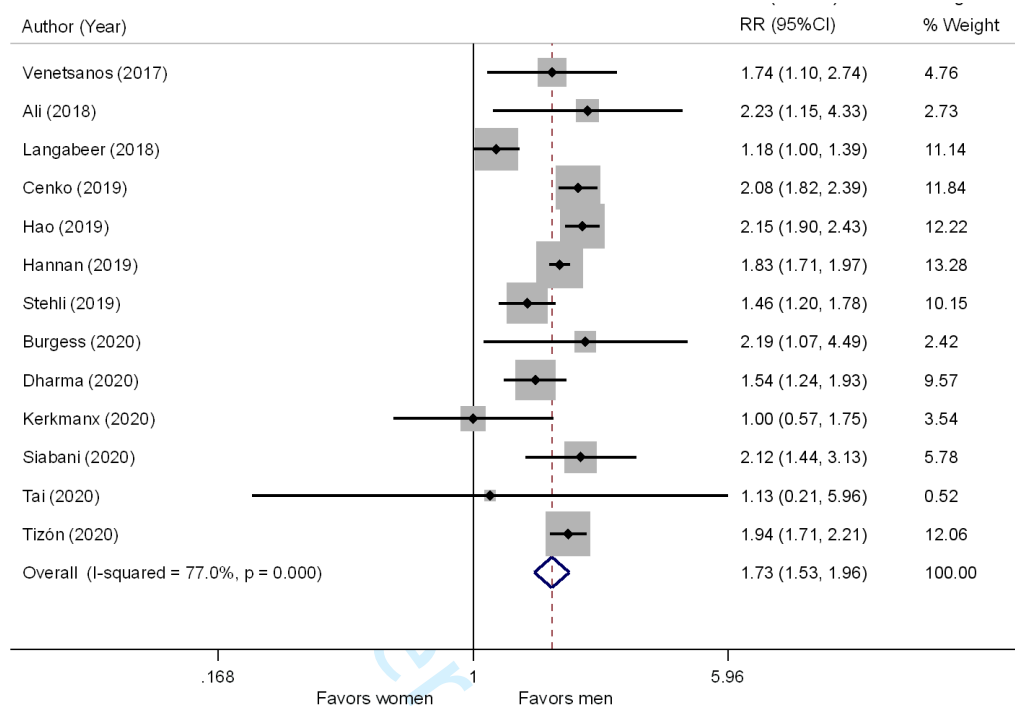
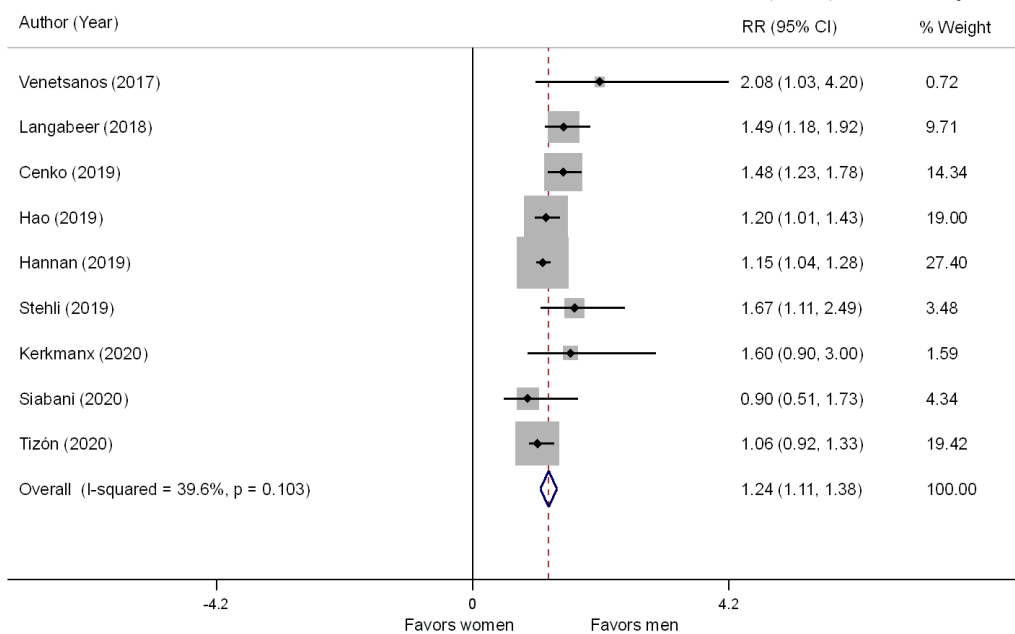


Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



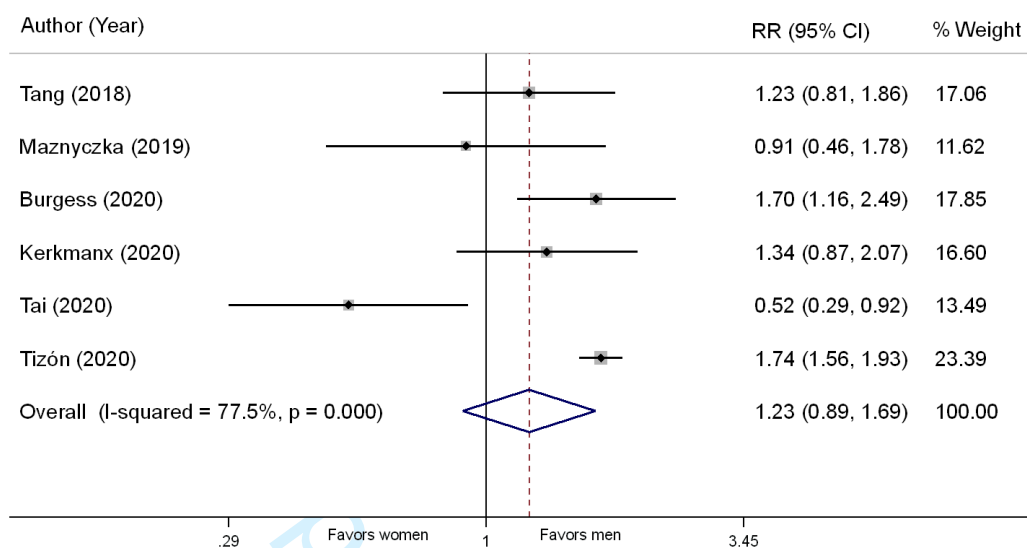
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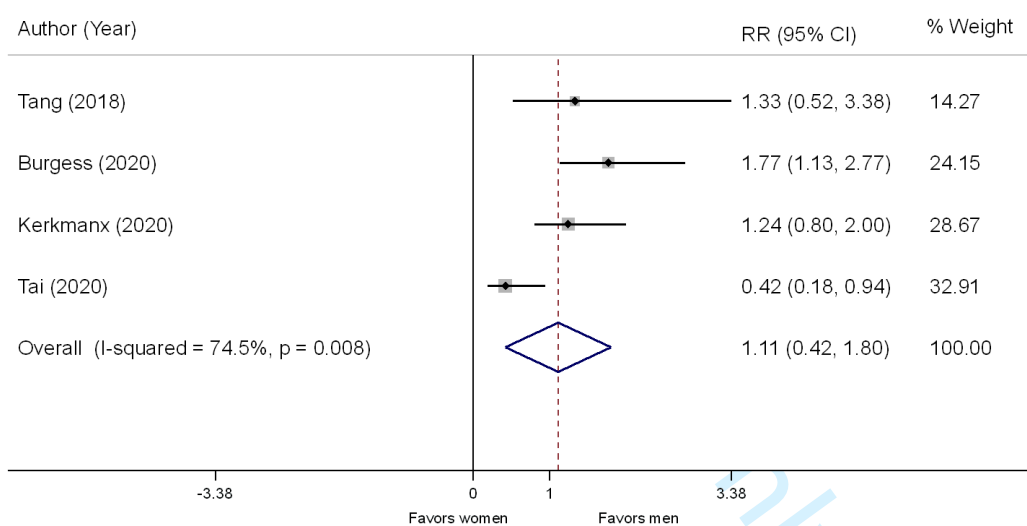
Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

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.

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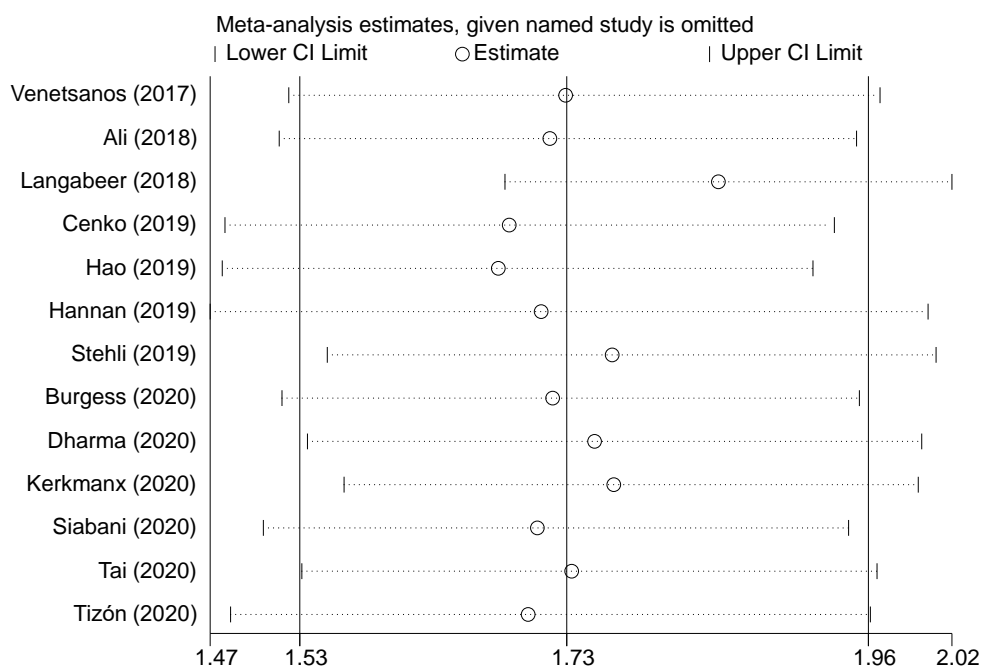
eTable 1 Table 3 Assessment of study quality using Newcastle-Ottawa scale.

<i>First Author</i>	<i>Year</i>	<i>Selection</i>				<i>Comparability</i>	<i>Outcome</i>			<i>Total point</i>
		Representativeness of the exposed cohort	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	
<i>Venetsanos</i>	2017	*	*	*	*	**	*	\	*	8
<i>Ali</i>	2018	\	\	*	*	\	*	\	*	4
<i>Langabeer</i>	2018	*	*	*	*	*	*	\	*	7
<i>Tang</i>	2018	\	\	*	*	**	*	*	*	7
<i>Cenko</i>	2019	*	*	*	*	**	*	\	*	8
<i>Hao</i>	2019	*	*	*	*	**	*	\	*	8
<i>Hannan</i>	2019	*	*	*	*	**	*	\	*	8
<i>Maznyczka</i>	2019	\	\	*	*	\	*	*	*	5

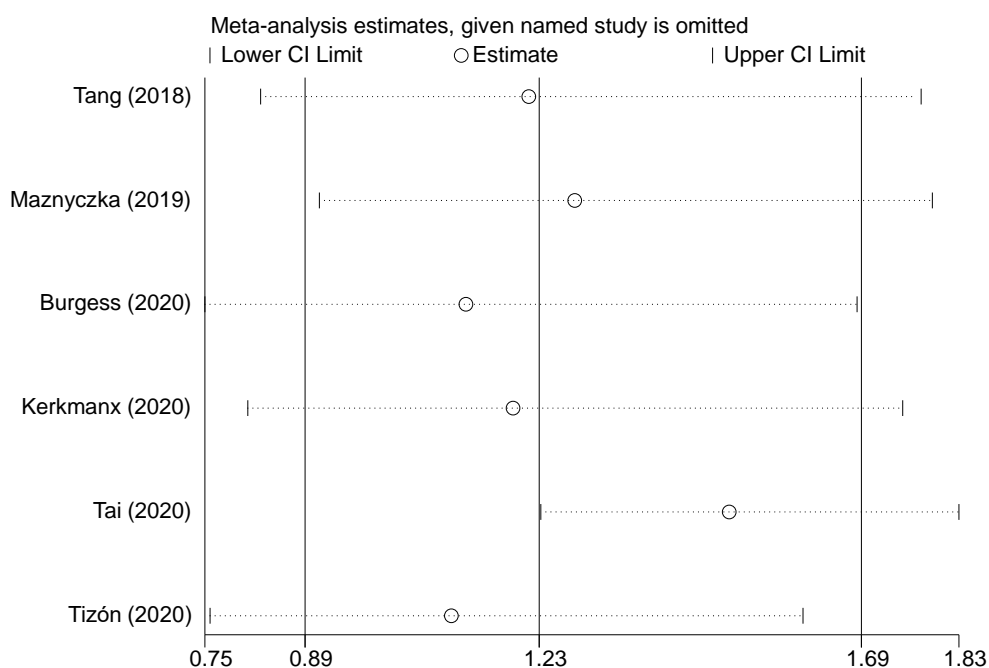
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<i>Stehli</i>	2019	*	*	*	*	**	*	\	*	8
<i>Burgess</i>	2020	\	\	*	*	**	*	*	*	7
<i>Dharma</i>	2020	\	\	*	*	*	*	*	*	6
<i>Kerkmanx</i>	2020	*	*	*	*	\	*	*	*	7
<i>Siabani</i>	2020	\	\	*	*	*	*	\	*	5
<i>Tai</i>	2020	\	\	*	*	**	*	*	*	7
<i>Tizón</i>	2020	*	*	*	*	**	*	*	*	9

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



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

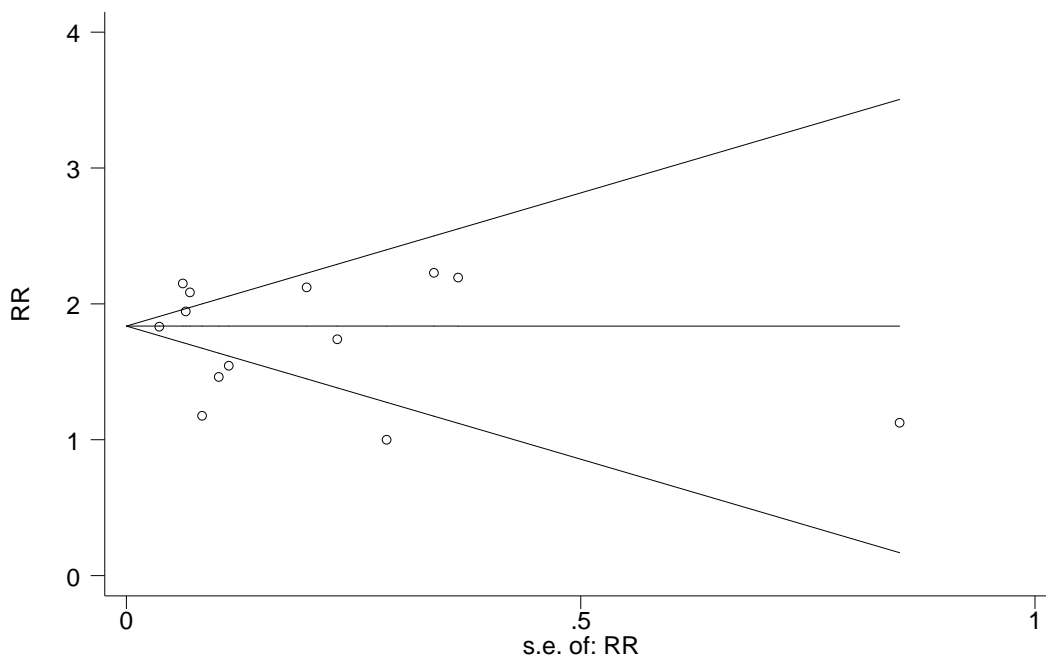


eFigure 3 Funnel plots for publication bias for unadjusted short-term (A) and long-term (B) mortality

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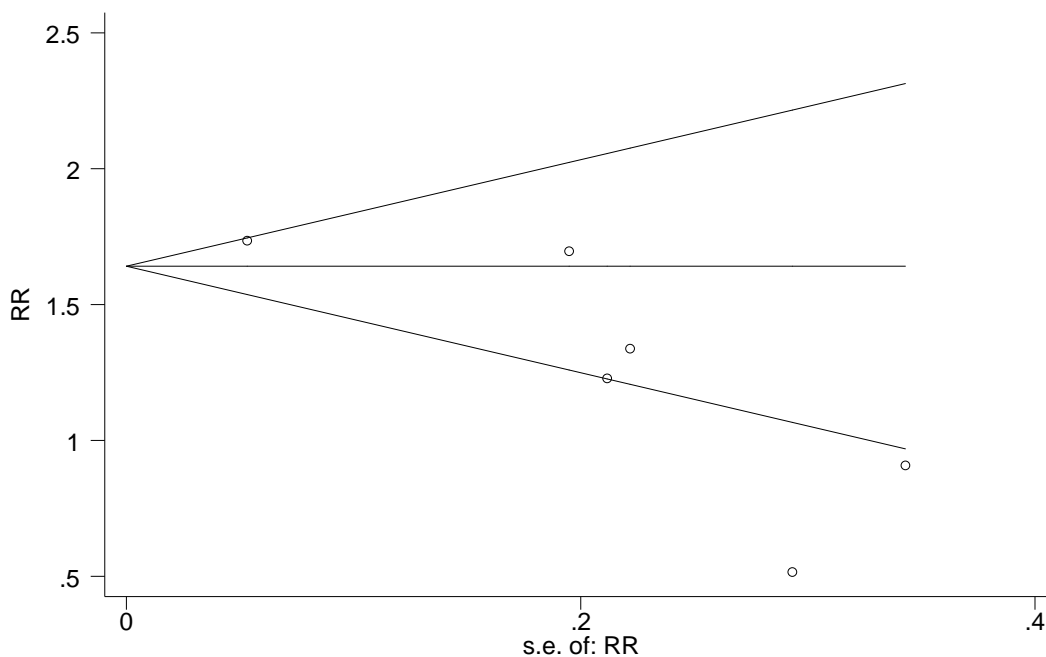
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Begg's funnel plot with pseudo 95% confidence limits



B

Begg's funnel plot with pseudo 95% confidence limits





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.	Page 5
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

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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

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BMJ Open

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

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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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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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8
9 **Short title : Sex differences in STEMI**
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11 **Authors:**

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For peer review only

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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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12 **Objectives:** To assess the effect of sex differences on short- and long-term mortality among
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14 patients with ST-segment elevation myocardial infarction (STEMI).
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19 **Design:** Systematic review and meta-analysis of contemporary available evidence.
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25 **Setting:** PubMed, Embase and Cochrane Library were searched for relevant studies
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27 reporting sex specific outcomes among patients with STEMI published between January
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29 1, 2010 to August 1, 2020. Risk ratio (RR) 95% 95% confidence intervals (CIs) were
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31 measured using DerSimonian and Laird random-effects model. Sensitivity analyses were
32
33 performed and publication bias was also checked. All statistical analyses were performed
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35 using STATA version 15.0.
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43 **Participants:** Studies providing data about short- or long-term mortality stratified by sex in
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45 patients with STEMI were included. Only study conducted in last ten years were included.
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51 **Primary and secondary outcome measures:** The primary outcome was all-cause death at
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53 short-(in-hospital or 30 days) and long-term (at least 12 months) follow-up.
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58 **Results**
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4 A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879
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6 [75.3%] male) were included. In the unadjusted analyses, female were at a higher risk of
7
8 short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, $P<0.001$, $I^2=77\%$) but not long-term
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10 mortality (RR, 1.23; 95%CI, 0.89-1.69, $P=0.206$, $I^2=77.5\%$). When adjusted effect
11
12 estimates from individual studies were used in meta-analysis, the association between
13
14 female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-
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16 1.38, $P<0.001$, $I^2=39.6\%$). And adjusted long-term mortality was also similar between
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18 female and male (RR, 1.11; 95%CI, 0.42-1.80, $P=0.670$, $I^2=74.5\%$).
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28 **Conclusions**

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

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4 mortality among patients with STEMI, we performed a systematic review and meta-
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6 analysis of all available evidence from last decade reporting sex-specific outcomes after
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8 STEMI.
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11 12 13 14 **Methods**

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19 The present systematic review and meta-analysis was performed following the principle
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21 of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
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23 statement.⁸
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30 *Literature search*

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32 We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library
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34 from January 1, 2010 to August 1, 2020 to identify studies from the last decade that
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36 described sex differences in in short- or long-term mortality among patients with STEMI.
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38 Both observational studies and randomized clinical trials were eligible. We queried MeSH
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40 and the abstract text for the following three search terms: gender part (including "gender",
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42 "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome
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44 part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac
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46 death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular
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48 mortality" or "short term mortality"); myocardial infarction part (including "myocardial
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50 infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation
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52 myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or
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4 "primary angioplasty") to identify relevant studies. There was no language restriction or
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6 age limit.
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10 11 *Study selection*

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14 According to the aim of our analyses, studies were included in this systematic review if
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16 data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality
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18 stratified by sex in patients with STEMI were reported. Two reviewers identified studies
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20 eligible for further review by performing an initial screen of titles or abstracts of the search
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22 results. Subsequently, a second screen of full texts eligibility was performed by another
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24 two reviewers. Studies had to fulfil the following criteria to be included in the present
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26 analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and
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28 ii) studies providing enough details to obtain numbers of events or incidence rates
29
30 according to sex; and iii) enrollment starting earlier than a decade ago. Editorials, letters,
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32 conference proceedings and abstracts were considered to be eligible only if sufficient
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34 information was available in abstracts or associated tables or figures. We excluded studies
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36 if they were review articles or case reports, or if they involved pregnant participants,
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38 critically ill patients, or provided insufficient data to allow for risk estimates to be calculated.
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48 Any disagreement was reviewed by a third reviewer and resolved by consensus.
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53 *Data extraction*

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56 Detailed data from selected studies were extracted independently by two reviewers using
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58 a standardized form independently. Data about study and participants characteristics,
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4 including year of study, sample size, time of enrollment, geographical location, endpoints
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6 of study, and follow-up duration, were collected. Any discrepancies were reviewed by a
7
8 third reviewer and resolved by consensus. The quality of included studies was evaluated
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10 by Newcastle-Ottawa scale using prespecified items comprised of patients' selection
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12 (representativeness and selection of patients, ascertainment of exposure), comparability
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14 of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy
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16 of follow-up).⁹ A quality score (0–9 points) was generated according to a maximum of 1
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18 point for each item.
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28 *Patient and public involvement*

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

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40 The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent
41
42 the effect of sex differences on mortality after STEMI. And data were combined using
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44 random-effects model of DerSimonian and Laird with inverse variance weighting. Random-
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46 effect model was used due to substantial clinical and statistical heterogeneity. Following
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48 analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality
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50 using raw number of death and total participants at risk for death specific to each sex, ii)
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52 adjusted RRs for short- and long-term all-cause mortality using adjusted RRs if they were
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54 described in those included studies.
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4 We assess heterogeneity across studies with Cochran's Q test and I2 test, with $P < 0.1$ or
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6 I2 $> 50\%$ considered significant. We also performed meta-regression to identify the
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8 potential sources of heterogeneity in the included studies. Furthermore, stratified analysis
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10 was conducted as well by dividing the included studies into different subgroups based on
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12 the Newcastle-Ottawa scale scores (> 7 points or ≤ 7 points) to assess the potential sources
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14 of heterogeneity. To assess the potential effect of publication bias, we inspected funnel
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16 plots for asymmetry and used the Egger's regression asymmetry test in which $P < 0.05$ was
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18 considered to indicate significant publication bias.
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24 Sensitivity analyses was conducted by excluding one study at a time and comparing the
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26 results with the complete one. In addition, we also performed sensitivity analyses by
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28 restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and
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30 restricting to studies with sample size bigger than 1000 participants. All statistical analyses
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32 were performed using STATA version 15.0 (Stata Corp, College Station, TX). Differences
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34 were considered statistically significant at $P < .05$ (2-sided).
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43 Results

44 45 46 47 48 *Literature search*

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50 Study selection details were outlined in Figure 1. The literature search identified 2,611
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52 potentially relevant articles. After screening based on title and abstract review, 2495
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54 records were excluded. A total of 116 full-text were finally assessed for eligibility, with 96
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56 papers excluded due to enrollment starting earlier than a decade ago or no sufficient
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4 gender specific data to analyze. Another 5 papers reviewed in detail were excluded after
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6 due to data from the same cohorts. A total of 15 studies were finally included in the present
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8
9 systematic review and meta-analysis.¹⁰⁻²⁴
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14 *Study characteristics*

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17 Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than
18
19 10,000 patients with STEMI. See Table 1 for further information of included studies.
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22 Baseline characteristics of participants were missing in some included studies, but all
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24 included studies provided sufficient data for analysis of sex differences in clinical outcomes.
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26
27 Except for 1 study, which was a prespecified gender analysis of randomized controlled
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29 trial, the remaining 14 were observational studies. Among the 10 included studies which
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31 reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension,
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33 and prior myocardial infarction/PCI, while some adjusted for renal insufficiency,
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35 and prior myocardial infarction/PCI, while some adjusted for renal insufficiency,
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37 cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset.
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40 Variables that were adjusted in the adjusted analyses from the included studies were
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42 presented in eTable 1 of the Supplementary Material. Results of assessment of study
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44 quality using Newcastle-Ottawa scale were shown in eTable 2 in the Supplementary
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48 Material.
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53 *Patient characteristics*

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

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24 Thirteen studies reported sex-specific unadjusted short-term mortality of patients with
25
26 STEMI. There were 2,873 of 31,409 (9.1%) cases of all-cause mortality in female
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28 compared with 4,380 of 95,610 (4.6%) in male. Female were at a significantly higher risk
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30 of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, $P<0.001$, $I^2=77\%$) compared with male
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32 (Figure 2 A). Nine studies involving 119,379 patients reported adjusted short-term mortality
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34 specific to sex. In adjusted analysis, the association between female and higher risk of
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36 short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, $P<0.001$, $I^2=39.6\%$)
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38 (Figure 2 B). However, the strength of association calculated with adjusted RRs from these
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40 9 studies was attenuated. Subgroup analysis demonstrated that the results of studies with
41
42 Newcastle-Ottawa scale >7 points (RR, 1.90; 95%CI, 1.73-2.09, $P=0.018$, $I^2=63.4\%$) and
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44 studies with ≤ 7 points (RR, 1.52; 95%CI, 1.20-1.93, $P=0.026$, $I^2=58.1\%$) were consistent
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46 in unadjusted short-term mortality (See eFigure 1 in the Supplementary Material).
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Long-term all-cause mortality

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4 Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and
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6 followed up for more than 1 year, and reported all-cause mortality for female and male.
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9 The incidence of long-term all-cause mortality was 13.9% (n=584) in female and 8.7%
10
11 (n=1202) in male. In unadjusted analysis, no significant sex difference was found in long-
12
13 term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I²=77.5%) (Figure 3 A). And the
14
15 adjusted analysis of the pooled results from four studies, also showed a similar risk of
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17 mortality at long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80,
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19 P=0.670, I²=74.5%) (Figure 3 B).
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28 *Meta-Regression Analysis, sensitivity analyses and publication bias*

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30 According to meta-regression analysis, differences in prevalence of diabetes (β coefficient,
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32 0.248; P=0.337), hypertension (β coefficient, -0.255; P=0.538), hyperlipidemia (β
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34 coefficient, 0.260; P=0.415), smoking (β coefficient, -0.040; P=0.255), prior MI (β
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36 coefficient, -2.725; P=0.126), and prior PCI (β coefficient, 0.109; P=0.896) between sexes
37
38 were not identified as significant sources of heterogeneity for short-term all-cause mortality.
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40 Given that not all included study provided information on confounders stratified by sex, the
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42 results of meta-regression analyses should be interpreted with caution.
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48 Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary
49
50 Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75;
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52 95%CI, 1.54-1.99, P<.001, I²=82.9%) both indicated that none of the studies affected the
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54 results of short-term mortality in this meta-analysis significantly. In analysis for long-term
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56 mortality, sensitivity analysis showed a possibly higher influence on the result attribute to
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4 the study of Tai et al (See eFigure 3 in the Supplementary Material). After removing this
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6 study from meta-analysis, the association of female with increased long-term mortality
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8 became significant (RR, 1.50; 95%CI, 1.23-1.83, P=0.148, I²=40.9%). We found no
9
10 evidence of publication bias across studies based on visual inspection of funnel plots (See
11
12 eFigure 4 in the Supplementary Material) and the results from Egger's tests for short-term
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14 mortality (P=0.462) and for long-term mortality (P=0.053).
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22 Discussion:

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27 Our systematic review and meta-analysis of contemporary literature on sex differences
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29 among patients with STEMI demonstrate that female have a higher risk of short- but not
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31 long-term mortality compared with male with STEMI. Furthermore, after adjustment for
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33 baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term
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35 mortality are attenuated but remain significant, while female have the similar long-term
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37 mortality with male.
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45 Our results are somewhat in accordance with several previously published meta-analysis.²

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48 ²⁵ A considerable number of studies have consistently suggested that women were at a
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50 higher risk of short-term mortality after ACS. However, whether risk of long-term mortality
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52 is also higher in women with ACS remains under debate. Some studies indicated that
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54 women with STEMI had a higher 1-year rate of death compared to men²⁶, while the 1-year
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56 mortality rate was conversely lower in women than men in some other studies^{23 24}. In our
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4 study, with respect to short-term mortality, the analyses of studies with high or low quality,
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6 and big or small sample size yielded similar results. However, in terms of long-term
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8 mortality, caution is needed when interpreting our finding of non-significant increased long-
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10 term mortality in adjusted analyses, due to the results of sensitivity analysis which showed
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12 a significant association between female and increased long-term mortality after removing
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14 one study from adjusted analyses.
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22 It is widely accepted that there are significant differences in outcomes of women and men
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24 with acute myocardial infarction. In our study, after adjusted for participants' baseline
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26 cardiovascular risk factors and clinical profiles, the strength of association between gender
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28 and short-term mortality was substantially attenuated, which suggested that poorer
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30 baseline cardiovascular risk profile partially explained the impact of sex differences on
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32 mortality. Multiple studies have shown that women with STEMI present at older age and
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34 have a higher burden of comorbidities, contributing to the sex differences in mortality after
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36 STEMI.²⁷ All studies included in our meta-analysis demonstrate that female patients are
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38 older and with more diabetes mellitus as well as hypertension. In addition, some sex-
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40 specific studies found that certain risk factors and comorbidities were more potent in
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42 women.²⁸ Diabetes mellitus , hypertension and smoking status are more strongly
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44 associated with increased risk of cardiac events in women compared with men.^{27 29}
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56 Notably, that these differences mentioned above still could not completely explain the gap
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58 in mortality between sexes. It has been proved that women with acute myocardial infarction
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4 were less likely to be treated with guideline directed medical therapy and less likely to
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6 receive primary reperfusion therapy including primary percutaneous coronary intervention
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8 or fibrinolysis.³⁰ Regarding medical therapy, numerous studies conducted around the world
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10 consistently demonstrate female survivors are receiving less optimal medical therapy after
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12 acute myocardial infarction during hospitalization or at discharge.^{31 32} Though there might
13
14 be no differences in treatment adherence between men and women, some studies report
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16 significant sex disparities in initiation of appropriate pharmacotherapy after myocardial
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18 infarction.³³ Results from these observational studies have shown women are receiving
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20 less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme
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22 inhibitors in all age groups, especially young women, and suggested that clinicians and
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24 patients may benefit from better education and awareness of undertreatment of younger
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26 women.^{33 34}

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37 Lower rates of revascularization are observed among women with STEMI compared with
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39 men in several studies despite proven benefit of this therapy.³⁵ Moreover, the sex
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41 differences might be driven by delays in presentation to hospital and women with STEMI
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43 were more likely to experience longer delays than men. Although a great improvement in
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45 emergency medical services and timely revascularization over the past decades, recent
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47 studies show that women with STEMI still present later and have a longer ischemic time
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49 than men. Previous studies have shown consistently that women have longer door-to
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51 balloon times and longer door-to needle times.^{36 37} In addition, women are also more likely
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53 to exhibit longer pre-hospital delays in seeking medical care after the development of
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4 symptoms suggestive of myocardial infarction. Although there have been significant
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6 reductions in patient and system delay in the last decade, women continue to have longer
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8 presentation and treatment times.³⁸ Sex differences also exist in clinical presentation of
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10 STEMI. Although chest pain was the most common ACS symptom in both sexes, women
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12 were more likely to present without chest pain than men.^{39 40} Lower rates of typical chest
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14 pain reported among women with STEMI may also influence provider decision-making to
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16 pursue less aggressive care including invasive revascularization.
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25 Some included studies of our meta-analysis enrolled STEMI patients in general¹⁴⁻¹⁶, while
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27 some others enrolled patients undergoing PCI for STEMI^{11 13 18}. The different prognosis of
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29 patients receiving reperfusion therapy or no-reperfusion therapy might be a potential
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31 source of heterogeneity of our study. Nevertheless, our results are completely consistent
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33 with a previous meta-analysis from Pancholy et al., which investigated sex differences in
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35 mortality among patients with STEMI treated with primary PCI.² Its results demonstrated
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37 that, when adjusted RRs were used, the increased risk for 1-year mortality in women was
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39 no longer significant and the risk of in-hospital mortality still significantly elevated. It should
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41 be noted that more than 50% of patients were treated with PCI in the most study conducted
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43 among the general STEMI patients and included by our analysis, even more than 90% in
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45 some included studies.^{12 24} The increasing rate of primary PCI in recent years might be a
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47 reason for the consistency of our findings and previous studies conducted specifically
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49 among STEMI patients undergoing PCI
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4 Complications including bleeding, heart failure and mechanical complications are more
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6 likely to develop in women with acute myocardial infarction and increase the risk of
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8 mortality.^{14 41 42} Bleeding secondary to antithrombotic therapies and invasive procedures is
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10 more frequent in women.⁴³ Three included studies reported incidence of bleeding following
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12 STEMI and they all found that women were at higher risk of bleeding.^{10 13 18} One study
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14 included in our analysis examined the relationships among sex, acute heart failure, and
15
16 related outcomes after STEMI.¹⁴ Its results demonstrate that women are at higher risk to
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18 develop de novo heart failure after STEMI and women with de novo heart failure have
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20 worse survival compared with man. However, we could not compare the incidence of these
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22 complications due to the lack of sufficient data. Mechanical complications requiring surgical
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24 intervention are also much more common in women after acute myocardial infarction and
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26 associated with high mortality rates.⁴⁴

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38 Several limitations of this meta-analysis should be considered. First, the included studies
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40 are all observational studies except one post hoc analysis of randomized controlled trial.
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42 Hence, there may be residual confounding bias inherent in the observational study design
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44 in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the
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46 same confounders and not all studies reported adjusted RRs. The confounders which were
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48 adjusted in the included studies might differ greatly across studies. Third, there was
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50 substantial heterogeneity in our meta-analysis, which could partly be attributed to the wide
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52 variability in the sample sizes, locations, and treatment regimens across included studies.
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58 Additionally, although we calculated adjusted RRs for all-cause mortality, it needed to be
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4 noted that relevant confounders might have differed across studies. Fourth, the analysis of
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6 long-term mortality, especially the adjusted analysis, included far fewer studies compared
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8 with analysis of short-term mortality. Hence, there might be significant bias in the results
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10 about long-term mortality.
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17 In conclusion, our meta-analysis, pooling data from contemporary literature, shows that
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19 women with STENI have a higher risk of short-term mortality but not long-term mortality.
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21 The effect of sex differences on mortality in patients with STEMI remain significant after
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23 adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that
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25 public awareness of increased risk and further improvements in management in women
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27 with STEMI are necessary.
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35 **Other Information:**

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40 **Contribution statement**

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42 Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis,
43
44 Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data
45
46 acquisition, Data analysis/interpretation. Jianan Li, Yang Li, Jianfeng Zheng and Runlin
47
48 Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.
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55 **Conflict of interest**

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57 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

1	Cenko	2019	12	Prospective	Clinical	Yes	Jan, 2010-	10,443	3,112	30-day all-cause	30 d
2			Europea		registry		Jul, 2018		(29.8)	mortality	
3			n								
4			countries								
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10											
11	Hao	2019	China	Prospective	Clinical	Yes	Nov, 2014-	50,203	11,016	In-hospital mortality	NA
12					registry		Jun, 2018		(21,9)		
13											
14											
15											
16											
17	Hannan	2019	US	Retrospective	Administrativ	Yes	Jan, 2013-	23,809	7,791	In hospital/30-day	30 d
18					e database		Dec, 2015		(32.7)	mortality	
19											
20											
21											
22	Maznyczka	2019	UK	Retrospective	Clinical	No	July, 2011-	324	87 (26.9)	All-cause death/ first	5 years
23					registry		Nov, 2012			heart failure	
24										hospitalization	
25											
26											
27											
28											
29											
30	Stehli	2019	Australia	Prospective	Clinical	Yes	2013-2016	6,431	1,317	In hospital/30-day major	30 d
31					registry				(20.5)	adverse events, and	
32										major bleeding	
33											
34											
35											
36											
37											
38	Burgess	2020	Australia	Prospective	Administrativ	No	Dec, 2010-	589	123 (21)	Cardiac death and	2 years
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				e database		Apr, 2014			myocardial infarction	
Dharma	2020	Indonesi a	Retrospective	Administrativ e database	No	Feb, 2011- Aug, 2019	6,557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherla nds	Retrospective	Administrativ e 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	Administrativ e 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
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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		
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	61.1	10,141	24,08	15,607	38,42	17,996 (85.4)	50,94	1,719	32,37	NA	NA	NA	NA
		(10.6)	(12.4)	(48.1)	2	(74.1)	6		4	(8.2)	7				
					(39.4		(62.9		(83.3		(53.0				
))))				
Hannan	2019	70.72	62.11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	868	2206
		(14.73)	(12.82)											(11.1)	(13.8
))
Maznyczk	2019	61.2	58.6(11.2	8 (9.2)	26	32 (36.8)	73	28 (32.2)	66	57	139	5 (5.7)	20	2	16
a		(12.2))		(11.0		(30.8		(27.8	(65.5)	(58.6		(8.4)	(2.3)	(6.8)
))))				
Stehli	2019	66.5	60.8	245	770	NA	NA	NA	NA	NA	NA	NA	NA	104	577
		(13.2)	(12.2)	(18.6)	(15.1									(7.9)	(11.3
)))

1	Burgess	2020	62.7	58.2	39	88	84 (68.3)	243	83 (67.5)	253	64	252	9 (7.3)	41	NA	NA
2			(52.7-	(50.6-	(31.7)	(18.9		(52.1		(52.3	(52.0)	(54.1		(8.8)		
3			73.2)	65.7)))))))				
4																
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8	Dharma	2020	60 (10)	55 (10)	403	1548	647 (69.6)	2,889	299 (32.2)	1,779	109	4,049	NA	NA	NA	NA
9					(43.4)	(27.5		(51.3		(31.6	(11.7)	(71.9				
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11																
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16	Kerkmanx	2020	68 (14)	61 (12)	39	66	101 (45.7)	178	56 (25.9)	110	88	258	30	79	33	77
17					(17.6)	(12.5		(33.6		(21.0	(41.1)	(49.3	(13.6)	(13.7	(14.4)	(14.2
18))))))))
19																
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23																
24	Siabani	2020	65.8	59.0	114	187	195 (63.7)	410	110 (36.7)	208	41	655	NA	NA	NA	NA
25			(11.3)	(12.4)	(37.7)	(16.2		(35.4		(18.5	(13.2)	(55.9				
26))))))				
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32	Tai	2020	78 (76-	78 (76-	96	116	217 (79.5)	319	NA	NA	14 (5.4)	239	NA	NA	36	78
33			81)	80)	(35.2)	(26.5		(72.8				(56.5			(13.5)	(18.1
34)))))
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1	Tizón	2020	69.9	60.9	844	1,927	1,192 (34.2)	2,722	878 (25.2)	2,375	474	2,711	NA	NA	NA	NA
2																
3			(13.7)	(12.6)	(24.2)	(17.2		(24.3		(21.2	(13.6)	(24.2				
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4 Figure 1 Flowchart of selection of studies included in meta-analysis.
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9 Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and
10 men with ST-segment elevation myocardial infarction.
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14 Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of
15 women compared with men with ST-segment elevation myocardial infarction using
16 random-effects model.
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25 Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and
26 men with ST-segment elevation myocardial infarction.
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Figure 1 Flowchart of selection of studies included in meta-analysis.

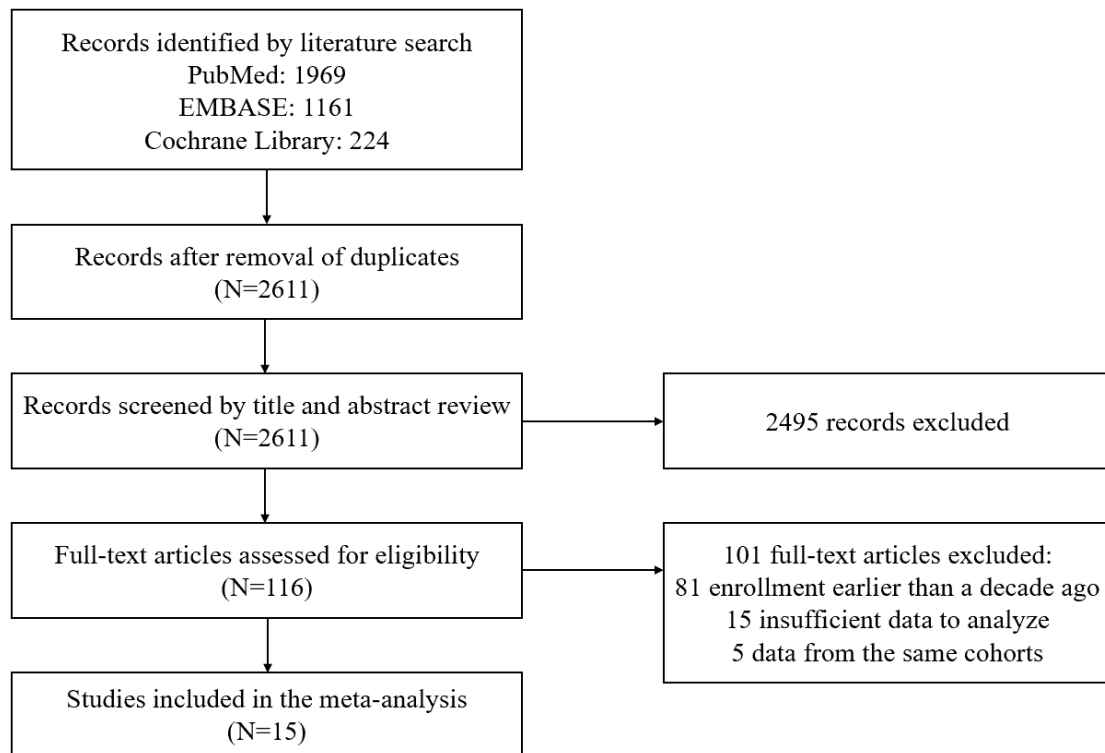
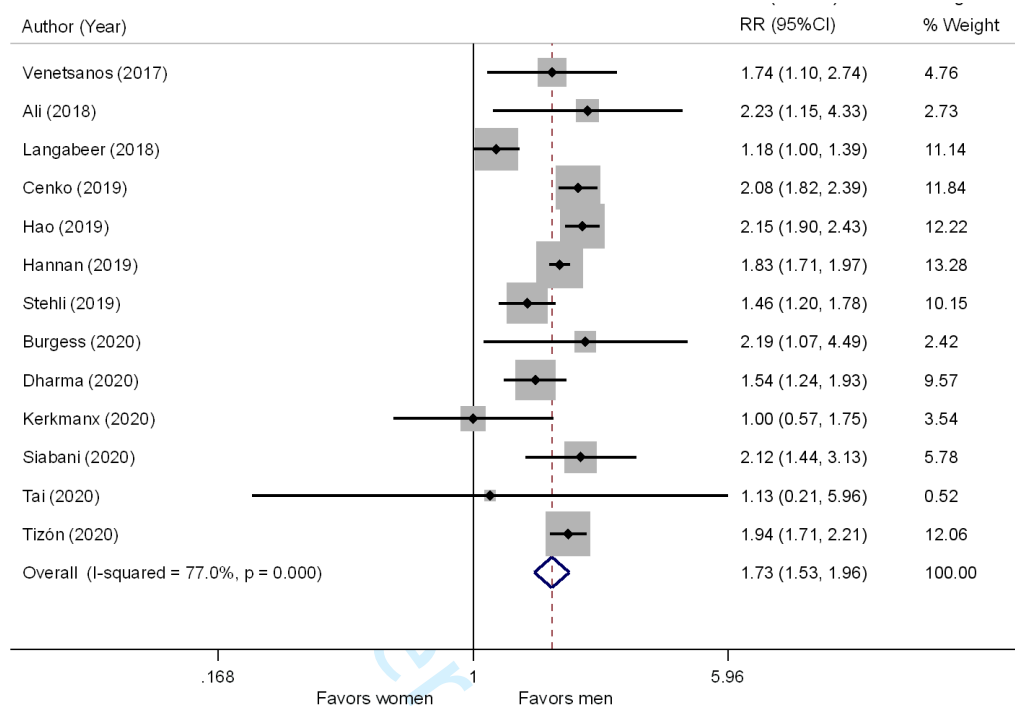
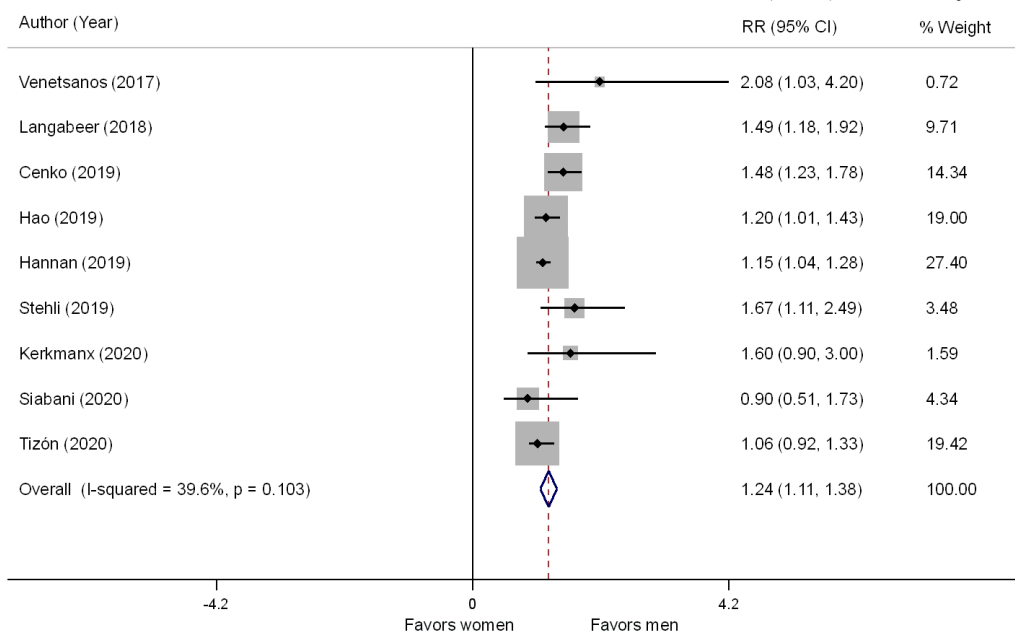


Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

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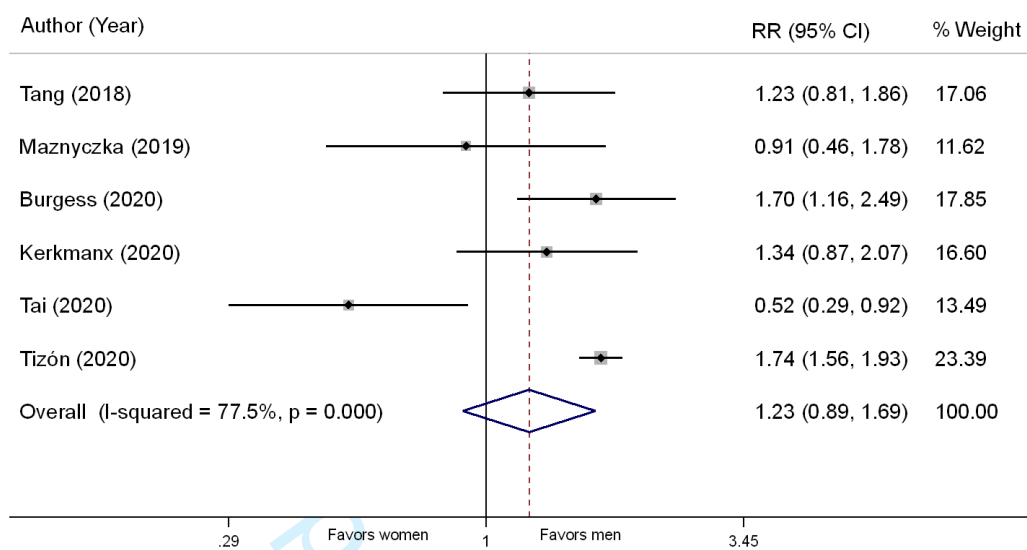
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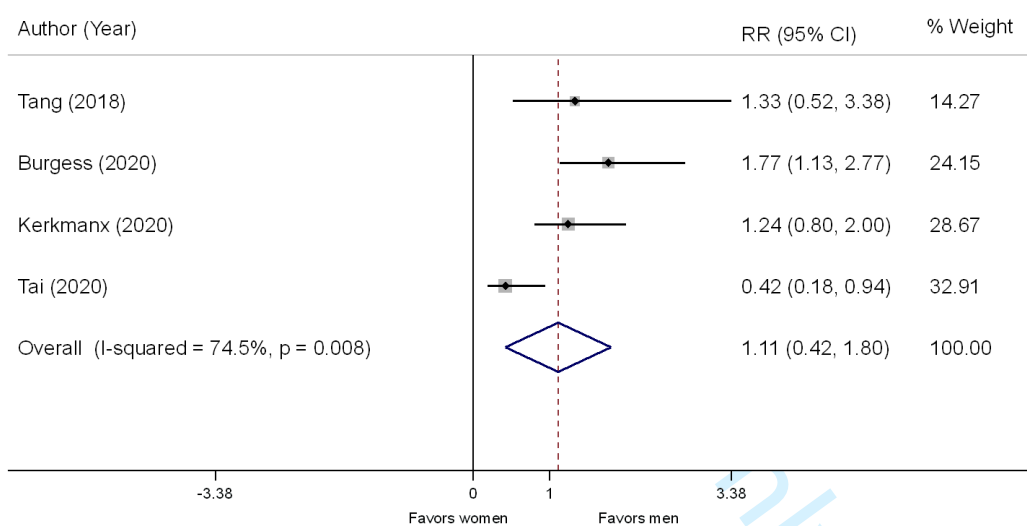
Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

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.

Table 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 \geq 25, hypertension, diabetes, current smoking, hypercholesterolemia, congestive heart failure, Killip class (at first presentation) \geq 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,

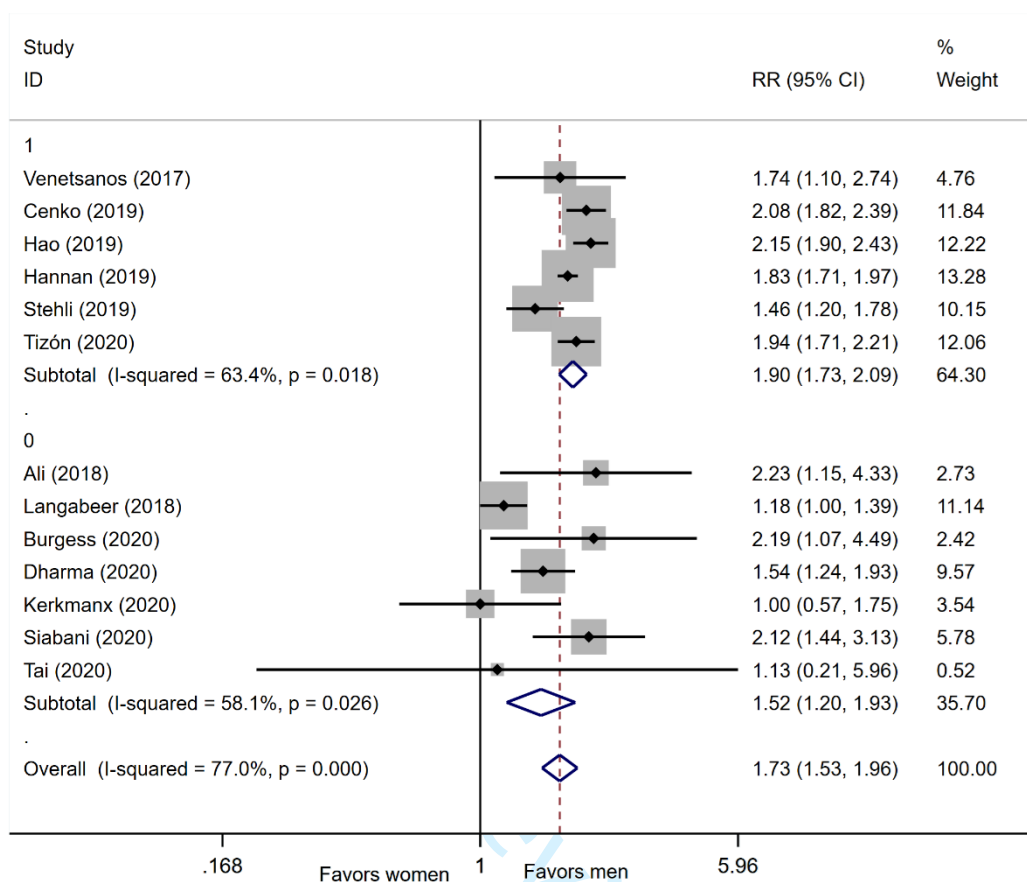
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eTable 2 Assessment of study quality using Newcastle-Ottawa scale.

First Author	Year	Selection				Comparability	Outcome			Total point
		Representativeness of the exposed cohort	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

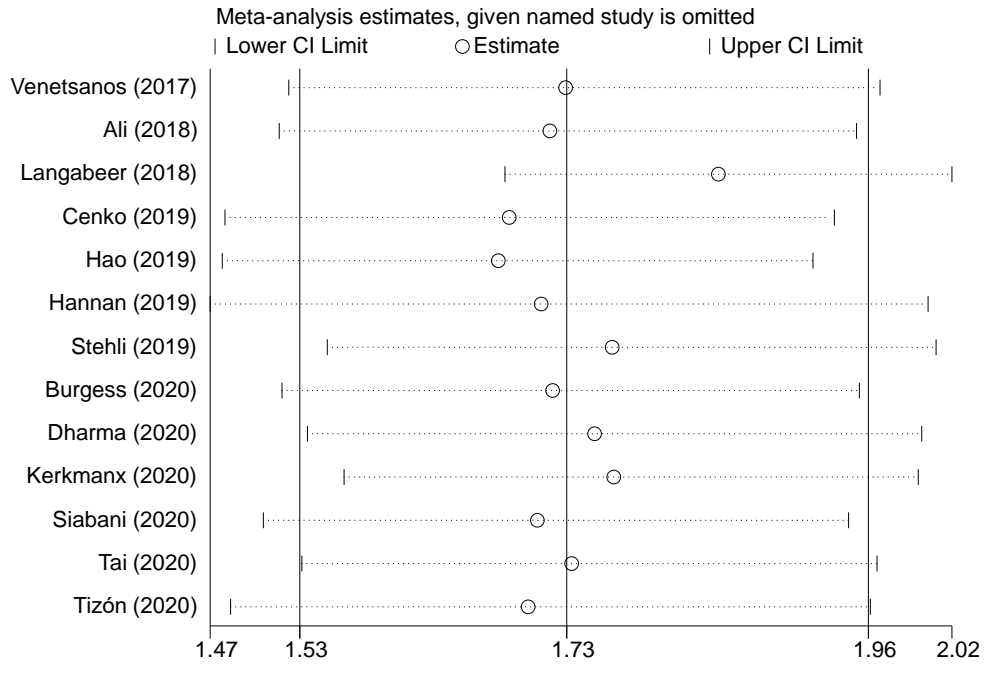
Burgess	2020	\	\	*	*	**	*	*	*	7
Dharma	2020	\	\	*	*	*	*	*	*	6
Kerkmanx	2020	*	*	*	*	\	*	*	*	7
Siabani	2020	\	\	*	*	*	*	\	*	5
Tai	2020	\	\	*	*	**	*	*	*	7
Tizón	2020	*	*	*	*	**	*	*	*	9

eFigure 1

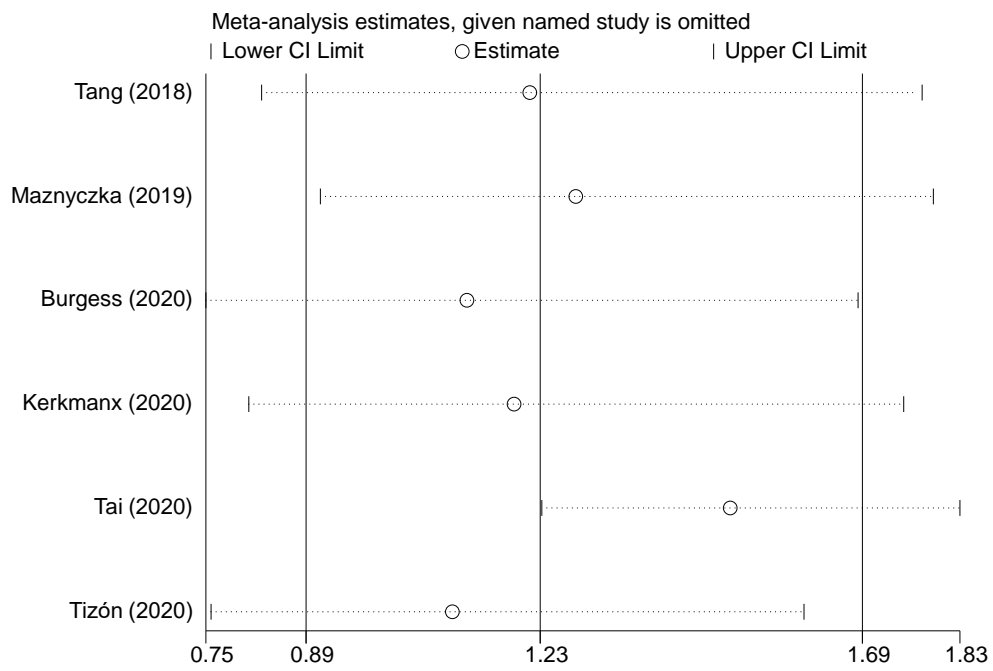


eFigure 2 Meta-influence analysis for unadjusted short-term mortality

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

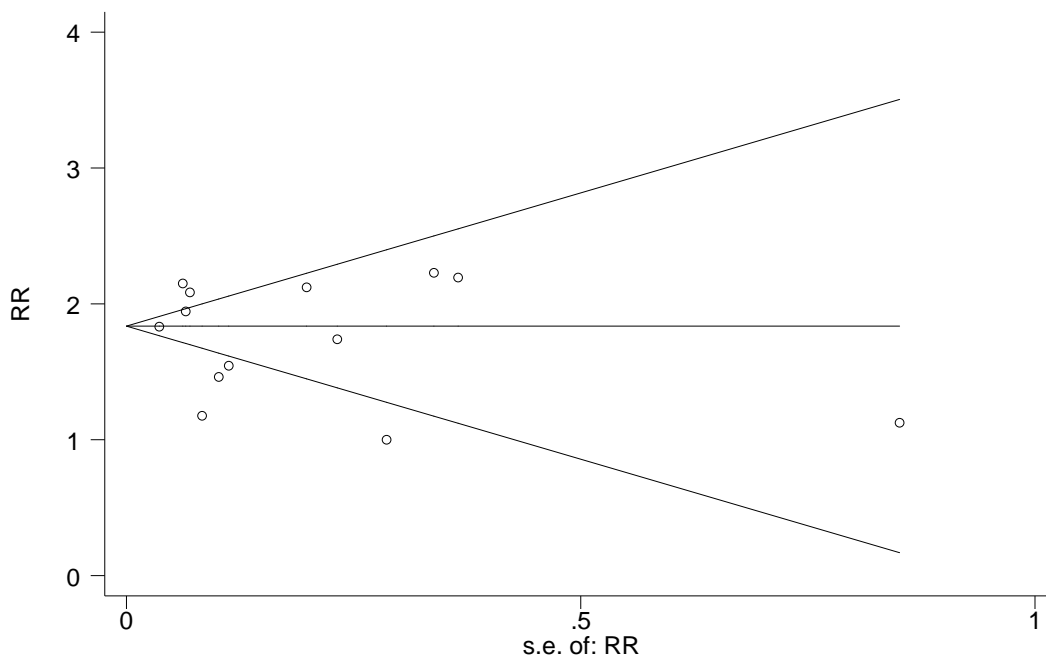


eFigure 4 Funnel plots for publication bias for unadjusted short-term (A) and long-term (B) mortality

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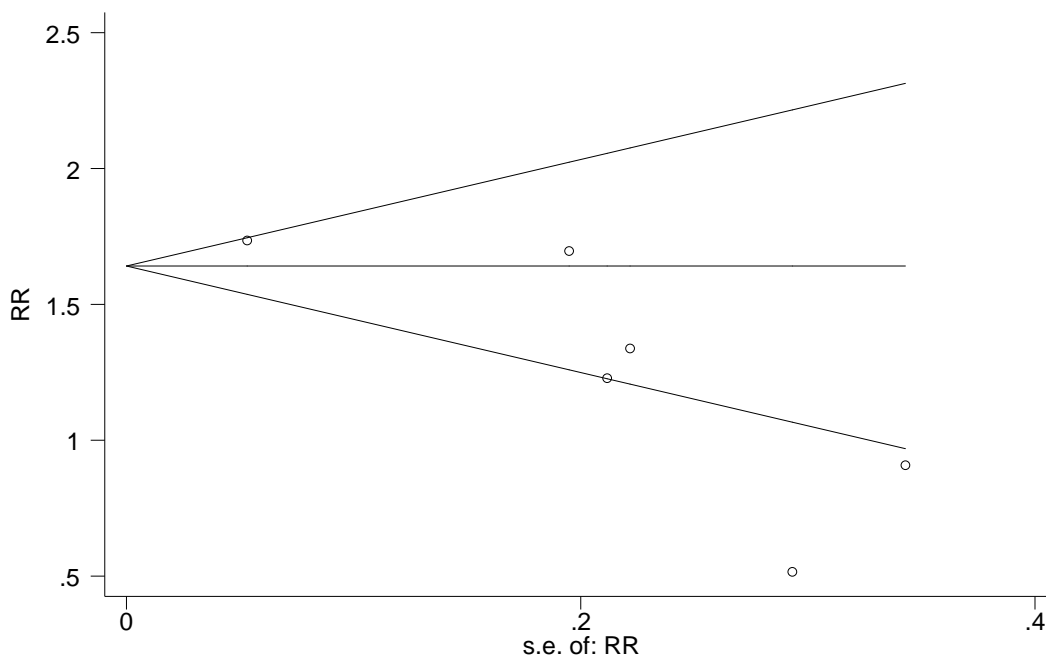
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Begg's funnel plot with pseudo 95% confidence limits



B

Begg's funnel plot with pseudo 95% confidence limits



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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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9 **Short title : Sex differences in STEMI**
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11 **Authors:**

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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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11 **Objectives:** To assess the effect of sex differences on short- and long-term mortality among
12 patients with ST-segment elevation myocardial infarction (STEMI).
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19 **Design:** Systematic review and meta-analysis of contemporary available evidence.
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24 **Setting:** PubMed, Embase and Cochrane Library were searched for relevant studies
25 reporting sex specific outcomes among patients with STEMI published between January
26 1, 2010 to August 1, 2020. Risk ratio (RR) 95% 95% confidence intervals (CIs) were
27 measured using DerSimonian and Laird random-effects model. Sensitivity analyses were
28 performed and publication bias was also checked. All statistical analyses were performed
29 using STATA version 15.0.
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43 **Participants:** Studies providing data about short- or long-term mortality stratified by sex in
44 patients with STEMI were included. Only study conducted in last ten years were included.
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50 **Primary and secondary outcome measures:** The primary outcome was all-cause death at
51 short-(in-hospital or 30 days) and long-term (at least 12 months) follow-up.
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58 **Results**
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4 A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879
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6 [75.3%] male) were included. In the unadjusted analyses, female were at a higher risk of
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8 short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I²=77%) but not long-term
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10 mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I²=77.5%). When adjusted effect
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12 estimates from individual studies were used in meta-analysis, the association between
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14 female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-
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16 1.38, P<0.001, I²=39.6%). And adjusted long-term mortality was also similar between
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18 female and male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I²=74.5%).
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29 Conclusions

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

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4 mortality among patients with STEMI, we performed a systematic review and meta-
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6 analysis of all available evidence from last decade reporting sex-specific outcomes after
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8 STEMI.
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11 12 13 14 **Methods**

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19 The present systematic review and meta-analysis was performed following the principle
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21 of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
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23 statement.⁸
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30 *Literature search*

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32 We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library
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34 from January 1, 2010 to August 1, 2020 to identify studies from the last decade that
35
36 described sex differences in in short- or long-term mortality among patients with STEMI.
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38 **Both observational studies and randomized clinical trials were eligible.** We queried MeSH
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40 and the abstract text for the following three search terms: gender part (including "gender",
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42 "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome
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44 part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac
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46 death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular
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48 mortality" or "short term mortality"); myocardial infarction part (including "myocardial
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50 infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation
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52 myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or
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4 "primary angioplasty") to identify relevant studies. There was no language restriction or
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6 age limit.
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10 11 *Study selection*

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14 According to the aim of our analyses, studies were included in this systematic review if
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16 data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality
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18 stratified by sex in patients with STEMI were reported. Two reviewers identified studies
19
20 eligible for further review by performing an initial screen of titles or abstracts of the search
21
22 results. Subsequently, a second screen of full texts eligibility was performed by another
23
24 two reviewers. Studies had to fulfil the following criteria to be included in the present
25
26 analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and
27
28 ii) studies providing enough details to obtain numbers of events or incidence rates
29
30 according to sex; and iii) enrollment starting earlier than a decade ago. Editorials, letters,
31
32 conference proceedings and abstracts were considered to be eligible only if sufficient
33
34 information was available in abstracts or associated tables or figures. We excluded studies
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36 if they were review articles or case reports, or if they involved pregnant participants,
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38 critically ill patients, or provided insufficient data to allow for risk estimates to be calculated.
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48 Any disagreement was reviewed by a third reviewer and resolved by consensus.
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52 53 *Data extraction*

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55 Detailed data from selected studies were extracted independently by two reviewers using
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57 a standardized form independently. Data about study and participants characteristics,
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4 including year of study, sample size, time of enrollment, geographical location, endpoints
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6 of study, and follow-up duration, were collected. Any discrepancies were reviewed by a
7
8 third reviewer and resolved by consensus. The quality of included studies was evaluated
9
10 by Newcastle-Ottawa scale using prespecified items comprised of patients' selection
11
12 (representativeness and selection of patients, ascertainment of exposure), comparability
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14 of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy
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16 of follow-up).⁹ A quality score (0–9 **points**) was generated according to a maximum of 1
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18 **point** for each item.
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Patient and public involvement

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

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38 The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent
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40 the effect of sex differences on mortality after STEMI. And data were combined using
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42 random-effects model of DerSimonian and Laird with inverse variance weighting. Random-
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44 effect model was used due to substantial clinical and statistical heterogeneity. Following
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46 analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality
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48 using raw number of death and total participants at risk for death specific to each sex, ii)
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50 adjusted RRs for short- and long-term all-cause mortality using adjusted RRs **if they were**
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52 described in **those** included studies.
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4 We assess heterogeneity across studies with Cochran's Q test and I2 test, with $P < 0.1$ or
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6 I2 $> 50\%$ considered significant. We also performed meta-regression to identify the
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8 potential sources of heterogeneity in the included studies. Furthermore, stratified analysis
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10 was conducted as well by dividing the included studies into different subgroups based on
11
12 the Newcastle-Ottawa scale scores (> 7 points or ≤ 7 points) to assess the potential sources
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14 of heterogeneity. To assess the potential effect of publication bias, we inspected funnel
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16 plots for asymmetry and used the Egger's regression asymmetry test in which $P < 0.05$ was
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18 considered to indicate significant publication bias.
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24 Sensitivity analyses was conducted by excluding one study at a time and comparing the
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26 results with the complete one. In addition, we also performed sensitivity analyses by
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28 restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and
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30 restricting to studies with sample size bigger than 1000 participants. All statistical analyses
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32 were performed using STATA version 15.0 (Stata Corp, College Station, TX). Differences
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34 were considered statistically significant at $P < .05$ (2-sided).
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43 Results

44 45 46 47 48 *Literature search*

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50 Study selection details were outlined in Figure 1. The literature search identified 2,611
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52 potentially relevant articles. After screening based on title and abstract review, 2495
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54 records were excluded. A total of 116 full-text were finally assessed for eligibility, with 96
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56 papers excluded due to enrollment starting earlier than a decade ago or no sufficient
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4 **gender specific data to analyze.** Another 5 papers reviewed in detail were excluded after
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6 due to data from the same cohorts. A total of 15 studies were finally included in the present
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8
9 systematic review and meta-analysis.¹⁰⁻²⁴
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13 14 *Study characteristics*

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17 Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than
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19 10,000 patients with STEMI. See Table 1 for further information of included studies.
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22 **Baseline characteristics of participants were missing in some included studies, but all**
23
24 **included studies provided sufficient data for analysis of sex differences in clinical outcomes.**
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27 Except for 1 study, which was a prespecified gender analysis of randomized controlled
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29 trial, the remaining 14 were observational studies. Among the 10 included studies which
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31 reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension,
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33 and prior myocardial infarction/PCI, while some adjusted for renal insufficiency,
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35 and prior myocardial infarction/PCI, while some adjusted for renal insufficiency,
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37 cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset.
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40 **Variables that were adjusted in the adjusted analyses from the included studies were**
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42 **presented in eTable 1 of the Supplementary Material.** Results of assessment of study
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44 quality using Newcastle-Ottawa scale were shown in eTable 2 in the Supplementary
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46
47
48 Material.
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51 52 53 *Patient characteristics*

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

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24 Thirteen studies reported sex-specific unadjusted short-term mortality of patients with
25
26 STEMI. There were 2,873 of 31,409 (9.1%) cases of all-cause mortality in female
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28 compared with 4,380 of 95,610 (4.6%) in **male**. **Female** were at a significantly higher risk
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30 of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, $P<0.001$, $I^2=77\%$) compared with male
31
32 (Figure 2 A). Nine studies involving 119,379 patients reported adjusted short-term mortality
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34 specific to sex. In adjusted analysis, the association between female and higher risk of
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36 short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38, $P<0.001$, $I^2=39.6\%$)
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38 (Figure 2 B). However, the strength of association calculated with adjusted RRs from these
39
40 9 studies was attenuated. **Subgroup analysis demonstrated that the results of studies with**
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42 **Newcastle-Ottawa scale >7 points (RR, 1.90; 95%CI, 1.73-2.09, $P=0.018$, $I^2=63.4\%$) and**
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44 **studies with ≤ 7 points (RR, 1.52; 95%CI, 1.20-1.93, $P=0.026$, $I^2=58.1\%$) were consistent**
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46 **in unadjusted short-term mortality (See eFigure 1 in the Supplementary Material).**
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59 *Long-term all-cause mortality*

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4 Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and
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6 followed up for more than 1 year, and reported all-cause mortality for female and male.
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9 The incidence of long-term all-cause mortality was 13.9% (n=584) in female and 8.7%
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11 (n=1202) in male. In unadjusted analysis, no significant sex difference was found in long-
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13 term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I²=77.5%) (Figure 3 A). And the
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15 adjusted analysis of the pooled results from four studies, also showed a similar risk of
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17 mortality at long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80,
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19 P=0.670, I²=74.5%) (Figure 3 B).
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28 *Meta-Regression Analysis, sensitivity analyses and publication bias*

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30 According to meta-regression analysis, differences in prevalence of diabetes (β coefficient,
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32 0.248; P=0.337), hypertension (β coefficient, -0.255; P=0.538), hyperlipidemia (β
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34 coefficient, 0.260; P=0.415), smoking (β coefficient, -0.040; P=0.255), prior MI (β
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36 coefficient, -2.725; P=0.126), and prior PCI (β coefficient, 0.109; P=0.896) between sexes
37
38 were not identified as significant sources of heterogeneity for short-term all-cause mortality.
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40 Given that not all included study provided information on confounders stratified by sex, the
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42 results of meta-regression analyses should be interpreted with caution.
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48 Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary
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50 Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75;
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52 95%CI, 1.54-1.99, P<.001, I²=82.9%) both indicated that none of the studies affected the
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54 results of short-term mortality in this meta-analysis significantly. In analysis for long-term
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56 mortality, sensitivity analysis showed a possibly higher influence on the result attribute to
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4 the study of Tai et al (See eFigure 3 in the Supplementary Material). After removing this
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6 study from meta-analysis, the association of female with increased long-term mortality
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8 became significant (RR, 1.50; 95%CI, 1.23-1.83, P=0.148, I²=40.9%). We found no
9
10 evidence of publication bias across studies based on visual inspection of funnel plots (See
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12 eFigure 4 in the Supplementary Material) and the results from Egger's tests for short-term
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14 mortality (P=0.462) and for long-term mortality (P=0.053).
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22 Discussion:

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27 Our systematic review and meta-analysis of contemporary literature on sex differences
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29 among patients with STEMI demonstrate that female have a higher risk of short- but not
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31 long-term mortality compared with male with STEMI. Furthermore, after adjustment for
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33 baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term
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35 mortality are attenuated but remain significant, while female have the similar long-term
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37 mortality with male.
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45 Our results are somewhat in accordance with several previously published meta-analysis.²

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48 ²⁵ A considerable number of studies have consistently suggested that women were at a
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50 higher risk of short-term mortality after ACS. However, whether risk of long-term mortality
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52 is also higher in women with ACS remains under debate. Some studies indicated that
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54 women with STEMI had a higher 1-year rate of death compared to men²⁶, while the 1-year
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56 mortality rate was conversely lower in women than men in some other studies^{23 24}. In our
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4 study, with respect to short-term mortality, the analyses of studies with high or low quality,
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6 and big or small sample size yielded similar results. However, in terms of long-term
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8 mortality, caution is needed when interpreting our finding of non-significant increased long-
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10 term mortality in adjusted analyses, due to the results of sensitivity analysis which showed
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12 a significant association between female and increased long-term mortality after removing
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14 one study from adjusted analyses.
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22 It is widely accepted that there are significant differences in outcomes of women and men
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24 with acute myocardial infarction. In our study, after adjusted for participants' baseline
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26 cardiovascular risk factors and clinical profiles, the strength of association between gender
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28 and short-term mortality was substantially attenuated, which suggested that poorer
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30 baseline cardiovascular risk profile partially explained the impact of sex differences on
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32 mortality. Multiple studies have shown that women with STEMI present at older age and
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34 have a higher burden of comorbidities, contributing to the sex differences in mortality after
35
36 STEMI.²⁷ All studies included in our meta-analysis demonstrate that female patients are
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38 older and with more diabetes mellitus as well as hypertension. In addition, some sex-
39
40 specific studies found that certain risk factors and comorbidities were more potent in
41
42 women.²⁸ Diabetes mellitus , hypertension and smoking status are more strongly
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44 associated with increased risk of cardiac events in women compared with men.^{27 29}
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56 Notably, that these differences mentioned above still could not completely explain the gap
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58 in mortality between sexes. It has been proved that women with acute myocardial infarction
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4 were less likely to be treated with guideline directed medical therapy and less likely to
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6 receive primary reperfusion therapy including primary percutaneous coronary intervention
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8 or fibrinolysis.³⁰ Regarding medical therapy, numerous studies conducted around the world
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10 consistently demonstrate female survivors are receiving less optimal medical therapy after
11
12 acute myocardial infarction during hospitalization or at discharge.^{31 32} Though there might
13
14 be no differences in treatment adherence between men and women, some studies report
15
16 significant sex disparities in initiation of appropriate pharmacotherapy after myocardial
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18 infarction.³³ Results from these observational studies have shown women are receiving
19
20 less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme
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22 inhibitors in all age groups, especially young women, and suggested that clinicians and
23
24 patients may benefit from better education and awareness of undertreatment of younger
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26 women.^{33 34}

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37 Lower rates of revascularization are observed among women with STEMI compared with
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39 men in several studies despite proven benefit of this therapy.³⁵ Moreover, the sex
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41 differences might be driven by delays in presentation to hospital and women with STEMI
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43 were more likely to experience longer delays than men. Although a great improvement in
44
45 emergency medical services and timely revascularization over the past decades, recent
46
47 studies show that women with STEMI still present later and have a longer ischemic time
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49 than men. Previous studies have shown consistently that women have longer door-to
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51 balloon times and longer door-to needle times.^{36 37} In addition, women are also more likely
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53 to exhibit longer pre-hospital delays in seeking medical care after the development of
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4 symptoms suggestive of myocardial infarction. Although there have been significant
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6 reductions in patient and system delay in the last decade, women continue to have longer
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8 presentation and treatment times.³⁸ Sex differences also exist in clinical presentation of
9
10 STEMI. Although chest pain was the most common ACS symptom in both sexes, women
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12 were more likely to present without chest pain than men.^{39 40} Lower rates of typical chest
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14 pain reported among women with STEMI may also influence provider decision-making to
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16 pursue less aggressive care including invasive revascularization.
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25 Some included studies of our meta-analysis enrolled STEMI patients in general¹⁴⁻¹⁶, while
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27 some others enrolled patients undergoing PCI for STEMI^{11 13 18}. The different prognosis of
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29 patients receiving reperfusion therapy or no-reperfusion therapy might be a potential
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31 source of heterogeneity of our study. Nevertheless, our results are completely consistent
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33 with a previous meta-analysis from Pancholy et al., which investigated sex differences in
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35 mortality among patients with STEMI treated with primary PCI.² Its results demonstrated
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37 that, when adjusted RRs were used, the increased risk for 1-year mortality in women was
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39 no longer significant and the risk of in-hospital mortality still significantly elevated. It should
40
41 be noted that more than 50% of patients were treated with PCI in the most study conducted
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43 among the general STEMI patients and included by our analysis, even more than 90% in
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45 some included studies.^{12 24} The increasing rate of primary PCI in recent years might be a
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47 reason for the consistency of our findings and previous studies conducted specifically
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49 among STEMI patients undergoing PCI
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4 Complications including bleeding, heart failure and mechanical complications are more
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6 likely to develop in women with acute myocardial infarction and increase the risk of
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8 mortality.^{14 41 42} Bleeding secondary to antithrombotic therapies and invasive procedures is
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10 more frequent in women.⁴³ Three included studies reported incidence of bleeding following
11
12 STEMI and they all found that women were at higher risk of bleeding.^{10 13 18} One study
13
14 included in our analysis examined the relationships among sex, acute heart failure, and
15
16 related outcomes after STEMI.¹⁴ Its results demonstrate that women are at higher risk to
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18 develop de novo heart failure after STEMI and women with de novo heart failure have
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20 worse survival compared with man. However, we could not compare the incidence of these
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22 complications due to the lack of sufficient data. Mechanical complications requiring surgical
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24 intervention are also much more common in women after acute myocardial infarction and
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26 associated with high mortality rates.⁴⁴

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38 Several limitations of this meta-analysis should be considered. First, the included studies
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40 are all observational studies except one post hoc analysis of randomized controlled trial.
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42 Hence, there may be residual confounding bias inherent in the observational study design
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44 in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the
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46 same confounders and not all studies reported adjusted RRs. **The confounders which were**
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48 **adjusted in the included studies might differ greatly across studies.** Third, there was
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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

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4 noted that relevant confounders might have differed across studies. Fourth, the analysis of
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6 long-term mortality, especially the adjusted analysis, included far fewer studies compared
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8 with analysis of short-term mortality. Hence, there might be significant bias in the results
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10 about long-term mortality.
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17 In conclusion, our meta-analysis, pooling data from contemporary literature, shows that
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19 women with STENI have a higher risk of short-term mortality but not long-term mortality.
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21 The effect of sex differences on mortality in patients with STEMI remain significant after
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23 adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that
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25 public awareness of increased risk and further improvements in management in women
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27 with STEMI are necessary.
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35 Other Information:

40 Contribution statement

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42 Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis,
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44 Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data
45
46 acquisition, Data analysis/interpretation. Jianan Li, Yang Li, Jianfeng Zheng and Runlin
47
48 Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.
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56 Conflict of interest

57
58 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

1	Cenko	2019	12	Prospective	Clinical	Yes	Jan, 2010-	10,443	3,112	30-day all-cause	30 d
2			Europea		registry		Jul, 2018		(29.8)	mortality	
3			n								
4			countries								
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10											
11	Hao	2019	China	Prospective	Clinical	Yes	Nov, 2014-	50,203	11,016	In-hospital mortality	NA
12					registry		Jun, 2018		(21,9)		
13											
14											
15											
16											
17	Hannan	2019	US	Retrospective	Administrativ	Yes	Jan, 2013-	23,809	7,791	In hospital/30-day	30 d
18					e database		Dec, 2015		(32.7)	mortality	
19											
20											
21											
22	Maznyczka	2019	UK	Retrospective	Clinical	No	July, 2011-	324	87 (26.9)	All-cause death/ first	5 years
23					registry		Nov, 2012			heart failure	
24										hospitalization	
25											
26											
27											
28											
29											
30	Stehli	2019	Australia	Prospective	Clinical	Yes	2013-2016	6,431	1,317	In hospital/30-day major	30 d
31					registry				(20.5)	adverse events, and	
32										major bleeding	
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37											
38	Burgess	2020	Australia	Prospective	Administrativ	No	Dec, 2010-	589	123 (21)	Cardiac death and	2 years
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				e database		Apr, 2014			myocardial infarction	
Dharma	2020	Indonesi a	Retrospective	Administrativ e database	No	Feb, 2011- Aug, 2019	6,557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherla nds	Retrospective	Administrativ e 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	Administrativ e 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
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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		
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	61.1	10,141	24,08	15,607	38,42	17,996 (85.4)	50,94	1,719	32,37	NA	NA	NA	NA
		(10.6)	(12.4)	(48.1)	2	(74.1)	6		4	(8.2)	7				
					(39.4		(62.9		(83.3		(53.0				
)))))				
Hannan	2019	70.72	62.11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	868	2206
		(14.73)	(12.82)											(11.1)	(13.8
)
Maznyczk a	2019	61.2	58.6(11.2	8 (9.2)	26	32 (36.8)	73	28 (32.2)	66	57	139	5 (5.7)	20	2	16
		(12.2))		(11.0		(30.8		(27.8	(65.5)	(58.6		(8.4)	(2.3)	(6.8)
))))				
Stehli	2019	66.5	60.8	245	770	NA	NA	NA	NA	NA	NA	NA	NA	104	577
		(13.2)	(12.2)	(18.6)	(15.1									(7.9)	(11.3
))

1	Burgess	2020	62.7	58.2	39	88	84 (68.3)	243	83 (67.5)	253	64	252	9 (7.3)	41	NA	NA
2			(52.7-	(50.6-	(31.7)	(18.9	(52.1	(52.3	(52.0)	(54.1	(8.8)					
3			73.2)	65.7)))))))						
4																
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9	Dharma	2020	60 (10)	55 (10)	403	1548	647 (69.6)	2,889	299 (32.2)	1,779	109	4,049	NA	NA	NA	NA
10					(43.4)	(27.5	(51.3	(31.6	(11.7)	(71.9						
11))))))						
12																
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16																
17	Kerkmanx	2020	68 (14)	61 (12)	39	66	101 (45.7)	178	56 (25.9)	110	88	258	30	79	33	77
18					(17.6)	(12.5	(33.6	(21.0	(41.1)	(49.3	(13.6)	(13.7	(14.4)	(14.2		
19))))))))))		
20																
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24	Siabani	2020	65.8	59.0	114	187	195 (63.7)	410	110 (36.7)	208	41	655	NA	NA	NA	NA
25			(11.3)	(12.4)	(37.7)	(16.2	(35.4	(18.5	(13.2)	(55.9						
26))))))						
27																
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31																
32	Tai	2020	78 (76-	78 (76-	96	116	217 (79.5)	319	NA	NA	14 (5.4)	239	NA	NA	36	78
33			81)	80)	(35.2)	(26.5	(72.8				(56.5			(13.5)	(18.1	
34)))))	
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1	Tizón	2020	69.9	60.9	844	1,927	1,192 (34.2)	2,722	878 (25.2)	2,375	474	2,711	NA	NA	NA	NA
2																
3			(13.7)	(12.6)	(24.2)	(17.2		(24.3		(21.2	(13.6)	(24.2				
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For peer review only

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4 Figure 1 Flowchart of selection of studies included in meta-analysis.
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9 Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and
10 men with ST-segment elevation myocardial infarction.
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13 Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of
14 women compared with men with ST-segment elevation myocardial infarction using
15 random-effects model.
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25 Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and
26 men with ST-segment elevation myocardial infarction.
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29 Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of
30 women compared with men with ST-segment elevation myocardial infarction using
31 random-effects model.
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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.	Page 5
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

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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

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

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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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9 **Short title : Sex differences in STEMI**
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11 **Authors:**

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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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12 **Objectives:** To assess the effect of sex differences on short- and long-term mortality among
13
14 patients with ST-segment elevation myocardial infarction (STEMI).
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19 **Design:** Systematic review and meta-analysis of contemporary available evidence.
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25 **Setting:** PubMed, Embase and Cochrane Library were searched for relevant studies
26
27 reporting sex specific outcomes among patients with STEMI published between January
28
29 1, 2010 to August 1, 2020. Risk ratio (RR) 95% 95% confidence intervals (CIs) were
30
31 measured using DerSimonian and Laird random-effects model. Sensitivity analyses were
32
33 performed and publication bias was also checked. All statistical analyses were performed
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35 using STATA version 15.0.
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43 **Participants:** Studies providing data about short- or long-term mortality stratified by sex in
44
45 patients with STEMI were included. Only study conducted in last ten years were included.
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51 **Primary and secondary outcome measures:** The primary outcome was all-cause death at
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53 short-(in-hospital or 30 days) and long-term (at least 12 months) follow-up.
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58 **Results**
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4 A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879
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6 [75.3%] male) were included. In the unadjusted analyses, female were at a higher risk of
7
8 short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, $P<0.001$, $I^2=77\%$) but not long-term
9
10 mortality (RR, 1.23; 95%CI, 0.89-1.69, $P=0.206$, $I^2=77.5\%$). When adjusted effect
11
12 estimates from individual studies were used in meta-analysis, the association between
13
14 female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-
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16 1.38, $P<0.001$, $I^2=39.6\%$). And adjusted long-term mortality was also similar between
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18 female and male (RR, 1.11; 95%CI, 0.42-1.80, $P=0.670$, $I^2=74.5\%$).
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28 **Conclusions**

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

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4 mortality among patients with STEMI, we performed a systematic review and meta-
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7 analysis of all available evidence from last decade reporting sex-specific outcomes after
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9 STEMI.
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11 12 13 14 **Methods**

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19 The present systematic review and meta-analysis was performed following the principle
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21 of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
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23 statement.⁸
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30 *Literature search*

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32 We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library
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34 from January 1, 2010 to August 1, 2020 to identify studies from the last decade that
35
36 described sex differences in in short- or long-term mortality among patients with STEMI.
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38 Both observational studies and randomized clinical trials were eligible. We queried MeSH
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40 and the abstract text for the following three search terms: gender part (including "gender",
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42 "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome
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44 part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac
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46 death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular
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48 mortality" or "short term mortality"); myocardial infarction part (including "myocardial
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50 infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation
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52 myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or
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4 "primary angioplasty") to identify relevant studies. There was no language restriction or
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6 age limit.
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10 11 *Study selection*

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14 According to the aim of our analyses, studies were included in this systematic review if
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16 data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality
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18 stratified by sex in patients with STEMI were reported. Two reviewers identified studies
19
20 eligible for further review by performing an initial screen of titles or abstracts of the search
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22 results. Subsequently, a second screen of full texts eligibility was performed by another
23
24 two reviewers. Studies had to fulfil the following criteria to be included in the present
25
26 analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and
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28 ii) studies providing enough details to obtain numbers of events or incidence rates
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30 according to sex; and iii) enrollment starting earlier than a decade ago. Editorials, letters,
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32 conference proceedings and abstracts were considered to be eligible only if sufficient
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34 information was available in abstracts or associated tables or figures. We excluded studies
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36 if they were review articles or case reports, or if they involved pregnant participants,
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38 critically ill patients, or provided insufficient data to allow for risk estimates to be calculated.
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48 Any disagreement was reviewed by a third reviewer and resolved by consensus.
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53 *Data extraction*

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56 Detailed data from selected studies were extracted independently by two reviewers using
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58 a standardized form independently. Data about study and participants characteristics,
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4 including year of study, sample size, time of enrollment, geographical location, endpoints
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6 of study, and follow-up duration, were collected. Any discrepancies were reviewed by a
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8 third reviewer and resolved by consensus. The quality of included studies was evaluated
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10 by Newcastle-Ottawa scale using prespecified items comprised of patients' selection
11
12 (representativeness and selection of patients, ascertainment of exposure), comparability
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14 of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy
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16 of follow-up).⁹ A quality score (0–9 points) was generated according to a maximum of 1
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18 point for each item.
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28 *Patient and public involvement*

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

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40 The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent
41
42 the effect of sex differences on mortality after STEMI. And data were combined using
43
44 random-effects model of DerSimonian and Laird with inverse variance weighting. Random-
45
46 effect model was used due to substantial clinical and statistical heterogeneity. Following
47
48 analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality
49
50 using raw number of death and total participants at risk for death specific to each sex, ii)
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52 adjusted RRs for short- and long-term all-cause mortality using adjusted RRs if they were
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54 described in those included studies. In terms of short-term mortality, the RRs for in-hospital
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4 and 30-day mortality were also calculated respectively.
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6 We assess heterogeneity across studies with Cochran's Q test and I² test, with P<0.1 or
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8 I² >50% considered significant. We also performed meta-regression to identify the
9
10 potential sources of heterogeneity in the included studies. The potential sources were
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12 differences in diabetes, hypertension, hyperlipidemia, smoking, prior MI, and prior PCI.
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14 Furthermore, stratified analysis was conducted as well by dividing the included studies into
15
16 different subgroups based on the Newcastle-Ottawa scale scores (>7 points or ≤7 points)
17
18 to assess the potential sources of heterogeneity. To assess the potential effect of
19
20 publication bias, we inspected funnel plots for asymmetry and used the Egger's regression
21
22 asymmetry test in which P<0.05 was considered to indicate significant publication bias.
23
24 Sensitivity analyses was conducted by excluding one study at a time and comparing the
25
26 results with the complete one. In addition, we also performed sensitivity analyses by
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28 restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and
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30 restricting to studies with sample size bigger than 1000 participants. All statistical analyses
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32 were performed using STATA version 15.0 (Stata Corp, College Station, TX). Differences
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34 were considered statistically significant at P < .05 (2-sided).
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48 **Results**

49 *Literature search*

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

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22 Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than
23
24 10,000 patients with STEMI. See Table 1 for further information of included studies.
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26 Baseline characteristics of participants were missing in some included studies, but all
27
28 included studies provided sufficient data for analysis of sex differences in clinical outcomes.
29
30 Except for 1 study, which was a prespecified gender analysis of randomized controlled
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32 trial, the remaining 14 were observational studies. Among the 10 included studies which
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34 reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension,
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36 and prior myocardial infarction/PCI, while some adjusted for renal insufficiency,
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38 cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset.
39
40 Variables that were adjusted in the adjusted analyses from the included studies were
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42 presented in eTable 1 of the Supplementary Material. Results of assessment of study
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44 quality using Newcastle-Ottawa scale were shown in eTable 2 in the Supplementary
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46 Material.
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Patient characteristics

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4 A total of 128,585 patients with STEMI (31,706 [24.7%] female and 96,879 [75.3%] male)
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6 were involved in the 15 included studies. Female tended to be older and had higher
7
8 prevalence of diabetes mellitus in all included studies. And in most studies, other important
9
10 comorbidities, including hypertension and hyperlipidemia, were more frequent in female.
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12 Greater proportions of male were smokers and had prior PCI or myocardial infarction.
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14 Besides, some studies reported that door-to-balloon time and symptom onset to balloon
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16 time were longer in female than male. Part of patient baseline characteristics were
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18 summarized in Table 2.
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28 *Short-term all-cause mortality*

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30 Thirteen studies reported sex-specific unadjusted short-term mortality (7 studies with 30-
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32 day mortality and 6 studies with in-hospital mortality) of patients with STEMI. There were
33
34 2,873 of 31,409 (9.1%) cases of all-cause mortality in female compared with 4,380 of
35
36 95,610 (4.6%) in male. Female were at a significantly higher risk of short-term mortality
37
38 (RR, 1.73; 95%CI, 1.53-1.96, $P<0.001$, $I^2=77\%$) compared with male (Figure 2 A). Nine
39
40 studies involving 119,379 patients reported adjusted short-term mortality specific to sex. In
41
42 adjusted analysis, the association between female and higher risk of short-term mortality
43
44 remained significant (RR, 1.24; 95%CI, 1.11-1.38, $P<0.001$, $I^2=39.6\%$) (Figure 2 B).
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46 However, the strength of association calculated with adjusted RRs from these 9 studies
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48 was attenuated.
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55 Subgroup analysis demonstrated that the results of studies with Newcastle-Ottawa
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57 scale >7 points (RR, 1.90; 95%CI, 1.73-2.09, $P=0.018$, $I^2=63.4\%$) and studies with ≤ 7
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4 points (RR, 1.52; 95%CI, 1.20-1.93, P=0.026, I²=58.1%) were consistent in unadjusted
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6 short-term mortality (See eFigure 1 in the Supplementary Material). The impact of sex on
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8 in-hospital (RR, 1.71; 95%CI, 1.27-2.31, P<.001, I²=86.4%) and 30-day mortality (RR, 1.81;
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10 95%CI, 1.62-2.02, P<.001, I²=56.6%) were consistent. The meta-analysis performed in
11
12 studies of patients undergoing PCI for STEMI also showed increased unadjusted mortality
13
14 (RR, 1.45; 95%CI, 1.05-2.00, P=0.026, I²=39.5%) in female patients.
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22 *Long-term all-cause mortality*

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24 Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and
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26 followed up for more than 1 year, and reported all-cause mortality for female and male.
27
28 The incidence of long-term all-cause mortality was 13.9% (n=584) in female and 8.7%
29
30 (n=1202) in male. In unadjusted analysis, no significant sex difference was found in long-
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32 term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I²=77.5%) (Figure 3 A). The
33
34 unadjusted long-term mortality was also similar between female and male patients
35
36 undergoing PCI (RR, 1.28; 95%CI, 0.95-1.73, P=0.108, I²=0.0%). And the adjusted
37
38 analysis of the pooled results from four studies, also showed a similar risk of mortality at
39
40 long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670,
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42 I²=74.5%) (Figure 3 B).
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53 *Meta-Regression Analysis, sensitivity analyses and publication bias*

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55 According to meta-regression analysis, differences in prevalence of diabetes (β coefficient,
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57 0.248; P=0.337; adjusted R²=1.31%; I²=80.86%; τ^2 =0.044), hypertension (β coefficient, -
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4 0.255; P=0.538; adjusted R²=24.22%; I²=41.04%; τ²=0.008), hyperlipidemia(β coefficient,
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6 0.260; P=0.415; adjusted R²=-1.84%; I²=83.59%; τ²=0.050), smoking (β coefficient, -
7
8 0.040; P=0.255; adjusted R²=17.86%; I²=79.41%; τ²=0.045), prior MI (β coefficient, -
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10 2.725; P=0.126; adjusted R²=60.30%; I²=60.19%; τ²=0.032), and prior PCI (β coefficient,
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12 0.109; P=0.896; adjusted R²=-58.31%; I²=61.73%; τ²=0.042) between sexes were not
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14 identified as significant sources of heterogeneity for short-term all-cause mortality. Given
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16 that not all included study provided information on confounders stratified by sex, the results
17
18 of meta-regression analyses should be interpreted with caution.
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25 Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary
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27 Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75;
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29 95%CI, 1.54-1.99, P<.001, I²=82.9%) both indicated that none of the studies affected the
30
31 results of short-term mortality in this meta-analysis significantly. In analysis for long-term
32
33 mortality, sensitivity analysis showed a possibly higher influence on the result attribute to
34
35 the study of Tai et al (See eFigure 3 in the Supplementary Material). After removing this
36
37 study from meta-analysis, the association of female with increased long-term mortality
38
39 became significant (RR, 1.50; 95%CI, 1.23-1.83, P<.001, I²=40.9%). We found no
40
41 evidence of publication bias across studies based on visual inspection of funnel plots (See
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43 eFigure 4 in the Supplementary Material) and the results from Egger's tests for short-term
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45 mortality (P=0.462) and for long-term mortality (P=0.053).
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56 Discussion:

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4 Our systematic review and meta-analysis of contemporary literature on sex differences
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6 among patients with STEMI demonstrate that female have a higher risk of short- but not
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8 long-term mortality compared with male with STEMI. Furthermore, after adjustment for
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10 baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term
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12 mortality are attenuated but remain significant, while female have the similar long-term
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14 mortality with male.
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22 Our results are somewhat in accordance with several previously published meta-analysis.²

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25 ²⁵ A considerable number of studies have consistently suggested that women were at a
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27 higher risk of short-term mortality after ACS. However, whether risk of long-term mortality
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29 is also higher in women with ACS remains under debate. Some studies indicated that
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31 women with STEMI had a higher 1-year rate of death compared to men²⁶, while the 1-year
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33 mortality rate was conversely lower in women than men in some other studies^{23 24}. In our
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35 study, with respect to short-term mortality, the analyses of studies with high or low quality,
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37 and big or small sample size yielded similar results. However, in terms of long-term
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39 mortality, caution is needed when interpreting our finding of non-significant increased long-
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41 term mortality in adjusted analyses, due to the results of sensitivity analysis which showed
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43 a significant association between female and increased long-term mortality after removing
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45 one study from adjusted analyses.
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56 It is widely accepted that there are significant differences in outcomes of women and men
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58 with acute myocardial infarction. In our study, after adjusted for participants' baseline
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4 cardiovascular risk factors and clinical profiles, the strength of association between gender
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6 and short-term mortality was substantially attenuated, which suggested that poorer
7
8 baseline cardiovascular risk profile partially explained the impact of sex differences on
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10 mortality. Multiple studies have shown that women with STEMI present at older age and
11
12 have a higher burden of comorbidities, contributing to the sex differences in mortality after
13
14 STEMI.²⁷ All studies included in our meta-analysis demonstrate that female patients are
15
16 older and with more diabetes mellitus as well as hypertension. In addition, some sex-
17
18 specific studies found that certain risk factors and comorbidities were more potent in
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20 women.²⁸ Diabetes mellitus, hypertension and smoking status are more strongly
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22 associated with increased risk of cardiac events in women compared with men.^{27 29}
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32 Notably, that these differences mentioned above still could not completely explain the gap
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34 in mortality between sexes. It has been proved that women with acute myocardial infarction
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36 were less likely to be treated with guideline directed medical therapy and less likely to
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38 receive primary reperfusion therapy including primary percutaneous coronary intervention
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40 or fibrinolysis.³⁰ Regarding medical therapy, numerous studies conducted around the world
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42 consistently demonstrate female survivors are receiving less optimal medical therapy after
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44 acute myocardial infarction during hospitalization or at discharge.^{31 32} Though there might
45
46 be no differences in treatment adherence between men and women, some studies report
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48 significant sex disparities in initiation of appropriate pharmacotherapy after myocardial
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50 infarction.³³ Results from these observational studies have shown women are receiving
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52 less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme
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4 inhibitors in all age groups, especially young women, and suggested that clinicians and
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6 patients may benefit from better education and awareness of undertreatment of younger
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8 women.^{33 34}
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14 Lower rates of revascularization are observed among women with STEMI compared with
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16 men in several studies despite proven benefit of this therapy.³⁵ Moreover, the sex
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18 differences might be driven by delays in presentation to hospital and women with STEMI
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20 were more likely to experience longer delays than men. Although a great improvement in
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22 emergency medical services and timely revascularization over the past decades, recent
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24 studies show that women with STEMI still present later and have a longer ischemic time
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26 than men. Previous studies have shown consistently that women have longer door-to
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28 balloon times and longer door-to needle times.^{36 37} In addition, women are also more likely
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30 to exhibit longer pre-hospital delays in seeking medical care after the development of
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32 symptoms suggestive of myocardial infarction. Although there have been significant
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34 reductions in patient and system delay in the last decade, women continue to have longer
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36 presentation and treatment times.³⁸ Sex differences also exist in clinical presentation of
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38 STEMI. Although chest pain was the most common ACS symptom in both sexes, women
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40 were more likely to present without chest pain than men.^{39 40} Lower rates of typical chest
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42 pain reported among women with STEMI may also influence provider decision-making to
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44 pursue less aggressive care including invasive revascularization.
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58 Some included studies of our meta-analysis enrolled STEMI patients in general¹⁴⁻¹⁶, while
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4 some others enrolled patients undergoing PCI for STEMI^{11 13 18}. The different prognosis of
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6 patients receiving reperfusion therapy or no-reperfusion therapy might be a potential
7
8 source of heterogeneity of our study. Nevertheless, our results are completely consistent
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10 with a previous meta-analysis from Pancholy et al., which investigated sex differences in
11
12 mortality among patients with STEMI treated with primary PCI.² Its results demonstrated
13
14 that, when adjusted RRs were used, the increased risk for 1-year mortality in women was
15
16 no longer significant and the risk of in-hospital mortality still significantly elevated. It should
17
18 be noted that more than 50% of patients were treated with PCI in the most study conducted
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20 among the general STEMI patients and included by our analysis, even more than 90% in
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22 some included studies.^{12 24} The increasing rate of primary PCI in recent years might be a
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24 reason for the consistency of our findings and previous studies conducted specifically
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26 among STEMI patients undergoing PCI
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38 Complications including bleeding, heart failure and mechanical complications are more
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40 likely to develop in women with acute myocardial infarction and increase the risk of
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42 mortality.^{14 41 42} Bleeding secondary to antithrombotic therapies and invasive procedures is
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44 more frequent in women.⁴³ Three included studies reported incidence of bleeding following
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46 STEMI and they all found that women were at higher risk of bleeding.^{10 13 18} One study
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48 included in our analysis examined the relationships among sex, acute heart failure, and
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50 related outcomes after STEMI.¹⁴ Its results demonstrate that women are at higher risk to
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52 develop de novo heart failure after STEMI and women with de novo heart failure have
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54 worse survival compared with man. However, we could not compare the incidence of these
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4 complications due to the lack of sufficient data. Mechanical complications requiring surgical
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6 intervention are also much more common in women after acute myocardial infarction and
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8 associated with high mortality rates.⁴⁴
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14 Several limitations of this meta-analysis should be considered. First, the included studies
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16 are all observational studies except one post hoc analysis of randomized controlled trial.
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18 Hence, there may be residual confounding bias inherent in the observational study design
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20 in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the
21
22 same confounders and not all studies reported adjusted RRs. The confounders which were
23
24 adjusted in the included studies might differ greatly across studies. Third, there was
25
26 substantial heterogeneity in our meta-analysis, which could partly be attributed to the wide
27
28 variability in the sample sizes, locations, and treatment regimens across included studies.
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30 Additionally, although we calculated adjusted RRs for all-cause mortality, it needed to be
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32 noted that relevant confounders might have differed across studies. Fourth, the analysis of
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34 long-term mortality, especially the adjusted analysis, included far fewer studies compared
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36 with analysis of short-term mortality. Hence, there might be significant bias in the results
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38 about long-term mortality.
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51 In conclusion, our meta-analysis, pooling data from contemporary literature, shows that
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53 women with STENI have a higher risk of short-term mortality but not long-term mortality.
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55 The effect of sex differences on mortality in patients with STEMI remain significant after
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57 adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that
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4 public awareness of increased risk and further improvements in management in women
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6 with STEMI are necessary.
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11 **Other Information:**

12 **Contribution statement**

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19 Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis,
20
21 Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data
22
23 acquisition, Data analysis/interpretation. Jianan Li, Yang Li, Jianfeng Zheng and Runlin
24
25 Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.
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32 **Conflict of interest**

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35 The authors declare that there is no conflict of interest.
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41
42
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45 or not-for-profit sectors.
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50 **Ethics approval**

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53 The institutional central committee at Fuwai Hospital approved that the study protocol and
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55 inform consent was not required for a systematic review and meta-analysis.
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4 **Data sharing statement**
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6 As this is a systematic review and meta-analysis, the data used in the study have already
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8
9 been published by the authors of the included studies. All data relevant to the study are
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11 included in the article or uploaded as supplementary information.
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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

1	Cenko	2019	12	Prospective	Clinical	Yes	Jan, 2010-	10,443	3,112	30-day all-cause	30 d
2			Europea		registry		Jul, 2018		(29.8)	mortality	
3			n								
4			countries								
5											
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10											
11	Hao	2019	China	Prospective	Clinical	Yes	Nov, 2014-	50,203	11,016	In-hospital mortality	NA
12					registry		Jun, 2018		(21,9)		
13											
14											
15											
16											
17	Hannan	2019	US	Retrospective	Administrativ	Yes	Jan, 2013-	23,809	7,791	In hospital/30-day	30 d
18					e database		Dec, 2015		(32.7)	mortality	
19											
20											
21											
22	Maznyczka	2019	UK	Retrospective	Clinical	No	July, 2011-	324	87 (26.9)	All-cause death/ first	5 years
23					registry		Nov, 2012			heart failure	
24										hospitalization	
25											
26											
27											
28											
29											
30	Stehli	2019	Australia	Prospective	Clinical	Yes	2013-2016	6,431	1,317	In hospital/30-day major	30 d
31					registry				(20.5)	adverse events, and	
32										major bleeding	
33											
34											
35											
36											
37											
38	Burgess	2020	Australia	Prospective	Administrativ	No	Dec, 2010-	589	123 (21)	Cardiac death and	2 years
39											
40											
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				e database		Apr, 2014			myocardial infarction	
Dharma	2020	Indonesi a	Retrospective	Administrativ e database	No	Feb, 2011- Aug, 2019	6,557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherla nds	Retrospective	Administrativ e 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	Administrativ e 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
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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		
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	61.1	10,141	24,08	15,607	38,42	17,996 (85.4)	50,94	1,719	32,37	NA	NA	NA	NA
		(10.6)	(12.4)	(48.1)	2	(74.1)	6		4	(8.2)	7				
					(39.4		(62.9		(83.3		(53.0				
))))				
Hannan	2019	70.72	62.11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	868	2206
		(14.73)	(12.82)											(11.1)	(13.8
))
Maznyczk	2019	61.2	58.6(11.2	8 (9.2)	26	32 (36.8)	73	28 (32.2)	66	57	139	5 (5.7)	20	2	16
a		(12.2))		(11.0		(30.8		(27.8	(65.5)	(58.6		(8.4)	(2.3)	(6.8)
))))				
Stehli	2019	66.5	60.8	245	770	NA	NA	NA	NA	NA	NA	NA	NA	104	577
		(13.2)	(12.2)	(18.6)	(15.1									(7.9)	(11.3
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1	Burgess	2020	62.7	58.2	39	88	84 (68.3)	243	83 (67.5)	253	64	252	9 (7.3)	41	NA	NA
2			(52.7-	(50.6-	(31.7)	(18.9		(52.1		(52.3	(52.0)	(54.1		(8.8)		
3			73.2)	65.7)))))))				
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8	Dharma	2020	60 (10)	55 (10)	403	1548	647 (69.6)	2,889	299 (32.2)	1,779	109	4,049	NA	NA	NA	NA
9					(43.4)	(27.5		(51.3		(31.6	(11.7)	(71.9				
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16	Kerkmanx	2020	68 (14)	61 (12)	39	66	101 (45.7)	178	56 (25.9)	110	88	258	30	79	33	77
17					(17.6)	(12.5		(33.6		(21.0	(41.1)	(49.3	(13.6)	(13.7	(14.4)	(14.2
18))))))))
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23																
24	Siabani	2020	65.8	59.0	114	187	195 (63.7)	410	110 (36.7)	208	41	655	NA	NA	NA	NA
25			(11.3)	(12.4)	(37.7)	(16.2		(35.4		(18.5	(13.2)	(55.9				
26))))))				
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32	Tai	2020	78 (76-	78 (76-	96	116	217 (79.5)	319	NA	NA	14 (5.4)	239	NA	NA	36	78
33			81)	80)	(35.2)	(26.5		(72.8				(56.5			(13.5)	(18.1
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1	Tizón	2020	69.9	60.9	844	1,927	1,192 (34.2)	2,722	878 (25.2)	2,375	474	2,711	NA	NA	NA	NA
2																
3			(13.7)	(12.6)	(24.2)	(17.2		(24.3		(21.2	(13.6)	(24.2				
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4 Figure 1 Flowchart of selection of studies included in meta-analysis.
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9 Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and
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13 Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of
14 women compared with men with ST-segment elevation myocardial infarction using
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25 Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and
26 men with ST-segment elevation myocardial infarction.
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29 Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of
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Figure 1 Flowchart of selection of studies included in meta-analysis.

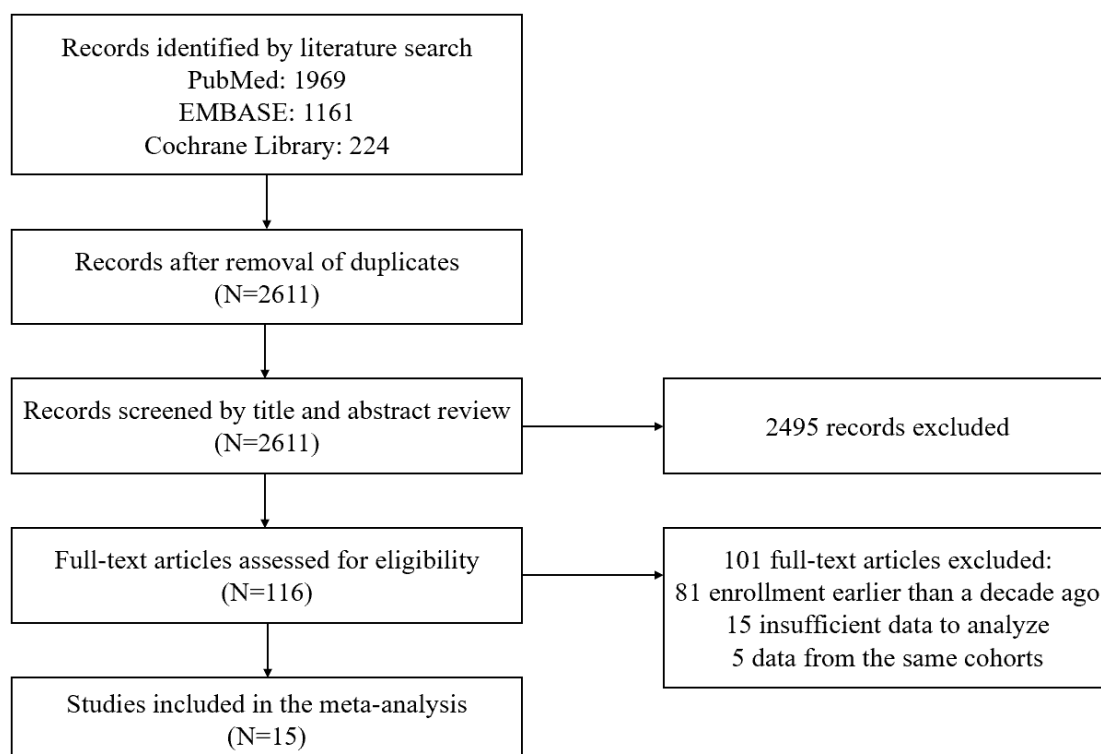
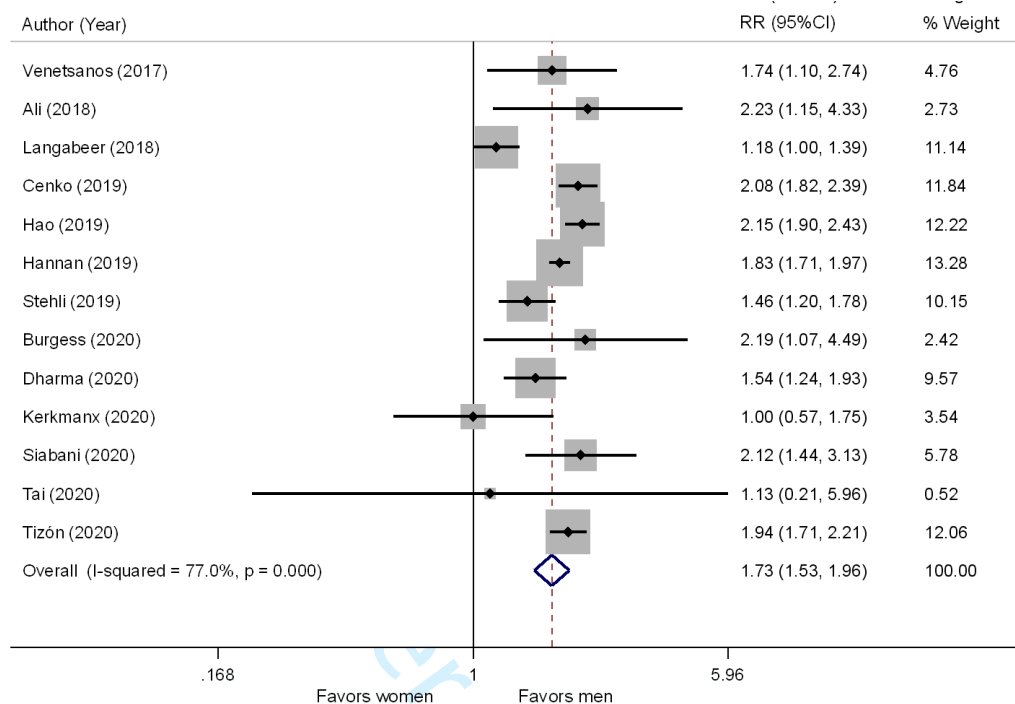
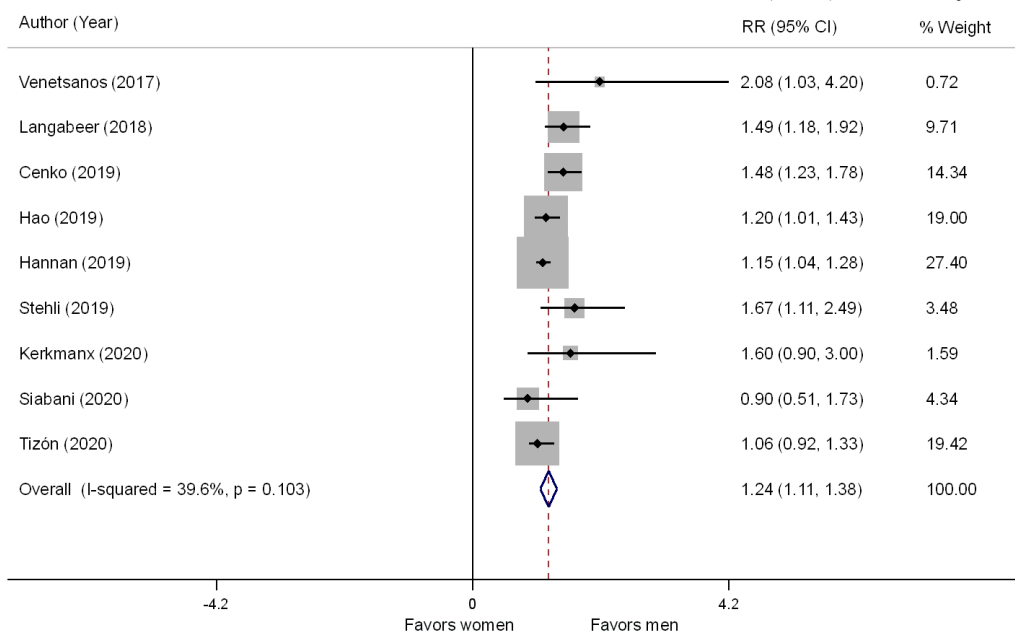


Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

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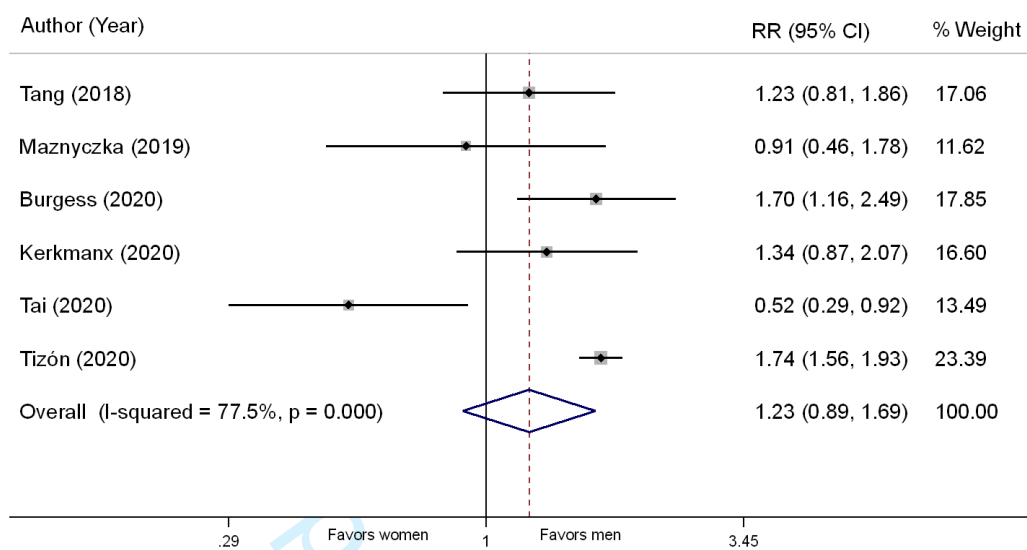
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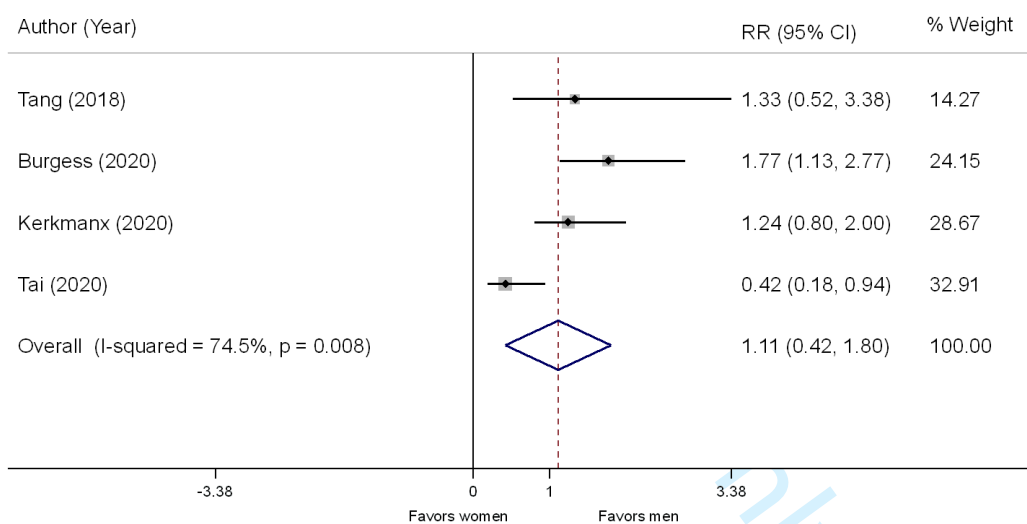
Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

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.

Table 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 \geq 25, hypertension, diabetes, current smoking, hypercholesterolemia, congestive heart failure, Killip class (at first presentation) \geq 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,

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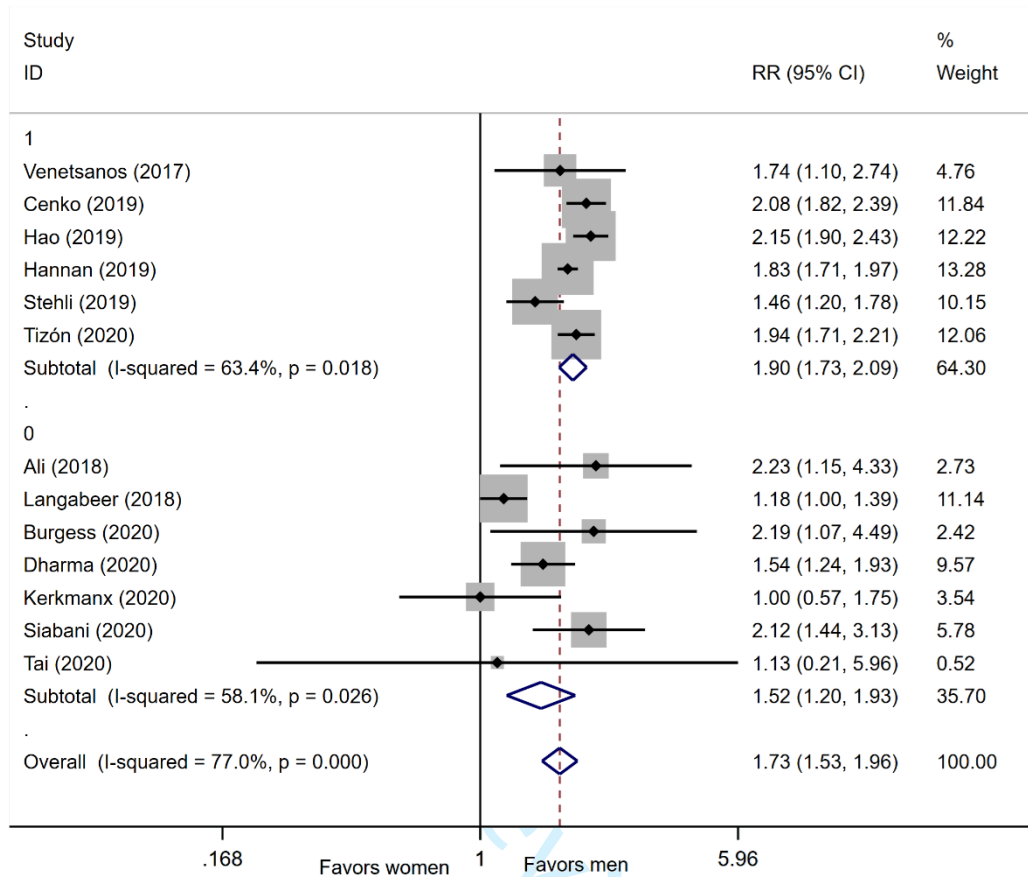
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eTable 2 Assessment of study quality using Newcastle-Ottawa scale.

First Author	Year	Selection				Comparability	Outcome			Total point
		Representativeness of the exposed cohort	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

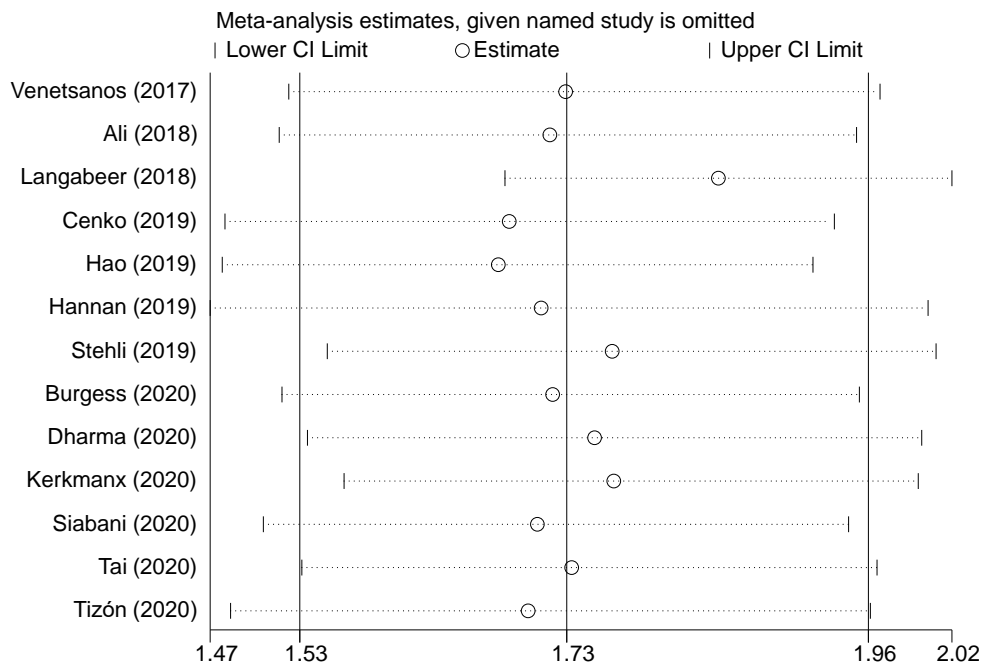
Burgess	2020	\	\	*	*	**	*	*	*	7
Dharma	2020	\	\	*	*	*	*	*	*	6
Kerkmanx	2020	*	*	*	*	\	*	*	*	7
Siabani	2020	\	\	*	*	*	*	\	*	5
Tai	2020	\	\	*	*	**	*	*	*	7
Tizón	2020	*	*	*	*	**	*	*	*	9

eFigure 1

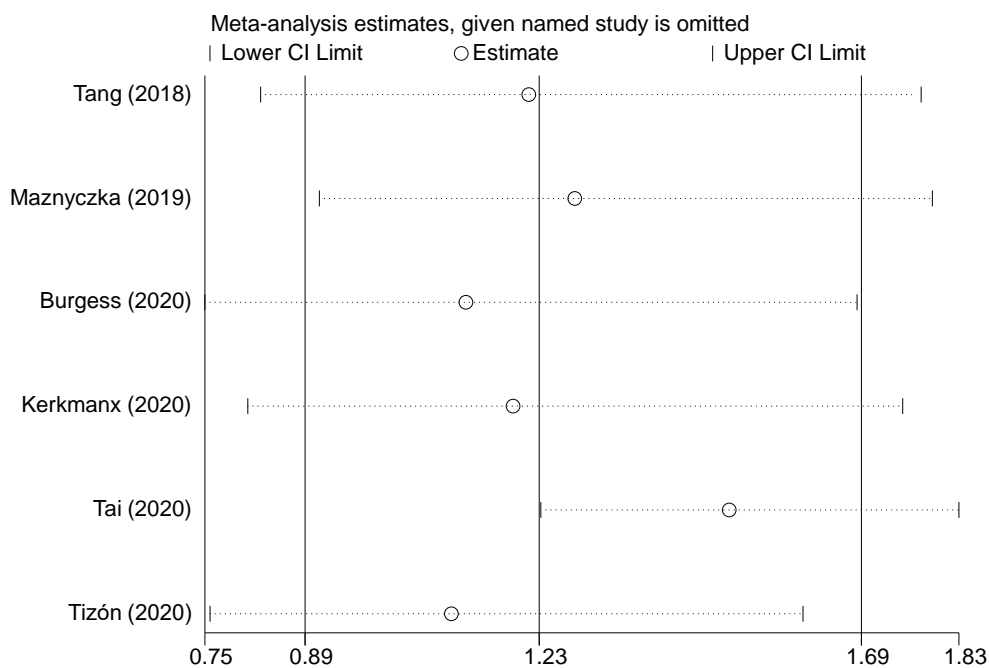


eFigure 2 Meta-influence analysis for unadjusted short-term mortality

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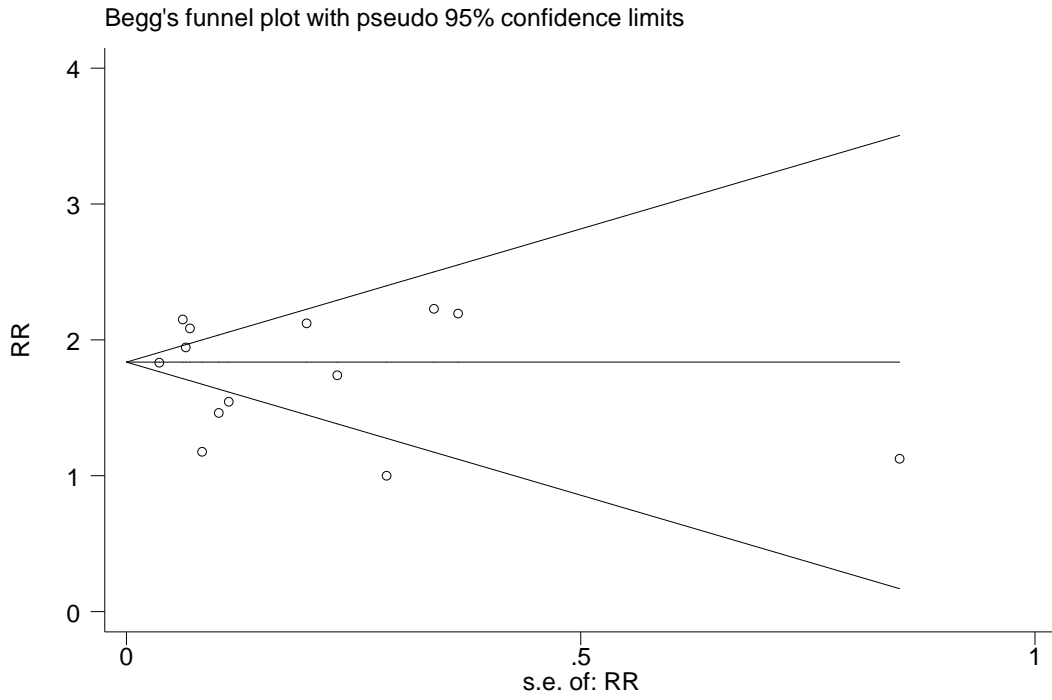


eFigure 3 Meta-influence analysis for unadjusted long-term mortality



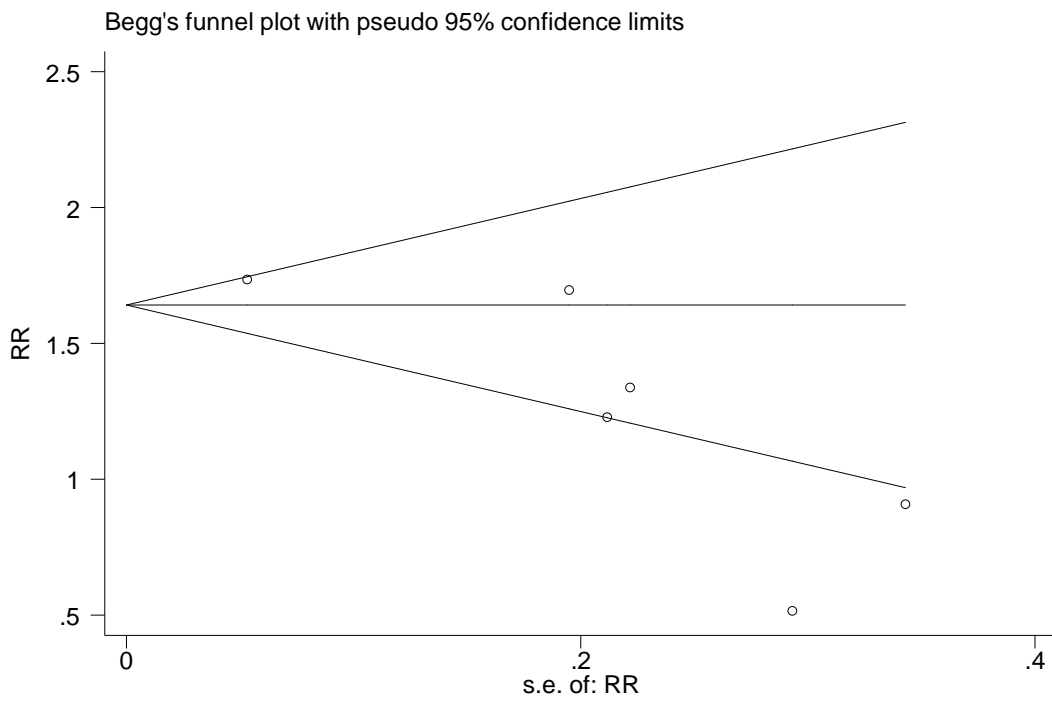
eFigure 4 Funnel plots for publication bias for unadjusted short-term (A) and long-term (B) mortality

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PRISMA 2020 Checklist

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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.	Page 5
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

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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

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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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9 **Short title : Sex differences in STEMI**
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11 **Authors:**

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For peer review only

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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
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6 **myocardial infarction: a systematic review and meta-analysis**
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11 **Objectives:** To assess the effect of sex differences on short- and long-term mortality among
12 patients with ST-segment elevation myocardial infarction (STEMI).
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19 **Design:** Systematic review and meta-analysis of contemporary available evidence.
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25 **Setting:** PubMed, Embase and Cochrane Library were searched for relevant studies
26 reporting sex specific outcomes among patients with STEMI published between January
27 1, 2010 to August 1, 2020. Risk ratio (RR) 95% 95% confidence intervals (CIs) were
28 measured using DerSimonian and Laird random-effects model. Sensitivity analyses were
29 performed and publication bias was also checked. All statistical analyses were performed
30 using STATA version 15.0.
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43 **Participants:** Studies providing data about short- or long-term mortality stratified by sex in
44 patients with STEMI were included. Only study conducted in last ten years were included.
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50 **Primary and secondary outcome measures:** The primary outcome was all-cause death at
51 short-(in-hospital or 30 days) and long-term (at least 12 months) follow-up.
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58 **Results**
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4 A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879
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6 [75.3%] male) were included. In the unadjusted analyses, female were at a higher risk of
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8 short-term mortality (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I²=77%) but not long-term
9
10 mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I²=77.5%). When adjusted effect
11
12 estimates from individual studies were used in meta-analysis, the association between
13
14 female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-
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16 1.38, P<0.001, I²=39.6%). And adjusted long-term mortality was also similar between
17
18 female and male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I²=74.5%).
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28 Conclusions

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

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4 mortality among patients with STEMI, we performed a systematic review and meta-
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6 analysis of all available evidence from last decade reporting sex-specific outcomes after
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8 STEMI.
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11 12 13 14 **Methods**

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19 The present systematic review and meta-analysis was performed following the principle
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21 of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
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23 statement.⁸
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30 *Literature search*

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32 We conducted a comprehensive search of the PubMed, EMBASE, and Cochrane Library
33
34 from January 1, 2010 to August 1, 2020 to identify studies from the last decade that
35
36 described sex differences in in short- or long-term mortality among patients with STEMI.
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38 **Both observational studies and randomized clinical trials were eligible.** We queried MeSH
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40 and the abstract text for the following three search terms: gender part (including "gender",
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42 "female", "male", "gender differences", "sex differences" or "sex characteristics"); outcome
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44 part (including "death", "mortality", "hospital mortality", "cardiac death", "sudden cardiac
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46 death", "all-cause mortality", "long term mortality", "one year mortality", "cardiovascular
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48 mortality" or "short term mortality"); myocardial infarction part (including "myocardial
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50 infarction", "acute myocardial infarction", "myocardial necrosis", "ST segment elevation
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52 myocardial infarction", "primary PCI", "primary percutaneous coronary intervention" or
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4 "primary angioplasty") to identify relevant studies. There was no language restriction or
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6 age limit.
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10 11 *Study selection*

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14 According to the aim of our analyses, studies were included in this systematic review if
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16 data about short- (in-hospital or 30 days) or long-term (at least 12 months) mortality
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18 stratified by sex in patients with STEMI were reported. Two reviewers identified studies
19
20 eligible for further review by performing an initial screen of titles or abstracts of the search
21
22 results. Subsequently, a second screen of full texts eligibility was performed by another
23
24 two reviewers. Studies had to fulfil the following criteria to be included in the present
25
26 analyses: i) studies reporting data on all-cause mortality specific to STEMI population; and
27
28 ii) studies providing enough details to obtain numbers of events or incidence rates
29
30 according to sex; and iii) enrollment starting earlier than a decade ago. Editorials, letters,
31
32 conference proceedings and abstracts were considered to be eligible only if sufficient
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34 information was available in abstracts or associated tables or figures. We excluded studies
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36 if they were review articles or case reports, or if they involved pregnant participants,
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38 critically ill patients, or provided insufficient data to allow for risk estimates to be calculated.
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48 Any disagreement was reviewed by a third reviewer and resolved by consensus.
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53 *Data extraction*

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56 Detailed data from selected studies were extracted independently by two reviewers using
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58 a standardized form independently. Data about study and participants characteristics,
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4 including year of study, sample size, time of enrollment, geographical location, endpoints
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6 of study, and follow-up duration, were collected. Any discrepancies were reviewed by a
7
8 third reviewer and resolved by consensus. The quality of included studies was evaluated
9
10 by Newcastle-Ottawa scale using prespecified items comprised of patients' selection
11
12 (representativeness and selection of patients, ascertainment of exposure), comparability
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14 of cohorts based on design or analysis, and outcome (assessment of outcomes, adequacy
15
16 of follow-up).⁹ A quality score (0–9 **points**) was generated according to a maximum of 1
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22 **point** for each item.

23 24 25 26 27 *Patient and public involvement*

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30 Due to the nature of the systematic review and meta-analysis, this study did not involve
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32 patients and the public in the design, or conduct, or reporting or dissemination plans.
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35 36 37 *Statistical analysis*

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40 The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent
41
42 the effect of sex differences on mortality after STEMI. And data were combined using
43
44 random-effects model of DerSimonian and Laird with inverse variance weighting. Random-
45
46 effect model was used due to substantial clinical and statistical heterogeneity. Following
47
48 analyses were performed: i) unadjusted RRs for short- and long-term all-cause mortality
49
50 using raw number of death and total participants at risk for death specific to each sex, ii)
51
52 adjusted RRs for short- and long-term all-cause mortality using adjusted RRs **if they were**
53
54 described in **those** included studies. **In terms of short-term mortality, the RRs for in-hospital**
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4 and 30-day mortality were also calculated respectively.
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6 We assess heterogeneity across studies with Cochran's Q test and I2 test, with $P < 0.1$ or
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8 I2 $> 50\%$ considered significant. We also performed meta-regression to identify the
9
10 potential sources of heterogeneity in the included studies. The potential sources were
11
12 differences in diabetes, hypertension, hyperlipidemia, smoking, prior MI, and prior PCI.
13
14 Furthermore, stratified analysis was conducted as well by dividing the included studies into
15
16 different subgroups based on the Newcastle-Ottawa scale scores (> 7 points or ≤ 7 points)
17
18 to assess the potential sources of heterogeneity. To assess the potential effect of
19
20 publication bias, we inspected funnel plots for asymmetry and used the Egger's regression
21
22 asymmetry test in which $P < 0.05$ was considered to indicate significant publication bias.
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24 Sensitivity analyses was conducted by excluding one study at a time and comparing the
25
26 results with the complete one. In addition, we also performed sensitivity analyses by
27
28 restricting to high-quality studies with a Newcastle-Ottawa scale of 5 points or more and
29
30 restricting to studies with sample size bigger than 1000 participants. All statistical analyses
31
32 were performed using STATA version 15.0 (Stata Corp, College Station, TX). Differences
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34 were considered statistically significant at $P < .05$ (2-sided).
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48 Results

49 50 51 52 53 *Literature search*

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

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22 Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than
23
24 10,000 patients with STEMI. See Table 1 for further information of included studies.

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27 Baseline characteristics of participants were missing in some included studies, but all
28
29 included studies provided sufficient data for analysis of sex differences in clinical outcomes.
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33 Except for 1 study, which was a prespecified gender analysis of randomized controlled
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35 trial, the remaining 14 were observational studies. Among the 10 included studies which
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37 reported adjusted analyses, most studied adjusted for age, diabetes mellitus, hypertension,
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39 and prior myocardial infarction/PCI, while some adjusted for renal insufficiency,
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41 and prior myocardial infarction/PCI, while some adjusted for renal insufficiency,
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43 cardiogenic shock, cardiac arrest at admission and occurrence time of symptom onset.
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47 Variables that were adjusted in the adjusted analyses from the included studies were
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49 presented in eTable 1 of the Supplementary Material. Results of assessment of study
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51 quality using Newcastle-Ottawa scale were shown in eTable 2 in the Supplementary
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53 Material.
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58 *Patient characteristics*

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

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30 Thirteen studies reported sex-specific unadjusted short-term mortality (7 studies with 30-
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32 day mortality and 6 studies with in-hospital mortality) of patients with STEMI. There were
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34 2,873 of 31,409 (9.1%) cases of all-cause mortality in female compared with 4,380 of
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36 95,610 (4.6%) in male. Female were at a significantly higher risk of short-term mortality
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38 (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I²=77%) compared with male (Figure 2 A). Nine
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40 studies involving 119,379 patients reported adjusted short-term mortality specific to sex. In
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42 adjusted analysis, the association between female and higher risk of short-term mortality
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44 remained significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I²=39.6%) (Figure 2 B).
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46 However, the strength of association calculated with adjusted RRs from these 9 studies
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48 was attenuated.
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55 Subgroup analysis demonstrated that the results of studies with Newcastle-Ottawa
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57 scale >7 points (RR, 1.90; 95%CI, 1.73-2.09, P=0.018, I²=63.4%) and studies with ≤7
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4 points (RR, 1.52; 95%CI, 1.20-1.93, P=0.026, I²=58.1%) were consistent in unadjusted
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6 short-term mortality (See eFigure 1 in the Supplementary Material). The impact of sex on
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8 in-hospital (RR, 1.71; 95%CI, 1.27-2.31, P<.001, I²=86.4%) and 30-day mortality (RR, 1.81;
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10 95%CI, 1.62-2.02, P<.001, I²=56.6%) were consistent. The meta-analysis performed in
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12 studies of patients undergoing PCI for STEMI also showed increased unadjusted mortality
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14 (RR, 1.45; 95%CI, 1.05-2.00, P=0.026, I²=39.5%) in female patients.
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22 *Long-term all-cause mortality*

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24 Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and
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26 followed up for more than 1 year, and reported all-cause mortality for female and male.
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28 The incidence of long-term all-cause mortality was 13.9% (n=584) in female and 8.7%
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30 (n=1202) in male. In unadjusted analysis, no significant sex difference was found in long-
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32 term mortality (RR, 1.23; 95%CI, 0.89-1.69, P=0.206, I²=77.5%) (Figure 3 A). The
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34 unadjusted long-term mortality was also similar between female and male patients
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36 undergoing PCI (RR, 1.28; 95%CI, 0.95-1.73, P=0.108, I²=0.0%). And the adjusted
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38 analysis of the pooled results from four studies, also showed a similar risk of mortality at
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40 long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670,
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42 I²=74.5%) (Figure 3 B).
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53 *Meta-Regression Analysis, sensitivity analyses and publication bias*

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55 According to meta-regression analysis, differences in prevalence of diabetes (β coefficient,
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57 0.248; P=0.337; adjusted R²=1.31%; I²=80.86%; τ^2 =0.044), hypertension (β coefficient, -
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4 0.255; P=0.538; adjusted R²=24.22%; I²=41.04%; τ²=0.008), hyperlipidemia(β coefficient,
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6 0.260; P=0.415; adjusted R²=-1.84%; I²=83.59%; τ²=0.050), smoking (β coefficient, -
7
8 0.040; P=0.255; adjusted R²=17.86%; I²=79.41%; τ²=0.045), prior MI (β coefficient, -
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10 2.725; P=0.126; adjusted R²=60.30%; I²=60.19%; τ²=0.032), and prior PCI (β coefficient,
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12 0.109; P=0.896; adjusted R²=-58.31%; I²=61.73%; τ²=0.042) between sexes were not
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14 identified as significant sources of heterogeneity for short-term all-cause mortality. Given
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16 that not all included study provided information on confounders stratified by sex, the results
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18 of meta-regression analyses should be interpreted with caution.
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25 Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary
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27 Material) or restricted to data from studies with sample size bigger than 1000 (RR, 1.75;
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29 95%CI, 1.54-1.99, P<.001, I²=82.9%) both indicated that none of the studies affected the
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31 results of short-term mortality in this meta-analysis significantly. In analysis for long-term
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33 mortality, sensitivity analysis showed a possibly higher influence on the result attribute to
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35 the study of Tai et al (See eFigure 3 in the Supplementary Material). After removing this
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37 study from meta-analysis, the association of female with increased long-term mortality
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39 became significant (RR, 1.50; 95%CI, 1.23-1.83, P<.001, I²=40.9%). We found no
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41 evidence of publication bias across studies based on visual inspection of funnel plots (See
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43 eFigure 4 in the Supplementary Material) and the results from Egger's tests for short-term
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45 mortality (P=0.462) and for long-term mortality (P=0.053).
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56 Discussion:

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4 Our systematic review and meta-analysis of contemporary literature on sex differences
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6 among patients with STEMI demonstrate that **female** have a higher risk of short- but not
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8 long-term mortality compared with **male** with STEMI. Furthermore, after adjustment for
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10 baseline cardiovascular risk factors and clinical profiles, the sex differences in short-term
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12 mortality are attenuated but remain significant, while **female** have the similar long-term
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14 mortality with **male**.
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22 Our results are somewhat in accordance with several previously published meta-analysis.²

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24 ²⁵ A considerable number of studies have consistently suggested that women were at a
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26 higher risk of short-term mortality after ACS. However, whether risk of long-term mortality
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28 is also higher in women with ACS remains under debate. Some studies indicated that
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30 women with STEMI had a higher 1-year rate of death compared to men²⁶, while the 1-year
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32 mortality rate was conversely lower in women than men in some other studies^{23 24}. In our
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34 study, with respect to short-term mortality, the analyses of studies with high or low quality,
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36 and big or small sample size yielded similar results. However, in terms of long-term
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38 mortality, caution is needed when interpreting our finding of non-significant increased long-
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40 term mortality in adjusted analyses, due to the results of sensitivity analysis which showed
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42 a significant association between female and increased long-term mortality after removing
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44 one study from adjusted analyses.
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56 It is widely accepted that there are significant differences in outcomes of women and men
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58 with acute myocardial infarction. In our study, after adjusted for participants' baseline
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4 cardiovascular risk factors and clinical profiles, the strength of association between gender
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6 and short-term mortality was substantially attenuated, which suggested that poorer
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8 baseline cardiovascular risk profile partially explained the impact of sex differences on
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10 mortality. Multiple studies have shown that women with STEMI present at older age and
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12 have a higher burden of comorbidities, contributing to the sex differences in mortality after
13
14 STEMI.²⁷ All studies included in our meta-analysis demonstrate that female patients are
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16 older and with more diabetes mellitus as well as hypertension. In addition, some sex-
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18 specific studies found that certain risk factors and comorbidities were more potent in
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20 women.²⁸ Diabetes mellitus, hypertension and smoking status are more strongly
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22 associated with increased risk of cardiac events in women compared with men.^{27 29}
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32 Notably, that these differences mentioned above still could not completely explain the gap
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34 in mortality between sexes. It has been proved that women with acute myocardial infarction
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36 were less likely to be treated with guideline directed medical therapy and less likely to
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38 receive primary reperfusion therapy including primary percutaneous coronary intervention
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40 or fibrinolysis.³⁰ Regarding medical therapy, numerous studies conducted around the world
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42 consistently demonstrate female survivors are receiving less optimal medical therapy after
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44 acute myocardial infarction during hospitalization or at discharge.^{31 32} Though there might
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46 be no differences in treatment adherence between men and women, some studies report
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48 significant sex disparities in initiation of appropriate pharmacotherapy after myocardial
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50 infarction.³³ Results from these observational studies have shown women are receiving
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52 less optimal medical therapy including aspirin, statins, and angiotensin-converting enzyme
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4 inhibitors in all age groups, especially young women, and suggested that clinicians and
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6 patients may benefit from better education and awareness of undertreatment of younger
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8 women.^{33 34}
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14 Lower rates of revascularization are observed among women with STEMI compared with
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16 men in several studies despite proven benefit of this therapy.³⁵ Moreover, the sex
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18 differences might be driven by delays in presentation to hospital and women with STEMI
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20 were more likely to experience longer delays than men. Although a great improvement in
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22 emergency medical services and timely revascularization over the past decades, recent
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24 studies show that women with STEMI still present later and have a longer ischemic time
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26 than men. Previous studies have shown consistently that women have longer door-to
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28 balloon times and longer door-to needle times.^{36 37} In addition, women are also more likely
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30 to exhibit longer pre-hospital delays in seeking medical care after the development of
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32 symptoms suggestive of myocardial infarction. Although there have been significant
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34 reductions in patient and system delay in the last decade, women continue to have longer
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36 presentation and treatment times.³⁸ Sex differences also exist in clinical presentation of
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38 STEMI. Although chest pain was the most common ACS symptom in both sexes, women
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40 were more likely to present without chest pain than men.^{39 40} Lower rates of typical chest
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42 pain reported among women with STEMI may also influence provider decision-making to
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44 pursue less aggressive care including invasive revascularization.
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58 **Some included studies of our meta-analysis enrolled STEMI patients in general¹⁴⁻¹⁶, while**
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4 some others enrolled patients undergoing PCI for STEMI^{11 13 18}. The different prognosis of
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6 patients receiving reperfusion therapy or no-reperfusion therapy might be a potential
7
8 source of heterogeneity of our study. Nevertheless, our results are completely consistent
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10 with a previous meta-analysis from Pancholy et al., which investigated sex differences in
11
12 mortality among patients with STEMI treated with primary PCI.² Its results demonstrated
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14 that, when adjusted RRs were used, the increased risk for 1-year mortality in women was
15
16 no longer significant and the risk of in-hospital mortality still significantly elevated. It should
17
18 be noted that more than 50% of patients were treated with PCI in the most study conducted
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20 among the general STEMI patients and included by our analysis, even more than 90% in
21
22 some included studies.^{12 24} The increasing rate of primary PCI in recent years might be a
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24 reason for the consistency of our findings and previous studies conducted specifically
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26 among STEMI patients undergoing PCI
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38 Complications including bleeding, heart failure and mechanical complications are more
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40 likely to develop in women with acute myocardial infarction and increase the risk of
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42 mortality.^{14 41 42} Bleeding secondary to antithrombotic therapies and invasive procedures is
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44 more frequent in women.⁴³ Three included studies reported incidence of bleeding following
45
46 STEMI and they all found that women were at higher risk of bleeding.^{10 13 18} One study
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48 included in our analysis examined the relationships among sex, acute heart failure, and
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50 related outcomes after STEMI.¹⁴ Its results demonstrate that women are at higher risk to
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52 develop de novo heart failure after STEMI and women with de novo heart failure have
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54 worse survival compared with man. However, we could not compare the incidence of these
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4 complications due to the lack of sufficient data. Mechanical complications requiring surgical
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6 intervention are also much more common in women after acute myocardial infarction and
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8 associated with high mortality rates.⁴⁴
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12
13 Several limitations of this meta-analysis should be considered. First, the included studies
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15 are all observational studies except one post hoc analysis of randomized controlled trial.
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17 Hence, there may be residual confounding bias inherent in the observational study design
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19 in our meta-analysis. Second, in adjusted analysis, not all included studies adjusted for the
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21 same confounders and not all studies reported adjusted RRs. **The confounders which were**
22
23 **adjusted in the included studies might differ greatly across studies.** Third, there was
24
25 substantial heterogeneity in our meta-analysis, which could partly be attributed to the wide
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27 variability in the sample sizes, locations, and treatment regimens across included studies.
28
29 **Additionally, although we calculated adjusted RRs for all-cause mortality, it needed to be**
30
31 **noted that relevant confounders might have differed across studies.** Fourth, the analysis of
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33 long-term mortality, especially the adjusted analysis, included far fewer studies compared
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35 with analysis of short-term mortality. Hence, there might be significant bias in the results
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37 about long-term mortality.
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51 In conclusion, our meta-analysis, pooling data from contemporary literature, shows that
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53 women with STENI have a higher risk of short-term mortality but not long-term mortality.
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55 The effect of sex differences on mortality in patients with STEMI remain significant after
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57 adjustment for baseline cardiovascular risk factors and clinical profiles, suggesting that
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4 public awareness of increased risk and further improvements in management in women
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6 with STEMI are necessary.
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10 11 **Other Information:**

12 13 **Contribution statement**

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18
19 Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis,
20
21
22 Manuscript preparation, Manuscript editing. Tingting Guo and Yong Wang: Data
23
24
25 acquisition, Data analysis/interpretation. J^anan Li, Yang Li, Jianfeng Zheng and Runlin
26
27
28 Gao: Manuscript revision/review. Hong Qiu: Manuscript final version approval.
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30
31

32 33 **Conflict of interest**

34
35 The authors declare that there is no conflict of interest.
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39

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44
45
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50 51 **Ethics approval**

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53 The institutional central committee at Fuwai Hospital approved that the study protocol and
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55
56 inform consent was not required for a systematic review and meta-analysis.
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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.

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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

1	Cenko	2019	12	Prospective	Clinical	Yes	Jan, 2010-	10,443	3,112	30-day all-cause	30 d
2			Europea		registry		Jul, 2018		(29.8)	mortality	
3			n								
4			countries								
5											
6											
7											
8											
9											
10											
11	Hao	2019	China	Prospective	Clinical	Yes	Nov, 2014-	50,203	11,016	In-hospital mortality	NA
12					registry		Jun, 2018		(21,9)		
13											
14											
15											
16											
17	Hannan	2019	US	Retrospective	Administrativ	Yes	Jan, 2013-	23,809	7,791	In hospital/30-day	30 d
18					e database		Dec, 2015		(32.7)	mortality	
19											
20											
21											
22	Maznyczka	2019	UK	Retrospective	Clinical	No	July, 2011-	324	87 (26.9)	All-cause death/ first	5 years
23					registry		Nov, 2012			heart failure	
24										hospitalization	
25											
26											
27											
28											
29											
30	Stehli	2019	Australia	Prospective	Clinical	Yes	2013-2016	6,431	1,317	In hospital/30-day major	30 d
31					registry				(20.5)	adverse events, and	
32										major bleeding	
33											
34											
35											
36											
37											
38	Burgess	2020	Australia	Prospective	Administrativ	No	Dec, 2010-	589	123 (21)	Cardiac death and	2 years
39											

				e database		Apr, 2014			myocardial infarction	
Dharma	2020	Indonesi a	Retrospective	Administrativ e database	No	Feb, 2011- Aug, 2019	6,557	929 (14.2)	All-cause mortality	30 d and 1 year
Kerkmanx	2020	Netherla nds	Retrospective	Administrativ e 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	Administrativ e 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
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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		
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	61.1	10,141	24,08	15,607	38,42	17,996 (85.4)	50,94	1,719	32,37	NA	NA	NA	NA
		(10.6)	(12.4)	(48.1)	2	(74.1)	6		4	(8.2)	7				
					(39.4		(62.9		(83.3		(53.0				
)))))				
Hannan	2019	70.72	62.11	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	868	2206
		(14.73)	(12.82)											(11.1)	(13.8
))
Maznyczk	2019	61.2	58.6(11.2	8 (9.2)	26	32 (36.8)	73	28 (32.2)	66	57	139	5 (5.7)	20	2	16
a		(12.2))		(11.0		(30.8		(27.8	(65.5)	(58.6		(8.4)	(2.3)	(6.8)
))))				
Stehli	2019	66.5	60.8	245	770	NA	NA	NA	NA	NA	NA	NA	NA	104	577
		(13.2)	(12.2)	(18.6)	(15.1									(7.9)	(11.3
))

1	Burgess	2020	62.7	58.2	39	88	84 (68.3)	243	83 (67.5)	253	64	252	9 (7.3)	41	NA	NA
2			(52.7-	(50.6-	(31.7)	(18.9	(52.1	(52.3	(52.0)	(54.1	(8.8)					
3			73.2)	65.7)))))))						
4																
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9	Dharma	2020	60 (10)	55 (10)	403	1548	647 (69.6)	2,889	299 (32.2)	1,779	109	4,049	NA	NA	NA	NA
10					(43.4)	(27.5	(51.3	(31.6	(11.7)	(71.9						
11))))))						
12																
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16																
17	Kerkmanx	2020	68 (14)	61 (12)	39	66	101 (45.7)	178	56 (25.9)	110	88	258	30	79	33	77
18					(17.6)	(12.5	(33.6	(21.0	(41.1)	(49.3	(13.6)	(13.7	(14.4)	(14.2		
19))))))))))		
20																
21																
22																
23																
24	Siabani	2020	65.8	59.0	114	187	195 (63.7)	410	110 (36.7)	208	41	655	NA	NA	NA	NA
25			(11.3)	(12.4)	(37.7)	(16.2	(35.4	(18.5	(13.2)	(55.9						
26))))))						
27																
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31																
32	Tai	2020	78 (76-	78 (76-	96	116	217 (79.5)	319	NA	NA	14 (5.4)	239	NA	NA	36	78
33			81)	80)	(35.2)	(26.5	(72.8				(56.5			(13.5)	(18.1	
34)))))	
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1	Tizón	2020	69.9	60.9	844	1,927	1,192 (34.2)	2,722	878 (25.2)	2,375	474	2,711	NA	NA	NA	NA
2																
3																
4			(13.7)	(12.6)	(24.2)	(17.2		(24.3		(21.2	(13.6)	(24.2				
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4 Figure 1 Flowchart of selection of studies included in meta-analysis.
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9 Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and
10 men with ST-segment elevation myocardial infarction.
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13 Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of
14 women compared with men with ST-segment elevation myocardial infarction using
15 random-effects model.
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25 Figure 3 Forest plots of relative risks of long-term all-cause mortality among women and
26 men with ST-segment elevation myocardial infarction.
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29 Forest plots showing unadjusted (A) and adjusted (B) long-term all-cause mortality of
30 women compared with men with ST-segment elevation myocardial infarction using
31 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

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

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7 **Short title : Sex differences in STEMI**
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4 **Contemporary sex differences in mortality among patients with ST-segment elevation**
5 **myocardial infarction: a systematic review and meta-analysis**
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9 **Objectives:** To assess the effect of sex differences on short- and long-term mortality among patients
10 with ST-segment elevation myocardial infarction (STEMI).
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15 **Design:** Systematic review and meta-analysis of contemporary available evidence.
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19 **Setting:** PubMed, Embase and Cochrane Library were searched for relevant studies reporting sex
20 specific outcomes among patients with STEMI published between January 1, 2010 to August 1,
21 2020. Risk ratio (RR) 95% confidence intervals (CIs) were measured using DerSimonian and
22 Laird random-effects model. Sensitivity analyses were performed and publication bias was also
23 checked. All statistical analyses were performed using STATA version 15.0.
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31 **Participants:** Studies providing data about short- or long-term mortality stratified by sex in patients
32 with STEMI were included. Only study conducted in last ten years were included.
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37 **Primary and secondary outcome measures:** The primary outcome was all-cause death at short-
38 (in-hospital or 30 days) and long-term (at least 12 months) follow-up.
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42 **Results**
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44 A total of fifteen studies involving 128,585 patients (31,706 [24.7%] female and 96,879 [75.3%]
45 male) were included. In the unadjusted analyses, female were at a higher risk of short-term mortality
46 (RR, 1.73; 95%CI, 1.53-1.96, P<0.001, I²=77%) but not long-term mortality (RR, 1.23; 95%CI,
47 0.89-1.69, P=0.206, I²=77.5%). When adjusted effect estimates from individual studies were used
48 in meta-analysis, the association between female and higher risk of short-term mortality remained
49 significant (RR, 1.24; 95%CI, 1.11-1.38, P<0.001, I²=39.6%). And adjusted long-term mortality
50 was also similar between female and male (RR, 1.11; 95%CI, 0.42-1.80, P=0.670, I²=74.5%).
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60 **Conclusions**

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

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

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

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

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

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

32 The risk ratios (RRs) and 95% confidence interval (CI) were primarily used to represent the effect
33 of sex differences on mortality after STEMI. And data were combined using random-effects model
34 of DerSimonian and Laird with inverse variance weighting. Random-effect model was used due to
35 substantial clinical and statistical heterogeneity. Following analyses were performed: i) unadjusted
36 RRs for short- and long-term all-cause mortality using raw number of death and total participants
37 at risk for death specific to each sex, ii) adjusted RRs for short- and long-term all-cause mortality
38 using adjusted RRs if they were described in those included studies. In terms of short-term mortality,
39 the RRs for in-hospital and 30-day mortality were also calculated respectively.
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48 We assess heterogeneity across studies with Cochran's Q test and I² test, with P<0.1 or I² >50%
49 considered significant. We also performed meta-regression to identify the potential sources of
50 heterogeneity in the included studies. The potential sources were differences in diabetes,
51 hypertension, hyperlipidemia, smoking, prior MI, and prior PCI. Furthermore, stratified analysis
52 was conducted as well by dividing the included studies into different subgroups based on the
53 Newcastle-Ottawa scale scores (>7 points or ≤7 points) to assess the potential sources of
54 heterogeneity. To assess the potential effect of publication bias, we inspected funnel plots for
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4 asymmetry and used the Egger's regression asymmetry test in which $P < 0.05$ was considered to
5 indicate significant publication bias.

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7 Sensitivity analyses was conducted by excluding one study at a time and comparing the results with
8 the complete one. In addition, we also performed sensitivity analyses by restricting to high-quality
9 studies with a Newcastle-Ottawa scale of 5 points or more and restricting to studies with sample
10 size bigger than 1000 participants. All statistical analyses were performed using STATA version
11 15.0 (Stata Corp, College Station, TX). Differences were considered statistically significant at P
12 $< .05$ (2-sided).
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20 21 **Results**

22 23 24 25 *Literature search*

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27 Study selection details were outlined in Figure 1. The literature search identified 2,611 potentially
28 relevant articles. After screening based on title and abstract review, 2495 records were excluded. A
29 total of 116 full-text were finally assessed for eligibility, with 96 papers excluded due to enrollment
30 starting earlier than a decade ago or no sufficient gender specific data to analyze. Another 5 papers
31 reviewed in detail were excluded after due to data from the same cohorts. A total of 15 studies were
32 finally included in the present systematic review and meta-analysis.¹⁰⁻²⁴
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40 41 *Study characteristics*

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43 Of the 15 included studies, 8 were multicenter studies and 4 studies enrolled more than 10,000
44 patients with STEMI. See Table 1 for further information of included studies. Baseline
45 characteristics of participants were missing in some included studies, but all included studies
46 provided sufficient data for analysis of sex differences in clinical outcomes. Except for 1 study,
47 which was a prespecified gender analysis of randomized controlled trial, the remaining 14 were
48 observational studies. Among the 10 included studies which reported adjusted analyses, most
49 studied adjusted for age, diabetes mellitus, hypertension, and prior myocardial infarction/PCI, while
50 some adjusted for renal insufficiency, cardiogenic shock, cardiac arrest at admission and occurrence
51 time of symptom onset. Variables that were adjusted in the adjusted analyses from the included
52 studies were presented in eTable 2 of the Supplementary Material. Results of assessment of study
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4 quality using Newcastle-Ottawa scale were shown in eTable 3 in the Supplementary Material.
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7 8 *Patient characteristics*

9 A total of 128,585 patients with STEMI (31,706 [24.7%] female and 96,879 [75.3%] male) were
10 involved in the 15 included studies. Female tended to be older and had higher prevalence of diabetes
11 mellitus in all included studies. And in most studies, other important comorbidities, including
12 hypertension and hyperlipidemia, were more frequent in female. Greater proportions of male were
13 smokers and had prior PCI or myocardial infarction. Besides, some studies reported that door-to-
14 balloon time and symptom onset to balloon time were longer in female than male. Part of patient
15 baseline characteristics were summarized in Table 2.
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23 24 25 *Short-term all-cause mortality*

26 Thirteen studies reported sex-specific unadjusted short-term mortality (7 studies with 30-day
27 mortality and 6 studies with in-hospital mortality) of patients with STEMI. There were 2,873 of
28 31,409 (9.1%) cases of all-cause mortality in female compared with 4,380 of 95,610 (4.6%) in male.
29 Female were at a significantly higher risk of short-term mortality (RR, 1.73; 95%CI, 1.53-1.96,
30 $P<0.001$, $I^2=77\%$) compared with male (Figure 2 A). Nine studies involving 119,379 patients
31 reported adjusted short-term mortality specific to sex. In adjusted analysis, the association between
32 female and higher risk of short-term mortality remained significant (RR, 1.24; 95%CI, 1.11-1.38,
33 $P<0.001$, $I^2=39.6\%$) (Figure 2 B). However, the strength of association calculated with adjusted RRs
34 from these 9 studies was attenuated.
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44 Subgroup analysis demonstrated that the results of studies with Newcastle-Ottawa scale >7 points
45 (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,
46 1.20-1.93, $P=0.026$, $I^2=58.1\%$) were consistent in unadjusted short-term mortality (See eFigure 1 in
47 the Supplementary Material). The impact of sex on in-hospital (RR, 1.71; 95%CI, 1.27-2.31, $P<0.001$,
48 $I^2=86.4\%$) and 30-day mortality (RR, 1.81; 95%CI, 1.62-2.02, $P<0.001$, $I^2=56.6\%$) were consistent.
49 The meta-analysis performed in studies of patients undergoing PCI for STEMI also showed
50 increased unadjusted mortality (RR, 1.45; 95%CI, 1.05-2.00, $P=0.026$, $I^2=39.5\%$) in female patients.
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60 *Long-term all-cause mortality*

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4 Six studies involved 18,018 patients with STEMI (4,191 female and 13,827 male) and followed up
5 for more than 1 year, and reported all-cause mortality for female and male. The incidence of long-
6 term all-cause mortality was 13.9% (n=584) in female and 8.7% (n=1202) in male. In unadjusted
7 analysis, no significant sex difference was found in long-term mortality (RR, 1.23; 95%CI, 0.89-
8 1.69, P=0.206, I²=77.5%) (Figure 3 A). The unadjusted long-term mortality was also similar
9 between female and male patients undergoing PCI (RR, 1.28; 95%CI, 0.95-1.73, P=0.108, I²=0.0%).
10 And the adjusted analysis of the pooled results from four studies, also showed a similar risk of
11 mortality at long-term follow-up in female compared with male (RR, 1.11; 95%CI, 0.42-1.80,
12 P=0.670, I²=74.5%) (Figure 3 B).

23 *Meta-Regression Analysis, sensitivity analyses and publication bias*

24 According to meta-regression analysis, differences in prevalence of diabetes (β coefficient, 0.248;
25 P=0.337; adjusted R²=1.31%; I²=80.86%; τ^2 =0.044), hypertension (β coefficient, -0.255; P=0.538;
26 adjusted R²=24.22%; I²=41.04%; τ^2 =0.008), hyperlipidemia (β coefficient, 0.260; P=0.415;
27 adjusted R²=-1.84%; I²=83.59%; τ^2 =0.050), smoking (β coefficient, -0.040; P=0.255; adjusted
28 R²=17.86%; I²=79.41%; τ^2 =0.045), prior MI (β coefficient, -2.725; P=0.126; adjusted R²=60.30%;
29 I²=60.19%; τ^2 =0.032), and prior PCI (β coefficient, 0.109; P=0.896; adjusted R²=-58.31%;
30 I²=61.73%; τ^2 =0.042) between sexes were not identified as significant sources of heterogeneity for
31 short-term all-cause mortality. Given that not all included study provided information on
32 confounders stratified by sex, the results of meta-regression analyses should be interpreted with
33 caution.

34 Sensitivity analysis by excluding one study at a time (See eFigure 2 in the Supplementary Material)
35 or restricted to data from studies with sample size bigger than 1000 (RR, 1.75; 95%CI, 1.54-1.99,
36 P<.001, I²=82.9%) both indicated that none of the studies affected the results of short-term mortality
37 in this meta-analysis significantly. In analysis for long-term mortality, sensitivity analysis showed
38 a possibly higher influence on the result attribute to the study of Tai et al (See eFigure 3 in the
39 Supplementary Material). After removing this study from meta-analysis, the association of female
40 with increased long-term mortality became significant (RR, 1.50; 95%CI, 1.23-1.83, P<.001,
41 I²=40.9%). We found no evidence of publication bias across studies based on visual inspection of
42 funnel plots (See eFigure 4 in the Supplementary Material) and the results from Egger's tests for
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3 short-term mortality (P=0.462) and for long-term mortality (P=0.053).
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7 **Discussion:**
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11 Our systematic review and meta-analysis of contemporary literature on sex differences among
12 patients with STEMI demonstrate that female have a higher risk of short- but not long-term mortality
13 compared with male with STEMI. Furthermore, after adjustment for baseline cardiovascular risk
14 factors and clinical profiles, the sex differences in short-term mortality are attenuated but remain
15 significant, while female have the similar long-term mortality with male.
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23 Our results are somewhat in accordance with several previously published meta-analysis.^{2 25} A
24 considerable number of studies have consistently suggested that women were at a higher risk of
25 short-term mortality after ACS. However, whether risk of long-term mortality is also higher in
26 women with ACS remains under debate. Some studies indicated that women with STEMI had a
27 higher 1-year rate of death compared to men²⁶, while the 1-year mortality rate was conversely lower
28 in women than men in some other studies^{23 24}. In our study, with respect to short-term mortality, the
29 analyses of studies with high or low quality, and big or small sample size yielded similar results.
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31 However, in terms of long-term mortality, caution is needed when interpreting our finding of non-
32 significant increased long-term mortality in adjusted analyses, due to the results of sensitivity
33 analysis which showed a significant association between female and increased long-term mortality
34 after removing one study from adjusted analyses.
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46 It is widely accepted that there are significant differences in outcomes of women and men with acute
47 myocardial infarction. In our study, after adjusted for participants' baseline cardiovascular risk
48 factors and clinical profiles, the strength of association between gender and short-term mortality
49 was substantially attenuated, which suggested that poorer baseline cardiovascular risk profile
50 partially explained the impact of sex differences on mortality. Multiple studies have shown that
51 women with STEMI present at older age and have a higher burden of comorbidities, contributing to
52 the sex differences in mortality after STEMI.²⁷ All studies included in our meta-analysis
53 demonstrate that female patients are older and with more diabetes mellitus as well as hypertension.
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4 In addition, some sex-specific studies found that certain risk factors and comorbidities were more
5 potent in women.²⁸ Diabetes mellitus , hypertension and smoking status are more strongly
6 associated with increased risk of cardiac events in women compared with men.^{27 29}
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11 Notably, that these differences mentioned above still could not completely explain the gap in
12 mortality between sexes. It has been proved that women with acute myocardial infarction were less
13 likely to be treated with guideline directed medical therapy and less likely to receive primary
14 reperfusion therapy including primary percutaneous coronary intervention or fibrinolysis.³⁰
15 Regarding medical therapy, numerous studies conducted around the world consistently demonstrate
16 female survivors are receiving less optimal medical therapy after acute myocardial infarction during
17 hospitalization or at discharge.^{31 32} Though there might be no differences in treatment adherence
18 between men and women, some studies report significant sex disparities in initiation of appropriate
19 pharmacotherapy after myocardial infarction.³³ Results from these observational studies have
20 shown women are receiving less optimal medical therapy including aspirin, statins, and angiotensin-
21 converting enzyme inhibitors in all age groups, especially young women, and suggested that
22 clinicians and patients may benefit from better education and awareness of undertreatment of
23 younger women.^{33 34}
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39 Lower rates of revascularization are observed among women with STEMI compared with men in
40 several studies despite proven benefit of this therapy.³⁵ Moreover, the sex differences might be
41 driven by delays in presentation to hospital and women with STEMI were more likely to experience
42 longer delays than men. Although a great improvement in emergency medical services and timely
43 revascularization over the past decades, recent studies show that women with STEMI still present
44 later and have a longer ischemic time than men. Previous studies have shown consistently that
45 women have longer door-to balloon times and longer door-to needle times.^{36 37} In addition, women
46 are also more likely to exhibit longer pre-hospital delays in seeking medical care after the
47 development of symptoms suggestive of myocardial infarction. Although there have been
48 significant reductions in patient and system delay in the last decade, women continue to have longer
49 presentation and treatment times.³⁸ Sex differences also exist in clinical presentation of STEMI.
50 Although chest pain was the most common ACS symptom in both sexes, women were more likely
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4 to present without chest pain than men.^{39 40} Lower rates of typical chest pain reported among women
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6 with STEMI may also influence provider decision-making to pursue less aggressive care including
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8 invasive revascularization.
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11 Some included studies of our meta-analysis enrolled STEMI patients in general¹⁴⁻¹⁶, while some
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13 others enrolled patients undergoing PCI for STEMI^{11 13 18}. The different prognosis of patients
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15 receiving reperfusion therapy or no-reperfusion therapy might be a potential source of heterogeneity
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17 of our study. Nevertheless, our results are completely consistent with a previous meta-analysis from
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19 Pancholy et al., which investigated sex differences in mortality among patients with STEMI treated
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21 with primary PCI.² Its results demonstrated that, when adjusted RRs were used, the increased risk
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23 for 1-year mortality in women was no longer significant and the risk of in-hospital mortality still
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25 significantly elevated. It should be noted that more than 50% of patients were treated with PCI in
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27 the most study conducted among the general STEMI patients and included by our analysis, even
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29 more than 90% in some included studies.^{12 24} The increasing rate of primary PCI in recent years
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31 might be a reason for the consistency of our findings and previous studies conducted specifically
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33 among STEMI patients undergoing PCI.
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37 Complications including bleeding, heart failure and mechanical complications are more likely to
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39 develop in women with acute myocardial infarction and increase the risk of mortality.^{14 41 42}
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41 Bleeding secondary to antithrombotic therapies and invasive procedures is more frequent in
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43 women.⁴³ Three included studies reported incidence of bleeding following STEMI and they all
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45 found that women were at higher risk of bleeding.^{10 13 18} One study included in our analysis
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47 examined the relationships among sex, acute heart failure, and related outcomes after STEMI.¹⁴ Its
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49 results demonstrate that women are at higher risk to develop de novo heart failure after STEMI and
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51 women with de novo heart failure have worse survival compared with man. However, we could not
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53 compare the incidence of these complications due to the lack of sufficient data. Mechanical
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55 complications requiring surgical intervention are also much more common in women after acute
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57 myocardial infarction and associated with high mortality rates.⁴⁴
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60 Several limitations of this meta-analysis should be considered. First, the included studies are all

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

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

36 37 38 **Other Information:**

39 40 41 42 **Contribution statement**

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44 Ziwei Xi: Study concepts, Study design, Literature research, Statistical analysis, Manuscript
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46 preparation, Manuscript editing. Tingting Guo and Yong Wang: Data acquisition, Data
47
48 analysis/interpretation. Jianan Li, Yang Li, Jianfeng Zheng and Runlin Gao: Manuscript
49
50 revision/review. Hong Qiu: Manuscript final version approval.

51 52 53 54 55 **Conflict of interest**

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58 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
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Author				, 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 (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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4 Figure 1 Flowchart of selection of studies included in meta-analysis.
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8 Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with
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10 ST-segment elevation myocardial infarction.

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12 Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women
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14 compared with men with ST-segment elevation myocardial infarction using random-effects model.
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Figure 1 Flowchart of selection of studies included in meta-analysis.

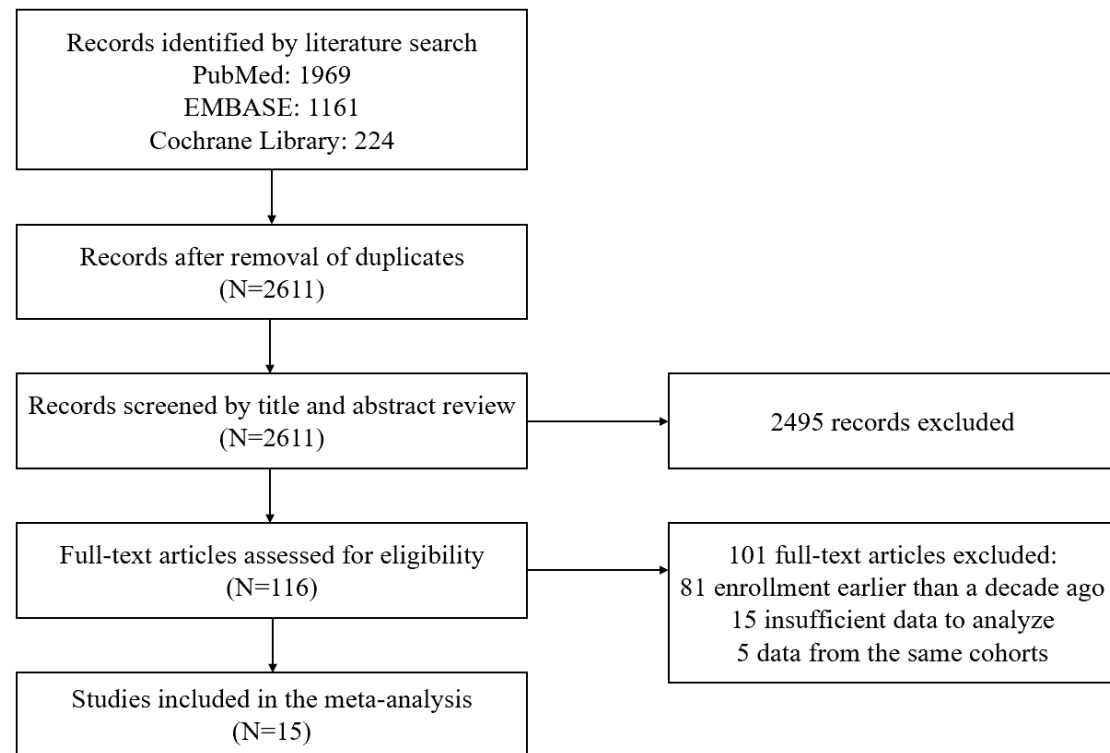
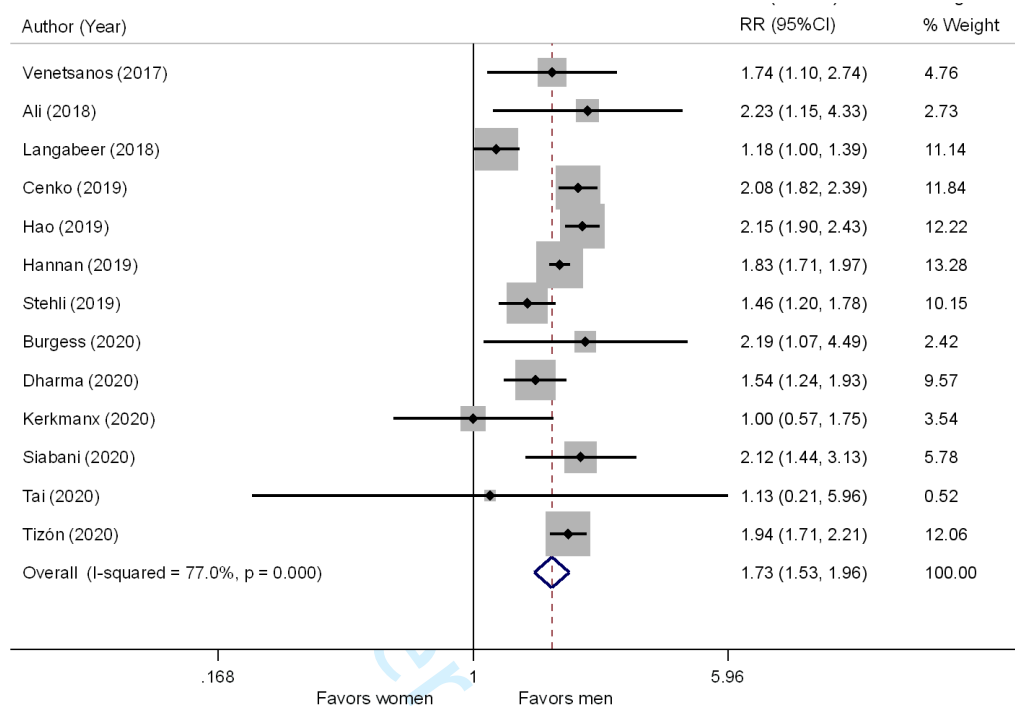
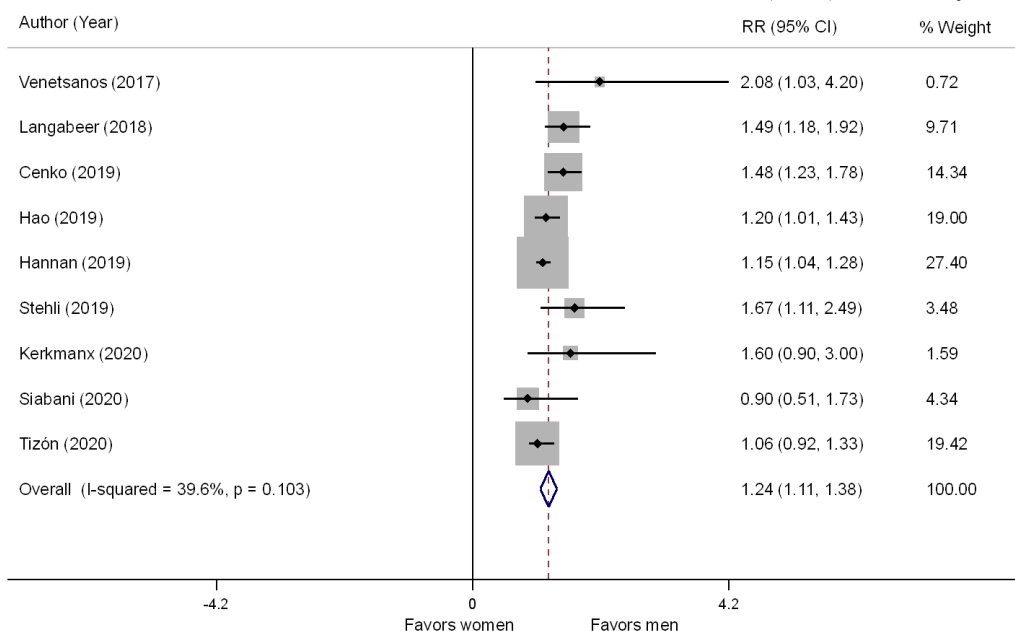


Figure 2 Forest plots of relative risks of short-term all-cause mortality among women and men with ST-segment elevation myocardial infarction.

A



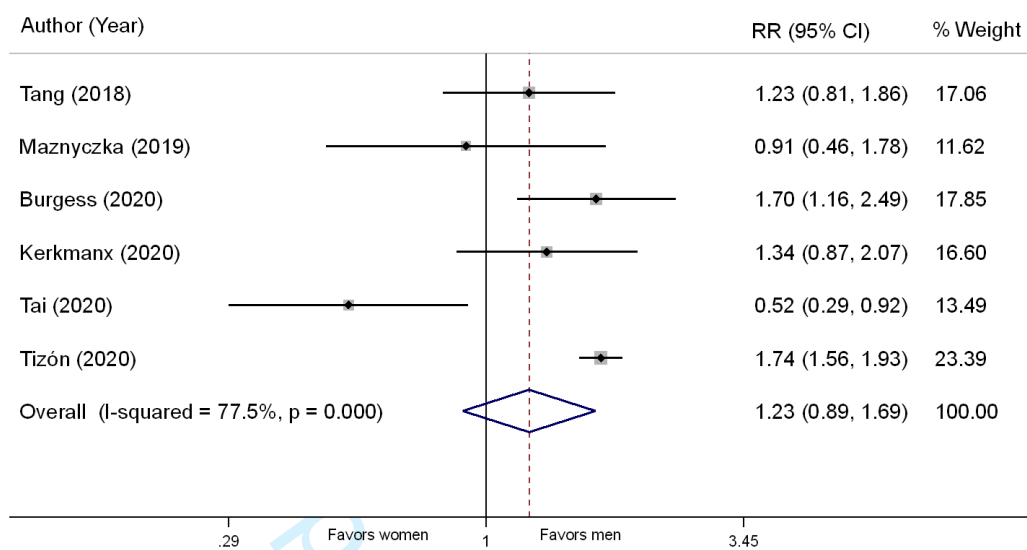
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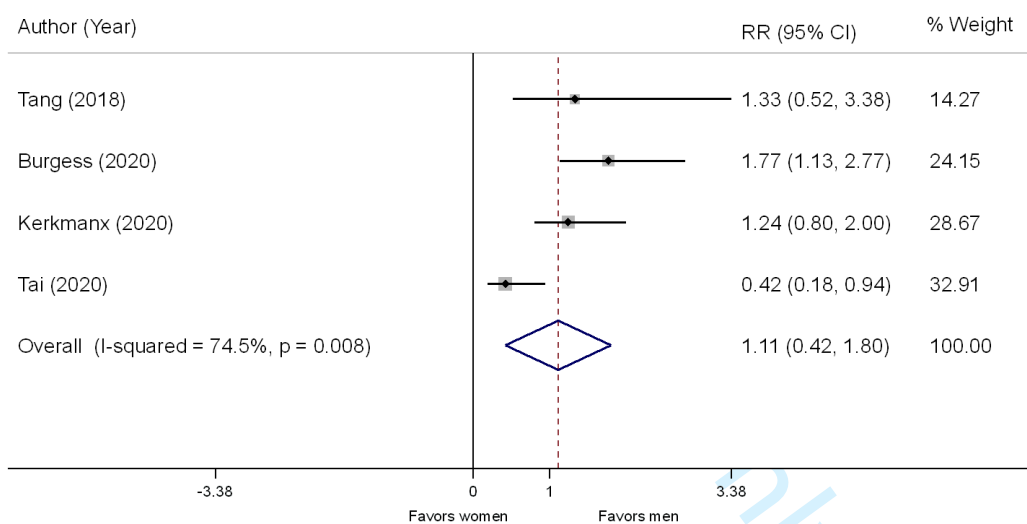
Forest plots showing unadjusted (A) and adjusted (B) short-term all-cause mortality of women compared with men with ST-segment elevation myocardial infarction using random-effects model.

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 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 IIb/IIIa 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

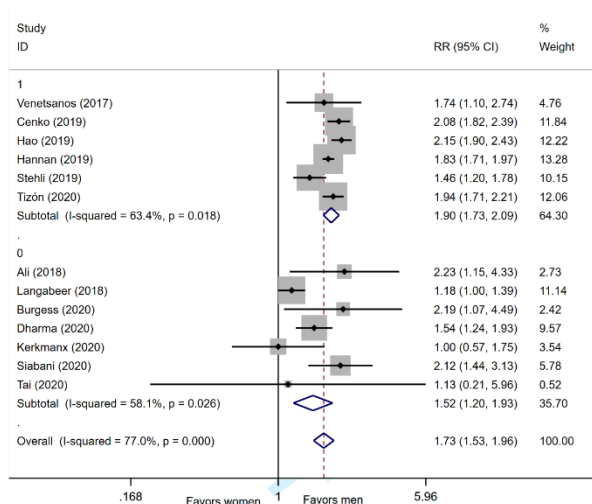
		smoking, prior angina pectoris, prior myocardial infarction, prior PCI, prior CABG, peripheral artery disease, prior stroke, ST-segment elevation in anterior leads (at ECG), systolic blood pressure at baseline, heart rate at baseline, serum creatinine at baseline, Killip Class ≥ 2
Hao	2019	Age, medical 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) $\geq II$, 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

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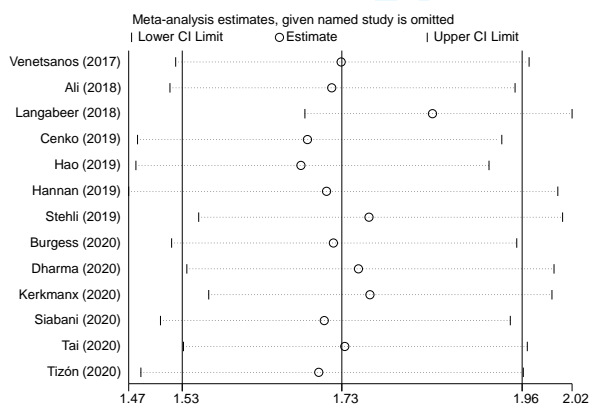
eTable 3 Assessment of study quality using Newcastle-Ottawa scale.

First Author	Year	Selection				Comparability	Outcome			Total points
		Representativeness of the exposed cohort	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

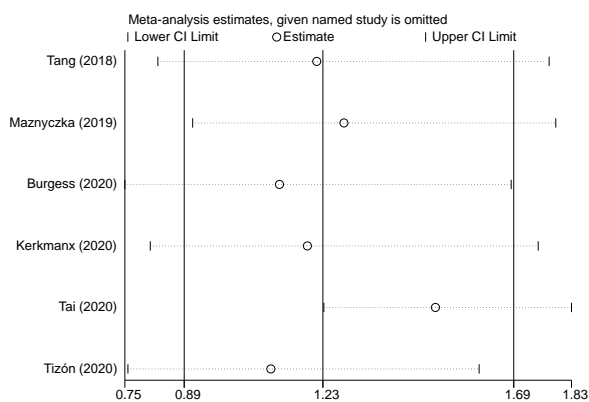
eFigure 1 Forest plots of relative risks of short-term all-cause mortality of studies with Newcastle-Ottawa scale >7 points and with ≤7 points.



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



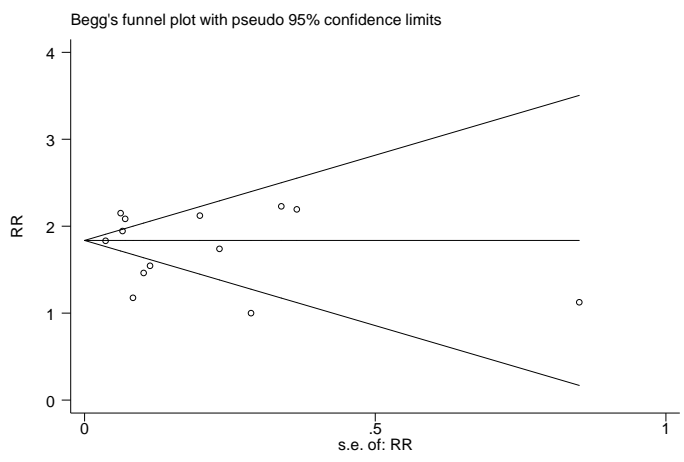
eFigure 3 Meta-influence analysis for unadjusted long-term mortality



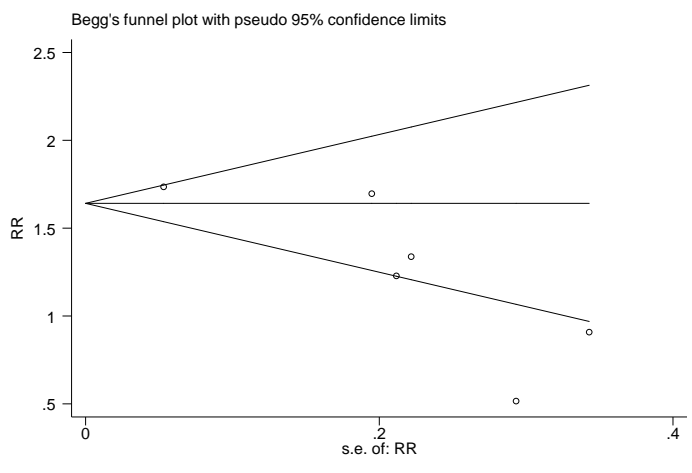
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eFigure 4 Funnel plots for publication bias for unadjusted short-term (A) and long-term (B) mortality

A



B





PRISMA 2020 Checklist

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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.	Page 5
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

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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

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