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Sex as a prognostic factor for mortality in critically ill adults with sepsis: a systematic review and meta-analysis

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ABSTRACT

Objective To assess the role of sex as an independent prognostic factor for mortality in patients with sepsis admitted to intensive care units (ICUs).

Design Systematic review and meta-analysis.

Data sources MEDLINE, Embase, Web of Science, ClinicalTrials.gov and the WHO Clinical Trials Registry from inception to 17 July 2020.

Study selection Studies evaluating independent associations between sex and mortality in critically ill adults with sepsis controlling for at least one of five core covariate domains prespecified following a literature search and consensus among experts.

Data extraction and synthesis Two authors independently extracted and assessed the risk of bias using Quality In Prognosis Studies tool. Meta-analysis was performed by pooling adjusted estimates. The Grades of Recommendations, Assessment, Development and Evaluation approach was used to rate the certainty of evidence.

Results From 14 304 records, 13 studies (80 520 participants) were included. Meta-analysis did not find sex-based differences in all-cause hospital mortality (OR 1.02, 95% CI 0.79 to 1.32; very low-certainty evidence) and all-cause ICU mortality (OR 1.19, 95% CI 0.79 to 1.78; very low-certainty evidence). However, females presented higher 28-day all-cause mortality (OR 1.18, 95% CI 1.05 to 1.32; very low-certainty evidence) and lower 1-year all-cause mortality (OR 0.83, 95% CI 0.68 to 0.98; low-certainty evidence). There was a moderate risk of bias in the domain adjustment for other prognostic factors in six studies, and the certainty of evidence was further affected by inconsistency and imprecision.

Conclusion The prognostic independent effect of sex on all-cause hospital mortality, 28-day all-cause mortality and all-cause ICU mortality for critically ill adults with sepsis was uncertain. Female sex may be associated with decreased 1-year all-cause mortality.

PROSPERO registration number CRD42019145054.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this systematic review is the first addressing the prognostic independent effect of sex on mortality for patients with sepsis following the recommended standards for reviews of prognostic factor studies.
⇒ The meta-analysis pooled adjusted estimates for at least one of five core covariate domains prespecified following a literature search and consensus among experts.
⇒ The certainty of the evidence was evaluated using the Grades of Recommendations, Assessment, Development and Evaluation approach.
⇒ Heterogeneity was substantial between the included studies.

INTRODUCTION

Sepsis, a life-threatening organ dysfunction produced by a dysregulated host response to inflammation,[1] is a leading cause of death in intensive care units (ICUs) and accounts for one of five deaths worldwide.[2–4] It is a heterogeneous illness affecting males more often than females.[5] Evaluating if outcomes differ by sex is a recognised health research priority.[6] It has been hypothesised that sex may have a prognostic effect on sepsis outcomes. Biological mechanisms concerning the relation between sex hormone metabolism and immune responses are known to underpin this hypothesis.[7–11] However, individual studies evaluating the relationship between sex and outcome of sepsis report conflicting and imprecise findings.[12–14]

Prognostic research that identifies patient characteristics associated with outcomes in people with a particular condition[15] can be collated in evidence syntheses to examine the role of sex in mortality among patients with sepsis. It may help in risk stratification of these patients by combining independent prognostic factors within prognostic models, which contribute to the selection of the most appropriate therapeutic options.[15] Using a systematic review search filter in PubMed, we

found two potentially relevant citations.[16 17] Their detailed assessment showed several weaknesses. For example, there was no definition of eligibility criteria concerning studies that capture independent associations, a feature that is critical for focussing the review on prognostic evidence.[18] In addition, specific tools[19] for the assessment of risk of bias in prognostic studies were not applied. Therefore, an evidence synthesis tailored to the specific methodological requirements of prognostic research is required to help delineate the significance of sex in sepsis outcomes in critically ill patients.

We conducted a systematic review and meta-analysis to summarise the available evidence to assess the role of sex as an independent prognostic factor for mortality in patients with sepsis admitted to the ICU.

METHODS

We registered the protocol with PROSPERO (CRD42019145054) and published it in full.[20] Online supplemental table 1 details the differences between the protocol and the review. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[21]

Eligibility criteria

We included studies (experimental or any observational design) that sought to confirm the independent prognostic effect of sex on mortality in critically ill adults with sepsis controlling for covariates (called phase 2-confirmatory studies, which means the objective statement outlined sex as a prognostic factor of interest and analyses adjusted for covariates).[18] We included patients aged 16 years and older with a sepsis diagnosis, as defined by the study authors, treated in an ICU. Studies including both adult and paediatric patients were eligible if adults represented more than 80% of the study sample. Sex and gender are distinct concepts, though often erroneously interchanged in the medical research reports.[22] We accepted any assessment of sex as a biological characteristic. We also appraised operational concepts of sex and gender provided by the study authors using the classification detailed in online supplemental table 2.[23] After a literature search and consensus among experts (online supplemental table 3), we prespecified the following core set of adjustment factors: age, severity score (Sequential Organ Failure Assessment score, Simplified Acute Physiology Score II or Acute Physiologic Assessment and Chronic Health Evaluation II), comorbidities (immunosuppression, pulmonary diseases, cancer, liver diseases or alcohol dependence), non-urinary source of infection, and inappropriate or late antibiotic coverage. The coprimary outcomes were all-cause hospital mortality and 28-day all-cause mortality. Secondary outcomes were 7-day all-cause hospital mortality, 1-year all-cause mortality and all-cause ICU mortality. Table 1 describes the review question according to the population, index, comparator, outcome(s), timing, setting.

Search strategy and selection process

We searched MEDLINE Ovid, Embase Elsevier and Web of Science for studies published from inception to 17 July 2020, and ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform for unpublished and ongoing studies, regardless of language. The search

Table 1 PICOTS system

Population	Index prognostic factor	Comparator	Outcome(s)	Timing	Setting
Adults with sepsis	Sex	Non-applicable to this review*	Primary outcomes		ICUs
			All-cause hospital mortality	The longest follow-up provided by the study authors (until death of hospital discharge)	
			28-day all-cause mortality	28 days from sepsis diagnosis	
			Secondary outcomes		
			7-day all-cause hospital mortality	7 days from sepsis diagnosis	
			1-year all-cause mortality	1 year from sepsis diagnosis	
			All-cause ICU mortality	The longest follow-up provided by the study authors (until death of ICU discharge)	

*Core set of adjustment factors: age, severity score (Sequential Organ Failure Assessment score, Simplified Acute Physiology Score II or Acute Physiologic Assessment and Chronic Health Evaluation II), comorbidities (immunosuppression, pulmonary diseases, cancer, liver diseases or alcohol dependence), non-urinary source of infection and inappropriate or late antibiotic coverage.
ICUs, intensive care units; PICOTS, population, index, comparator, outcome(s), timing, setting.

strings included terms related to the population (sepsis), the prognostic factor (sex), prognostic study methods and the outcome (mortality). Furthermore, we handsearched conference proceedings from 2010 to 2019 of the foremost critical care and infectious diseases symposia. Online supplemental table 4 presents the full search strategy.

We used the online software EPPI-Reviewer V.4 to manage the study selection process.[24] Pairs of review authors independently screened the title and abstracts, and when appropriate, full texts to determine their eligibility. We used a consensus method and consulted a third author if disagreement remained.

Data extraction and risk of bias assessment

Two authors independently extracted data and reached a consensus using electronic extraction templates in EPPI-Reviewer V.4. We used the checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies for prognostic factors guidance for data collection.[25] We contacted all study authors for missing information. Two authors independently assessed the risk of bias of the included studies, agreed on ratings and a third author participated when required. We applied an outcome-level approach and amended the Quality In Prognosis Studies (QUIPS) tool using four categories (low, moderate, high or unclear risk).[19 25 26] We defined studies controlling for less than three of the aforementioned covariates as 'minimally adjusted for other prognostic factors or moderate risk', and those controlling for at least three of these covariates as 'adequately adjusted or low risk of bias' for the QUIPS adjustment domain.[27] We assessed selective reporting bias by: (1) searching for a prospective study protocol or registration, (2) dealing with related conference abstracts and (3) carefully examining the study methods section.[19]

Data synthesis

For each study and prognostic factor estimate, we extracted the measures of associations alongside its CIs. We transformed association measures into an OR with its 95% CIs to allow statistical pooling whenever adequate.[28] We estimated no data from Kaplan-Meier curves because of the risk of overestimation of events and censorship concerns.[29] We presented results consistently, so associations above one indicated a higher mortality for female participants. We pooled estimates in meta-analyses when valid data were available. For the primary analyses, we used estimates from the model that adjusted for more covariates from the core of adjustment factors. We performed random-effects meta-analyses applying the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment,[30] using RevMan V.5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and the template for conversion provided by IntHout.[31] We examined statistical heterogeneity computing prediction intervals when the random-effects meta-analysis contained at least three studies.[30 32] We also calculated I^2 and τ^2 statistics to provide further quantifications of statistical heterogeneity. We planned to explore possible methodological causes of heterogeneity performing subgroup analyses. We undertook a single prespecified subgroup analysis for prospective vs retrospective studies when appropriate. We compared differences between subgroups by performing a test of interaction.[33] We carried out no subgroup analyses based on other study characteristics because there were insufficient studies. We conducted sensitivity analyses accounting for the risk of bias excluding studies with either a high or moderate risk of bias in one of the following QUIPS key domains: study attrition, prognostic factor measurement, outcome measurement and adjustment for other prognostic factors. Additionally, we explored potential differences between meta-analyses based on unadjusted (crude) and adjusted estimates, and the impact of the unique information reported in abstract conferences.[34] We could not perform further sensitivity analyses as no other comparisons met the predefined criteria. Although we planned to assess publication bias for each meta-analysis including ≥10 studies by funnel plot representation and Peter's test at a 10% level,[35] no meta-analysis met this criterion.

Assessment of the certainty of evidence

We assessed the certainty of evidence using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach and guidance for prognosis studies (online supplemental table 5).[27 36–41] We tabulated our findings for each outcome using the GRADEpro GDT software.[42] We described results for prognostic effect estimate considering the certainty of evidence and its clinical importance (important effect, slight effect and little or no effect). As we found no well-established clinically important thresholds for prognostic effects, we agreed a priori on an absolute risk difference of at least ±10‰ as clinically important difference.

Patient and public involvement

No patients or the general public involved.

RESULTS

Our searches threw a total of 14 304 records. After removing duplicates, we screened 13 115 titles and abstracts and identified 146 full texts for further examination. Finally, the review included 13 studies[43–55] (figure 1). One study included[55] was reported as a conference abstract. Thus, we examined database information published elsewhere[56] to obtain further details on study methods. The included studies involved a total of 80 520 adult participants (45.25% females). Table 2 and online supplemental table 6 display their characteristics. Online supplemental table 7 and online supplemental table 8 show the sepsis definition and covariates included in the adjusted models of each study, respectively. Although four studies[47 50 53 54] had phase 2 designs and provided adjusted data on mortality, their time frames differed from ours and/or reported unadjusted estimates for some of the review outcomes. Hence, we only used those data for sensitivity analyses.

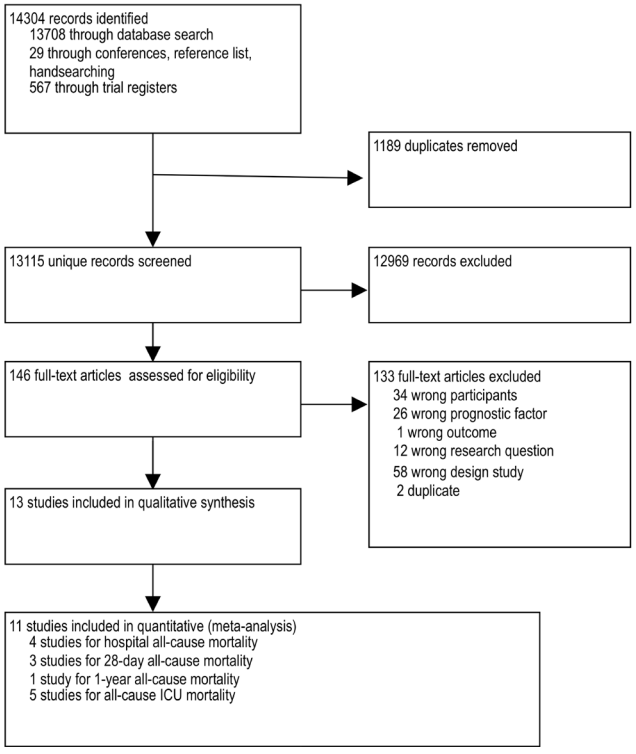

Figure 1 Flow diagram. ICU, intensive care unit.

Online supplemental figure 1 depicts the risk of bias assessment at outcome level of each included study using QUIPS. Over half of the studies[43 45 46 48–50 54] were at low risk for study participation, study attrition, and outcome measurement domains. While three studies[51 52 55] described baseline characteristics inadequately, and another two[44 47] provided insufficient data on drop-outs. All studies were at unclear risk for the prognostic factor domain, given that none defined sex. The risk of bias for the adjustment for other prognosis factors domain was low for half of the studies[43 44 47 52 54 55] and moderate for the others[45 46 48–51] because of an acceptable or minimal adjustment, respectively. Three studies[45 50 55] were at unclear risk for the statistical analysis and reporting domain, while the remaining studies were at low risk of bias.

Evidence synthesis

Online supplemental table 9 presents the summary outcome estimates for each study. Table 3 displays 'Summary of findings' for each review outcome.

Primary outcomes

We investigated the independent prognostic effect of sex on all-cause hospital mortality. We found seven studies[43–45 47 50 53 55] (38 016 recruited participants) addressing this question. Among the five studies[43–45 47 55] (30 349 analysed participants) that provided adjusted results, four of them[43 44 47 55] (28 915 analysed participants) presented sufficiently similar data allowing quantitative synthesis. Meta-analysis showed inconclusive results on sex-based differences in all-cause hospital mortality (OR 1.02, 95% CI 0.79 to 1.32; I^2=64%; very low-certainty evidence) (figure 2A). The 95% prediction interval ranged from 0.5 to 2.08. Sensitivity analyses results remained unaltered either excluding the study[55] only reported as a conference abstract (OR 0.95, 95% CI 0.55 to 1.64), or using unadjusted estimates (OR 1.00, 95% CI 0.88 to 1.14) (online supplemental figure 2 and online supplemental figure 3, respectively).

We examined sex-based differences in 28-day all-cause mortality. We found six studies[44 49 50 52–54] (20 930 recruited participants) addressing this question. Three studies[44 49 52] (12 579 analysed participants) provided adjusted results. Meta-analysis found higher 28-day all-cause mortality in the female group (OR 1.18, 95% CI 1.05 to 1.32; I^2=0%; very low-certainty evidence) (figure 2B). Considering a risk of 24% for 28-day all-cause mortality in male patients, 31 more female patients per 1000 will die (95% CI from 9 to 54 more), as compared with male patients. The 95% prediction interval ranged from 0.56 to 2.5. Sensitivity analysis results were inconclusive either pooling only studies with low or uncertain risk of bias for all key QUIPS domains (OR 1.17, 95% CI 0.88 to 1.56) or unadjusted estimates (OR 1.05, 95% CI 0.84 to 1.32) (online supplemental figure 4).

Secondary outcomes

No study evaluated the prognostic role of sex on 7-day all-cause hospital mortality. We sought sex-related differences in 1-year all-cause mortality. Of two studies[50 53] investigating this question, only one[50] (6134 analysed patients) provided adjusted estimates reporting as Cox proportional hazard regression with OR (95% CI). We were unable to get further clarification from the study authors; therefore, we considered this a misspelling error, and so we transformed their estimate (assumed HR) into OR. This study showed lower 1-year all-cause mortality in the female group (OR 0.83, 95% CI 0.68 to 0.98; low-certainty of evidence). Considering a risk of 50.5% for 1-year all-cause mortality in male patients, 46 fewer female patients per 1000 will die (95% CI from 95 to 5 fewer), as compared with male patients. Sensitivity analysis results using unadjusted estimates were inconclusive (OR 0.86, 95% CI 0.54 to 1.37) (online supplemental figure 5).

We evaluated sex-related all-cause ICU mortality. We found seven studies[43 46–48 51 53 54] (51 936 recruited participants) addressing this question. Five studies[43 46 48 51 54] (31 562 analysed participants) provided adjusted estimates. One of them[48] reported adjusted OR stratified by age, and after failing to get an overall adjusted estimate from the study author, we considered it as two substudies. Pooled adjusted estimates found inconclusive results on sex-based differences in all-cause ICU mortality (OR 1.19, 95% CI 0.79 to 1.78; I^2=69%; very low-certainty evidence) (online supplemental figure 6). The 95% prediction interval ranged from 0.49 to 2.89. Results of analyses comparing subgroups by longitudinal designs showed no differences (p=0.83). Sensitivity analysis results including only studies with low or uncertain risk of bias for all key

Table 2 Characteristics of included studies

Study	Study dates	Study design	Sites	Population	Primary outcome	Sample size N of study participants (N with outcome)	Inclusion criteria	Exclusion criteria
Adrie *et al* 2007[43]	1997–2005	Prospective nested case–control	12	Adults admitted to the ICU for severe community-acquired sepsis	ICU mortality Post-ICU mortality	1692 (1608)	>16 years old; ICU stays >24 hours; community-acquired severe sepsis	NS
Caceres *et al* 2013[44]	2006–2007	Retrospective cohort	4	Adults admitted to the ICU for hospital-acquired pneumonia	All-cause mortality	416 (319)	≥18 years old; ICU admission; clinical suspicion of pneumonia	None
Dara *et al* 2012[55]	1998–2007	Retrospective cohort	28	Adults admitted to the ICU for septic shock	Hospital mortality	8670 (8670)	Consecutive adults with septic shock patients	NS
Luethi *et al* 2010[48]	2008–2014	Post hoc analysis of an RCT	51	Adults presented to the ED with septic shock. Data were available for ICU setting	90-day all-cause illness severity-adjusted mortality	1387 (1387)	≥18 years old; septic shock	NS
Madsen *et al* 2014[45]	2005–2012	Retrospective cohort	1	Adults admitted to the ICU for severe sepsis or septic shock	SSC resuscitation bundle completion	814 (814)	>18 years old presenting to the ED with criteria for severe sepsis/septic shock	Only comfort measures within the first 24 hours; non-ICU admission
Mahmood *et al* 2012[51]	2004–2008	Retrospective cohort	NS*	Adults admitted to the ICU (sepsis subgroup)	ICU mortality	27 935 (27 935)	Consecutive adults in the APACHE IV database; sepsis subgroup	Readmission to the ICU
Nachtigall *et al* 2011[46]	January/March 2006; February/May 2007	Prospective cohort	1	Adults admitted to mixed ICUs with a special focus on sepsis patients (sepsis subgroup)	ICU mortality	327 (327)	Consecutive adults (≥18 years); ICU stays >36 hours; sepsis criteria for at least 1 day during the ICU stay	NS
Pietropaoli *et al* 2010[47]	2003–2006	Retrospective cohort	98	Adults admitted to the ICU for severe sepsis or septic shock	Hospital mortality	18 757 (18 318)	≥16 years old; severe sepsis/septic shock patients; data from the first ICU admission	If gender, age, or hospital mortality was missing
Sakr *et al* 2013[54]	April/Sep 2006[14]	Post hoc analysis of a prospective cohort	24	Adults admitted to the medical and/or surgical ICU for severe sepsis	ICU mortality	305 (305)	>18 years old; severe sepsis; data from the first ICU admission	NS
Samuelsson *et al* 2015[52]	2008–2012	Retrospective cohort	65	Adults admitted to the ICU (sepsis subgroup)	30-day mortality	9830 (9830)	Consecutive SAPS III–scored adults ICU (>15 years old); validated mortality data in the registry; sespsis subgroup	Reasons for not being able to obtain mortality data: non-Swedish residency and patients with concealed identity

Continued

Table 2 Continued

Study	Study dates	Study design	Sites	Population	Primary outcome	Sample size N of study participants (N with outcome)	Inclusion criteria	Exclusion criteria
Sunden-Cullberg *et al* 2020[49]	2008–2015	Retrospective cohort	42	Adults admitted to the ICU for sepsis or shock septic via the ED within 24 hours	Sepsis bundle completion; 30-day mortality	2720 (2430)	≥18 years old; ICU admission within 24 hours of arrival to an ED; community-acquired severe sepsis or septic shock	Data non-registered simultaneously in two selected registries, alongside SAPS3 data. Multiple registrations.
van Vught *et al* 2017[53]	2011–2014	Prospective cohort	2	Adults admitted to the ICU for sepsis	90-day mortality	1533 (1815 admissions†)	Consecutive patients >18 years old; sepsis; expected ICUs stay >24 hours; data from multiple ICU admission‡	Transfer from other ICUs
Xu *et al* 2019[50]	2001–2012	Retrospective cohort	1	Adults admitted to the ICU for sepsis	1 year mortality	6134 (6134)	All adults diagnosed with sepsis, severe sepsis, or septic shock in the database	<18 years old

*Information reported as 'large number of ICUs'.
†van Vught analysed 1815 admissions for its primary outcome. Data were available at the patient level for the review outcomes.
‡ICU demographic and long-term follow-up data from the first ICU admission, host response data from overall admissions.
APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; ED, emergency department; ICU, intensive care unit; NS, not stated; RCT, randomised controlled trial; SAPS, Simplified Acute Physiology Score; SSC, surviving sepsis campaign.

Table 3 Summary of findings

Outcomes	Anticipated absolute prognostic effects*			Effect estimate (95% CI) (95% prediction interval)	No of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk in males	Risk in females (95% CI)	ARD in females (95% CI)†			
All-cause hospital mortality (median observed length of stay ranged from 6 to 26 days)	303 per 1 000‡	307 per 1 000 (255 to 364)	4 more per 1000 (47 fewer to 62 more)	OR 1.02 (0.79 to 1.32) (0.5 to 2.08)	28 915 (4 observational phase 2 studies)	⊕◯◯◯ VERY LOW§¶**
28-day all-cause mortality	240 per 1 000‡	271 per 1 000 (249 to 294)	31 more per 1000 (9 more to 54 more)	OR 1.18 (1.05 to 1.32) (0.56 to 2.50)	12 579 (3 observational phase 2 studies)	⊕◯◯◯ VERY LOW§**††‡‡
1-year all-cause mortality	505 per 1 000‡	459 per 1 000 (410 to 500)	46 fewer per 1000 (95 fewer to 5 fewer)	OR 0.83 (0.68 to 0.98) N/M	6134 (1 observational phase 2 study)	⊕⊕◯◯ LOW**††§§¶¶
All-cause ICU mortality (median observed length of stay ranged from 2.7 to 13 days)	200 per 1 000‡	229 per 1 000 (167 to 308)	29 more per 1000 (33 fewer to 108 more)	OR 1.19 (0.80 to 1.78) (0.49 to 2.89)	31 562 (5 observational phase 2 studies)	⊕◯◯◯ VERY LOW§¶**

Not meaningful: <3 studies for computing of the 95% prediction interval a meaningful estimate.
*The risk in the female group (and its 95% CI) is based on the assumed risk in the male participants group and the estimated effect of sex (OR and its 95% CI).
†We considered an ARD of at least ±10‰ as large enough to be clinically meaningful. Thus, we defined the clinical importance of the absolute prognostic effect for all the review outcomes as follows: important improvement (ARR of at least 10‰), slight improvement (10‰<ARR≤5‰), minimal or no effect (−5‰<ARD<5‰), slight worsening (5‰≤ARI<10‰), and important worsening (ARI of at least 10‰).
‡The assumed risk in male participants is based on the median risk among the male participants in the included studies. We consider this risk reflects the context of ICUs in high-resource countries adequately.
§Downgraded by two levels for very serious inconsistency due to a wide 95% prediction interval ranging from an increased mortality in male sex to an increased mortality in female sex that could not be explained for any reason.
¶Downgraded by two levels for very serious imprecision because the 95% CI of the ARD in our assumed risk scenario ranges from an important improvement to an important worsening in the prognosis of female participants compared with male participants. Besides, the OSS was smaller than the OIS required.
**Publication bias not assessed because of the scarce number of included studies (<10).
††Downgraded by one level for serious imprecision because the CI 95% of the ARD in our assumed risk scenario exceeds one of our clinical importance thresholds (ie, it is compatible with an important or a slight prognostic effect). The OSS was greater than the OIS.
‡‡Downgraded by one level for serious indirectness because one study[52] was responsible for 85% of the weight reported in-hospital and out-hospital mortality.
§§Downgraded by one level for serious risk of bias because the effect estimate comes from a study with moderate and unclear risk of bias for half of the QUIPS domains.
¶¶Inconsistency not assessed because a single study was considered.
ARD, absolute risk difference; ARI, absolute risk increase; ARR, absolute risk reduction; GRADE, Grades of Recommendations, Assessment, Development and Evaluation; ICU, intensive care unit; N/M, not meaningful; OIS, optimal information size; OSS, observed sample size; QUIPS, Quality In Prognosis Studies.

QUIPS domains were inconclusive (OR 1.24, 95% CI 0.001 to 1223). Sensitivity analysis results using unadjusted estimates remained unaltered (OR 1.15, 95% CI 0.87 to 1.52) (online supplemental figure 7).

DISCUSSION

Main findings

Our systematic review assessed whether sex is an independent prognostic factor for mortality among adults with sepsis admitted to ICUs. We are uncertain of the independent prognostic effect of sex for all-cause hospital mortality, 28-day all-cause mortality and all-cause ICU mortality in critically patients, as the certainty of the evidence was very low. Female sex may be associated with an important reduction in 1-year all-cause mortality (low-certainty evidence). However, the CI of the absolute reduction is also compatible with a slight protective effect.

Strengths and weaknesses of the study

Strengths of our review include a comprehensive and non-language-restricted search strategy covering unpublished resources, the inclusion of observational phase 2 explanatory studies, which initially provide high certainty of the evidence for prognosis,[18] and an available published protocol to which we adhered.[20] We also prespecified a core set of adjustment factors based on a literature review, the consensus among clinician review authors, and inputs from reviewers during the protocol publication process.[20] We handled the unique information from a conference abstract by contacting the study authors, examining register details published elsewhere,

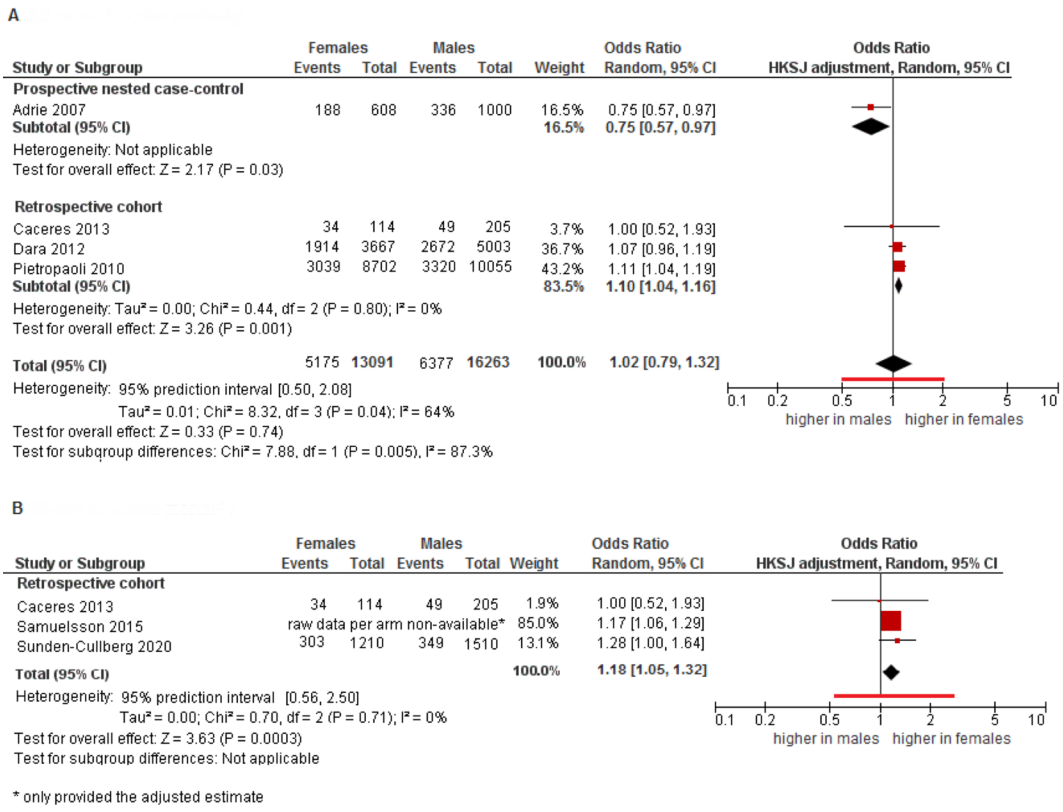

Figure 2 Forest plots of adjusted analyses for association between sex and all-cause hospital mortality (A) and 28-day all-cause mortality (B). HKSJ, Hartung-Knapp-Sidik-Jonkman.

and exploring sensitivity analysis without these results.[34] We performed the HKSJ procedure, which yields a wider and more rigorous confidence interval,[30] and applied the GRADE framework adaptations for prognostic factor research to rate the certainty in pooled estimates.[25 38–40] We established a clinical threshold based on the premise that sex is a non-modifiable factor that affects the entire population; therefore, an absolute risk difference of 10‰ on mortality may lead to a clinically important impact. Besides, a more demanding threshold, for example, ±20‰, would not modify the certainty of evidence assessment.

Some limitations of this review arise from poor reporting in the included studies. First, included studies referred to an unclear or inadequate definition of sex. Although we anticipated no biological assessments, we expected at least a statement based on sexual dimorphism observed by healthcare staff. Although we meta-analysed studies providing all-cause hospital mortality to improve precision, additional analyses to explore potential differences between short and medium/long-term outcomes could not be performed because only two out of four included studies reporting the length of stay.[43 44] Another issue is the ambiguous definitions used for the 28-day mortality outcome. Some studies provided a clear description linked to in-hospital mortality, while others combined in-hospital and out-hospital events or omitted further details. After requesting additional clarifications, only Samuelsson *et al* replied.[52] We pooled these studies and downgraded evidence certainty for indirectness. As well, clinical heterogeneity was substantial between the included studies, which differed regarding the sepsis definition used (ie, diagnostic criteria and sepsis and/or septic shock), illness severity measurements and score ratings, comorbidity burden, as well as in clinical practice (ie, treatment protocols). We quantified statistical heterogeneity using 95% prediction intervals, which help to assess the inconsistency criteria in GRADE, where usually large study sample sizes may result in narrow CIs alongside high I^2.[39 57 58] However, these intervals are still imprecise when meta-analysis includes few studies.[58] For hospital mortality, 28-day mortality, and ICU mortality, prediction intervals contained the value of null effect, suggesting that sex may not be prognostic in at least some situations.[30 57] Also, most prespecified subgroup analyses were not feasible because of the scarcity of studies. Another limitation is that we cannot provide information about the cause of death, which is particularly relevant for late mortality. Lastly, the included studies were mainly conducted in North America and Western Europe.

Implications for clinical practice

The certainty of evidence for all-cause hospital mortality, 28-day all-cause mortality and ICU mortality was very low. Consequently, the available evidence to inform healthcare providers is limited. Female sex may be associated with an important reduction in 1-year all-cause mortality (low-certainty evidence). Based on a risk of 50.5% for

1-year all-cause mortality among male patients, 46 fewer female patients per 1000 will die (95% CI from 95 to 5 fewer). Studies examining long-term mortality after sepsis suggest that epigenetic regulation may cause post-sepsis immunosuppression and atherosclerosis phenomena.[59] Thus, sex as an independent prognostic factor for late mortality may suggest the development of targeted interventions.[15]

Implications for research

Our systematic review and meta-analysis offer information for future research in this field. To our knowledge, this is the first synthesis on sex and mortality in adults with sepsis admitted to ICUs following the recommended standards for systematic reviews of prognosis factors. Our core set of adjustment factors may be a supporting source for prognostic factors selection in multivariable modelling in further study designs. This review also contributes to identifying knowledge gaps. Our meta-analysis failed to provide definitive evidence on all-cause hospital mortality, 28-day all-cause mortality and all-cause ICU mortality in critically ill patients with sepsis. These inconclusive results showed a lack of evidence supporting sex as an independent prognostic factor in these patients, not as evidence of a lack of prognostic effect. Moreover, no studies looked at 7-day mortality and a single study investigated long-term mortality. Therefore, well-designed prospective studies are needed to test the adjusted prognostic role of sex in patients with sepsis admitted to ICUs. Finally, addressing the architecture for tracking of prognosis research is required. Academics, journals, editors and librarians may boost preregistering protocols to help both reduce the risk of publication bias and detect selective outcome reporting bias. Also, they may encourage a proper indexing process in electronic databases to enhance the reliability of searches.

CONCLUSIONS

Our systematic review and meta-analysis found uncertain evidence as to whether sex has an independent prognostic impact on all-cause hospital mortality, 28-day all-cause mortality and all-cause ICU mortality among critically ill adults with sepsis since the certainty of the evidence was very low. Female sex may be associated with decreased 1-year all-cause mortality (low-certainty evidence). High-quality research is needed to test the adjusted prognostic value of sex for predicting mortality in adults with sepsis admitted to ICUs.

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Supplemental material

Sex as a prognostic factor for mortality in critically ill adults with sepsis: a systematic review and meta-analysis

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Content:

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Supplemental Table 1. Differences between the protocol and the review

Modified element	Explanation
Wording primary outcomes	We modify the wording for primary outcomes for clarity purposes, following the suggestion of peer reviewers. "All-cause hospital mortality" and "28-day all-cause mortality", instead of All-cause mortality (the longest follow-up provided by study authors)" and 28-day all-cause hospital mortality", respectively.
All-cause ICU mortality	We added all-cause ICU mortality as secondary outcome. We considered all-cause ICU mortality as a relevant outcome and non-subsidiary of pooling with hospital mortality outcomes.
Subgroup analyses	We were not able to undertake subgroup analyses comparing cohort versus case-control studies because there were insufficient studies.
Sensitivity analyses	We added sensitivity analysis after excluding the unique data from conference abstracts. We also carried out sensitivity analyses by pooling crude estimates. We were not able to perform the following sensitivity analyses specified in the protocol as no comparisons met the predefined criteria: - Excluding only studies with a high risk of bias in one QUIPS key domain. - Excluding studies that provided an adjusted estimated but did not adjusted for all our core set of additional prognostic factors.

Supplemental Table 2. Assessment of the use of terms sex and gender in the included studies

Adequate (any of the following):	Inadequate (any of following):
- Sex for biological characteristics. - Gender for socially constructed roles, behaviours, and identities. - Females or males for sex. - Women or men for gender.	- Gender for biological characteristics. - Sex for socially constructed roles, behaviours, and identities. - Females or males for gender. - Women or men for sex.

Supplemental Table 3. Process of defining the core set of adjustment factors

Step	Method	Potential additional prognostic factors identified
1. Preliminary searches to identify potential prognostic factors on mortality in patients with sepsis	1. PubMed search: (sepsis[Title]) AND "prognostic factor"[Title] 2. Embase: 'prognostic factor':ti AND 'sepsis':ti 3. Search in Uptodate 4. Initial discussion with review team members	1. Hypertriglyceridemia 2. Positive fluid balance 3. Red cell distribution width 4. Duration of SIRS before organ failure 5. Heart-type fatty acid-binding protein 6. D-dimer 7. Low serum level of high-density lipoprotein colesterol 8. Serum N-terminal pro-brain natriuretic peptide level 9. Immunosuppression 10. Cancer 11. Liver diseases 12. Alcohol dependence 13. Non-urinary source of infection 14. Inappropriate or late antibiotic coverage
2. Identify prognostic models for mortality in patients with sepsis	We considered factors included in the SOFA prognostic model	1. PaO2 2. FiO2 3. On mechanical ventilation 4. Platelets, $\times 10^3/\mu L$ 5. Glasgow Coma Scale 6. Bilirubin, mg/dL (µmol/L) 7. Mean arterial pressure OR administration of vasoactive agents required 8. Creatinine, mg/dL (µmol/L) (or urine output
3. Final list of key additional prognostic factors	We defined the final list of core set of adjustment factors by consensus	1. Age 2. Severity score at baseline (SOFA, SAPS II, APACHE II score) 3. Comorbidities: immunosuppression, pulmonary diseases, cancer, liver diseases, alcohol dependence 4. Non-urinary source of infection 5. Inappropriate or late antibiotic coverage

Supplemental Table 4. Search strategy

Full search string for MEDLINE Ovid (consulted 17th July 2020)
1. exp Sepsis/
2. exp Shock, Septic/
3. (septic* or sepsis* or SIRS).ti,ab.
4. "septic shock".ti,ab.
5. "endotoxic shock".ti,ab.
6. "toxic shock".ti,ab.
7. "severe sepsis".ti,ab.
8. "blood stream infection".ti,ab.
9. (septic?emia or "systemic inflammatory response syndrome" or py?emia).ti,ab.
10. (multi?organ adj5 failure).ti,ab.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp Sex Factors/
13. exp Sex Characteristics/
14. exp Sex Distribution/
15. exp Sex/
16. exp Sex Ratio/
17. exp Women's Health/
18. exp Men's Health/
19. boy*.ti,ab.
20. female*.ti,ab.
21. gender.ti,ab.
22. girl*.ti,ab.
23. male*.ti,ab.
24. men.ti,ab.
25. sex.ti,ab.
26. women.ti,ab.
27. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 11 and 27
29. exp Mortality/
30. mortality.ti,ab.
31. dead.ti,ab.
32. death*.ti,ab.
33. died.ti,ab.
34. fatality.ti,ab.
35. fatalities.ti,ab.
36. survivor.ti,ab.
37. survival.ti,ab.
38. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 28 and 38
40. incidence.sh.
41. follow up studies.sh.
42. "prognos*".ab,ti.
43. "predict*".ab,ti.
44. "course*".ab,ti.
45. 40 or 41 or 42 or 43 or 44
46. 39 and 45
47. exp Animals/ not humans.sh.

48. 46 not 47	
Full search string for Embase Elsevier (consulted 17th July 2020)	
#1	'sepsis'/mj
#2	'septic shock'/mj
#3	septic*:ab,ti OR sepsis*:ab,ti OR sirs:ab,ti
#4	'septic shock':ab,ti
#5	'endotoxic shock':ab,ti
#6	'toxic shock':ab,ti
#7	'severe sepsis':ab,ti
#8	'blood stream infection':ab,ti
#9	septic?emia:ab,ti OR 'systemic inflammatory response syndrome':ab,ti OR py?emia:ab,ti
#10	multi$organ NEAR/5 failure
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	'sex factor'/mj
#13	'sexual characteristics'/mj
#14	'sex ratio'/mj
#15	'sex'/mj
#16	'women`s health'/mj
#17	'men`s health'/mj
#18	boy*:ab,ti
#19	female*:ab,ti
#20	gender:ab,ti
#21	girl*:ab,ti
#22	male*:ab,ti
#23	men:ab,ti
#24	sex:ab,ti
#25	women:ab,ti
#26	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27	#11 AND #26
#28	'mortality'/mj
#29	mortality:ab,ti
#30	dead:ab,ti
#31	death:ab,ti
#32	died:ab,ti
#33	'fatality':ab,ti
#34	fatalities:ab,ti
#35	survivor:ab,ti
#36	survival:ab,ti
#37	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
#38	#27 AND #37
#39	'disease course'/mj
#40	risk:kw
#41	diagnos*:kw
#42	'follow-up':kw
#43	epidemiology:lnk
#44	outcome:ab,ti
#45	#39 OR #40 OR #41 OR #42 OR #43 OR #44
#46	#38 AND #45
#47	'animal'/exp
#48	'human'/exp

#49 #47 NOT #48
#50 #46 NOT #49 AND ([embase]/lim OR [pubmed-not-medline]/lim)
Full search string for Web of Science (consulted 17th July 2020)
1 TOPIC: (sepsis) OR TOPIC: ("septic shock") OR TOPIC: ("Systemic inflammatory response syndrome") OR TOPIC: ("multiple organ failure")
2 TITLE: ("septic shock") OR TITLE ("endotoxic shock") OR TITLE: ("toxic shock") OR TITLE: ("severe sepsis") OR TITLE: ("blood stream infection") OR TITLE: (septic?emia) OR TITLE: (py?emia) OR TITLE: (septic*) OR TITLE: (sepsis*) OR TITLE: (SIRS)
3 #2 OR #1
4 TOPIC: ("sex factors" OR "sex distribution" OR "Sex characteristics" OR "Sex ratio" OR sex OR "women's health" OR "men's health") OR TITLE: (boy* OR male* OR girl* OR female* OR gender OR women OR men OR sex)
5 #4 AND #3
6 TOPIC: (mortality) OR TITLE: (mortality OR death OR dead OR died OR fatality OR fatalities OR survivor OR survival)
7 #6 AND #5
8 TOPIC: (incidende OR "follow up studies") OR TITLE: (prognos* OR predict* OR course*)
9 #8 AND #7
Trials registries (consulted 12th December 2019)
- ClinicalTrials.gov www.clinicaltrials.gov
- World Health Organization International Clinical Trials Registry Platform apps.who.int/trialsearch/
Hand-searched conference proceedings
- Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 50th edition 2010 to 59th edition 2019.
- European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 20th edition 2010 to 29th edition 2019.
- Society for Healthcare Epidemiology of America (SHEA): IDWeek 2012 to 2019 editions.
- International Conference on Prevention and Infection Control (ICPIC): 2011, 2013, 2015, 2017, 2019
- Society of Critical Care Medicine (SCCM): 39th edition 2010 to 48th edition 2019.
- International Symposium on Intensive Care and Emergency Medicine (ISICEM): 30th edition 2010 to 39th edition 2019.
- European Society of Intensive Care Medicine (ESICM): 23rd edition 2010 to 32nd edition 2019.

Supplemental Table 5. Guide to judge the certainty of evidence for prognostic factors GRADE

We initially assigned high certainty of the evidence for phase-2 confirmatory designs, i.e., studies that sought to test independent associations between the prognostic factor and outcomes	
We considered that the following factors may downgrade the certainty of evidence:	
Risk of bias	We rated as having: 1) serious limitations when most evidence was from studies at moderate or unclear risk of bias for most of the QUIPS domains; 2) very serious limitations when most evidence was from studies at high risk of bias for most of the QUIPS domains.
Inconsistency	We judged inconsistency relying on variability in point estimates using prediction intervals, extent of overlap of these intervals, and considering where point estimates lie in relation to clinical decision thresholds. We pre-specified subgroup analyses to explore differences across categories. In case of a single study within the existing body of evidence estimated the effect, we considered this criterion as "not applicable".
Indirectness	We downgraded the certainty of evidence whether participant population, prognostic factor, and/or outcomes fully represented no the review question. We judged indirectness for the prognostic factor based on characteristics of the primary independent variable, regardless of the adequacy of used terms, since we assessed insufficient details of sex and gender definitions provided or non-stated in the prognostic factor measurement QUIPS domain.
Imprecision	We judged imprecision considering: - Optimal information size - Compatibility of the 95% confidence interval of the absolute risk difference with our pre-defined clinical thresholds (minimal prognostic effects that were considered as clinically relevant for decision-making)
Publication bias	We planned to assess the presence of publication bias for each meta-analysis containing ≥10 studies by funnel plot representation and Peter's test at a 10% level.
We considered that the following factors may upgrade the certainty of evidence:	
Large effect estimate	We assessed size effect estimate considering: i) For meta-analysis: We considered upgrading the certainty of evidence for moderate or large pooled effects. Arbitrary thresholds define moderate odds ratio (1.5 ≤ OR ≤ 2), or large (OR > 2) ii) For narrative summary: We considered upgrading the certainty of evidence for moderate or large effects reported by most of the primary studies.
Dose response	We considered no dose response because of the feature of our prognostic factor of interest (dichotomous)

Abbreviations: OR: Odds ratio; QUIPS: Quality in prognosis studies.

Supplemental Table 6. Descriptive summary of included studies

	Adrie 2017	Caceres 2013	Dara 2012	Luethi 2020	Madsen 2014	Mahmood 2012	Nachtigall 2011
Methods							
Study design	Nested case-control	Cohort	Cohort	Post-hoc analysisis	Cohort	Cohort	Cohort
Database	OutcomeRea	IMPACT-HAP	CATSS	ARISE	SSC Database	APACHE IV	Not reported
Sample size calculation	Not reported	Not reported	Not reported	Not reported	Reported	Not reported	Not reported
Participants*							
Females; Males	631 (37); 1,061 (63)	145 (35); 271 (65)	3667 (42.3); 5003 (57.7)	562 (40.5); 825 (54)	365 (45); 449 (55)	13221 (47.3); 14714 (52.7)	130 (40); 197 (60)
Sociodemographics							
Age	69 (57-77); 65 (51-75)	62.4 (16.9); 55.7 (16.5)	62.8 (15.9) ; 62.3 (16.6)	62 (17.1); 63.5 (15.8)	66.2 (18); 66.3 (16.2)	Not reported §	68 (57-78); 64 (50-72)
Race	Not reported	Not reported		Not reported	284 (78.5); 370 (82.4)	Not reported §	Not reported
Caucasian							
African-American							
Latin							
Other/unknown							
Socioeconomic status	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Comorbidities						Not reported §	
Respiratory	123 (19.5); 266 (25)	37 (25.5); 54 (20.2)	Not reported	53 (8.3); 90 (9.5)	Not reported		20 (15.4); 27 (13.7)
Cardiac	71 (11.2); 123 (11.6)	32 (22.1); 58 (21.6)	(9.9) ; (11.2)	46 (7.2); 128 (13.5)	77 (21.1); 97 (21.6)		Not reported
Renal	19 (3); 29 (2.7)	31 (21.4); 45 (16.9)	Not reported	21 (3.3); 43 (4.5)	Not reported		24 (18.5); 37 (18.8)
Diabetes	Not reported	46 (31.7); 74 (27.6)	Not reported	27 (4.2); 58 (6.1)	Not reported		Not reported
Immunosuppression	119 (18.9); 207 (19.5)	60 (41.4); 101 (37.8)	(1.8) ; (3.3)	Not reported	Not reported		18 (13.8); 11 (5.6)
Liver disease	28 (4.4); 66 (6.2)	Not reported	(10) ; (16.9)	26 (4.1); 57 (6)	Not reported		8 (6.2); 17 (8.6)
Cancer	Not reported	Not reported	Not reported	87 (13.6); 161 (16.9)	Not reported		Not reported
Severity score							
APACHE II	19 (14-24); 19 (14-24)	22.1 (7.6); 19.9 (7.2)	25.9 (8.2) ; 25.5 (8.1)	48.1 (20.4); 50.2 (20.0) ‡	Not reported		Not reported
SAPS II	44 (33-58); 45 (34-60)	Not reported	Not reported	Not reported	Not reported		40 (29-53); 39 (28-51)
SOFA	6 (4-9); 6 (4-9)	Not reported	Not reported	3.7 (2.7); 4.2 (2.8)	6.2 (2.9); 7.2 (3.2)		5 (3-7); 6 (4-9)
Infection site							
Urinary source of infection	68 (10.8); 51 (4.8)	N/A	Not reported	138 (21.6); 170 (17.9)	Not reported	Not reported §	31 (23.8); 14 (7.1)
Prognosis factor							
Independent variable	Gender	Gender	Gender	Gender	Gender	Gender	Gender
Sex/ gender definition	Not reported	Not reported	Not reported	Reported	Not reported	Not reported	Not reported
Terms used	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, female, male	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men
Appropriateness of terms use	Inadequate	Inadequate	Inadequate	Unclear	Inadequate	Inadequate	Inadequate

Extracted outcomes							
Primary outcomes							
All-cause hospital mortality	Yes	Yes	Yes	No	Yes	No	No
28-day all-cause mortality	No	Yes	No	No	No	No	No
Secondary outcomes							
7-day all-cause hospital mortality	No	No	No	No	No	No	No
1-year all-cause mortality	No	No	No	No	No	No	No
All-cause ICU mortality	Yes	No	Yes	Yes	No	Yes	Yes
Follow-up	Not reported	Hospital discharge, death or 28 days after penumonia diagnosis, whichever ocurred first	Not reported	Not reported	Not reported	Not reported	Not reported
Identification							
Country	France	United States	Canada, United States, Saudi Arabia	Australia, New Zealand, Finland, Hong Kong, Ireland	United States	United States	Germany
Funding source	Educational grants from Aventis Pharma, France, and Wyeth; and public funds	Pfizer. University of Lousville Foundation responsible for project oversight	Unrestricted grants from Eli-Lilly, Pfizer, Bayer, Astellas, Merck, Mantioba Research Council, Health Sciences Centre Foundation, Innovations and Opportunities Foundation, Deacon Foundation	National Health and Medical Research Council	Alpert Medical School of Brown University	Not reported	Not reported
Conflict of interest	None	Declared	Declared	Declared	Not reported	None	Declared
Identifier or protocol	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Notes	Authors used conditional logistic regression with matching on age, death propensity score, and center. Email sent to study authors in May 2020; no reply received.	28-day mortality reported, authors were contacted for clarification in May 2020; no reply received.	Email sent to study authors in March 2020; no reply received	Baseline data available only for main cohort (N=1,591 participants). Email sent to study authors in May 2020; reply received but we were unable to get additional data.	Email sent to study authors in May 2020; no reply received.	Baseline data available only for main cohort (N=261,255 participants) Email sent to study authors in June 2020; no reply received.	Email sent to study authors in May 2020; no reply received.

Continued

	Pietropaoli 2010	Sakr 2013	Samuelsson 2015	Sunden-Cullberg 2020	van Vught 2017	Xu 2019
Methods						
Study design	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort
Database	Cerner Project IMPACT	Piademont Intensive Care Unit Network	SIR	NQSR and SIR	MARS	MIMIC-III
Sample size calculation	Reported	Not reported	Not reported	Not reported	Not reported	Not reported
Participants*						
Females; Males	8,702 (46); 10,055 (54)	85 (27.9); 220 (72.1)	Not reported §	1,210 (44.5); 1,510 (55.5)	595 (38.8); 938 (61.2)	2,677 (43.6); 3,457 (56.4)
Sociodemographics						
Age	68 (54-75); 65 (52-76)	67.7 (14.3); 63.1 (15)	Not reported §	68 (56–77); 68(58–77)	59.4 (16.2); 60.8 (14.8)	65-89 (50.4); 65-89 (51.1)‖
Race		Not reported	Not reported §	Not reported		
Caucasian	6,439 (74); 7,541 (75)				510 (85.7); 839 (89.4)	1,915 (71.5); 2,597 (75.1)
African-American	1,218 (14); 1,207 (12)					369 (13.8);273 (7.9)
Latin	435 (5); 603 (6)					70 (2.6); 143 (4.1)
Other/unknown	610 (7); 704 (7)					238 (8.9); 325 (9.4)
Socioeconomic status	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Comorbidities			Not reported §	Not reported		Not reported
Respiratory	870 (10); 1005 (10)	3 (3.5); 18 (8.2)			72 (12.1); 138 (14.7)	
Cardiac	522 (6); 704 (7)	8 (9.4); 17 (7.7)			131 (22); 232 (24.7)	
Renal	522 (6); 603 (6)	16 (18.8); 40 (18.2)			86 (14.5); 131 (14)	
Diabetes	Not reported	18 (21.2); 34 (15.5)			124 (20.8); 183 (19.5)	
Immunosuppression	1,131 (13); 1,307 (13)	Not reported			Not reported	
Liver disease	261 (3); 402 (4)	Not reported			Not reported	
Cancer	1,218 (14); 1,709 (17)	4 (4.7); 6 (2.7)			136 (22.9); 245 (26.1)	
Severity score						
APACHE II	21 (15-27); 21 (15-27)	Not reported		Not reported	79 (62-99); 76 (58-98)†	Not reported
SAPS II	35 (15-64); 33 (14-64)	55 (18.8); 55.3(17.5)		64 (55–73); 65 (56–75)¶	Not reported	21.39 (5.73); 21.06 (5.6)
SOFA	Not reported	9.1 (3.3); 9.8 (3.7)		Not reported	7 (5-9); 7 (4-9)	6.97 (3.52); 7.29 (3.75)
Infection site						
Urinary source of infection	2,698 (31); 1,910 (19)	5 (5.9); 13 (5.9)	Not reported §	258 (21.3); 301(19.9)	Not reported	Not reported
Prognosis factor						
Independent variable	Gender	Gender	Gender/Sex	Sex	Gender	Sex
Sex/ gender definition	Reported	Not reported	Not reported	Reported	Not reported	Not reported
Terms used	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men	Gender, sex, female, male, woman/men, man/men
Appropriateness of terms use	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Extracted outcomes						
Primary outcomes						
All-cause hospital mortality	Yes	No	No	No	Yes	Yes

28-day all-cause mortality	No	Yes	Yes	Yes	Yes	Yes
Secondary outcomes						
7-day all-cause hospital mortality	No	No	No	No	No	No
1-year all-cause mortality	No	No	No	No	Yes	Yes
All-cause ICU mortality	Yes	Yes	No	No	Yes	No
Follow-up	Not stated	Death or ICU discharge	30 days	30 days	1 year	1 year
Identification						
Country	Brazil, Canada, US	Italy	Sweden	Sweden	Netherlands	United States
Funding source	National Heart, Lung and Blood Institute	Regione Piamonte, *progetti finalizzati di ricerca*	Regional Health Care Authorities in the Halland and Skåne regions of Sweden	Karolinska Institute, Swedish Government Funds for Clinical Research	Center for Translational Molecular Medicine, project MARS	Guangzhou Science and Technology Programs, the Guangdong Provincial Key Laboratory Construction Projection on Organ and Transplant Immunology, and the Guangdong Provincial International Cooperation Base of Science and Technology
Conflict of interest	None	None	None	None	Declared	None
Identifier or protocol	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Notes	Email sent to study authors in April 2020; no reply received.	ICU mortality mismatched published data, authors were contacted for clarification in April 2020; reply received. 28-day mortality reported, authors were contacted again for clarification in May 2020; no reply received.	30-day mortality reported, authors were contacted for clarification in June 2020; reply received (outcome included 30-day in- and out-hospital mortality). Sepsis subgroup comparison was adjusted at P<0.001.	30-day mortality reported, authors were contacted for clarification in June 2020; no reply received.	30-day mortality reported, authors were contacted for clarification in May 2020; no reply received.	Cox analyes reported as OR without additional clarification, and 30-day mortality reported, authors were contacted for clarification in July 2020; no reply received.

*Categorical variables expressed as numerical values and percentages, and continuous variables expressed as median and IQR, or mean and standard deviation as the study may be.

† APACHE IV

‡ APACHE III

§ Participant characteristics only available for whole ICU cohort

¶ SAPS III

|| Age reported by the study authors as percentage of participants in different age groups. Age expressed as age group (percentage).

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation; ARISE: Australasian resuscitation in sepsis evaluation; CATSS: Cooperative antimicrobial therapy of septic shock; ICU: Intensive care unit; IMPACT: abbreviation not detailed; IMPACT- HAP: Improving medicine through pathway assessment of critical therapy in hospital-acquired pneumonia; F: Females; M: Males; MARS: Molecular diagnosis and risk stratification of sepsis; MIMIC: Medical information mart for intensive care III; N/A: Not applicable; NQSR: National quality sepsis registry; SAPS: Simplified Acute Physiology Score; SIR: Swedish intensive care registry; SOFA: Sequential Organ Failure Assessment score; SSC: Surviving sepsis campaign.

Supplemental Table 7. Sepsis definition provided by the study authors

Study	Sepsis-related term for defining health condition	Operational definition
Adrie 2007*	Sepsis severe	Severe sepsis was defined as infection with two or more criteria for systemic inflammatory response syndrome and at least one criterion for organ dysfunction
Caceres 2013	Severe infection, hospital-acquired pneumonia	Severe infection was defined as hospital-acquired pneumonia, including ventilator-associated pneumonia and health-care associated pneumonia
Dara 2012	Sepsis shock	Non-provided
Luethi 2010	Septic shock	Septic shock was defined as two or more criteria for systemic inflammatory response syndrome and refractory hypotension (systolic blood pressure of b90 mmHg or a mean arterial pressure of 65 mmHg after an intravenous fluid challenge), or hyperlactatemia (blood lactate level of ≥4.0 mmol/L), or both.
Madsen 2014	Severe sepsis and septic shock	Severe sepsis or septic shock as defined by Surviving Sepsis Campaign.
Mahmood 2012	Sepsis	Non-provided
Nachtigall 2011	Sepsis	Sepsis, severe sepsis, and septic shock was defined according to the national and international sepsis guidelines, requering two or more criteria for systemic inflammatory response syndrome associated with an infection
Pietropaoli 2010	Severe sepsis and septic shock	Severe sepsis was defined as development of at least one severe acute organ dysfunction within 3 days of a presumed infection.
Sakr 2013	Severe sepsis	Sepsis syndromes were diagnosed according to the criteria proposed by the American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference [Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion, or hypotension]
Samuelsson 2015	Sepsis	Non-provided
Sunden-Cullberg 2020	Severe sepsis and septic shock	Severe sepsis and septic shock were diagnosed using a modified version of the 1992 sepsis definition, in practice accepting a diagnosis of severe sepsis on the basis of infection plus organ dysfunction
van Vught 2017†	Sepsis	Sepsis was defined as an infection diagnosed with a "probable" or "definite" likelihood, plus at least one additional variable as described in the 2001 International Sepsis Definitions. Shock was defined by the use of vasopressors.
Xu 2019‡	Sepsis, severe sepsis and shock septic	Non-provided

Supplemental Table 8. Prognostic factors in adjusted models for mortality in included studies

Study	Prognostic factors included in adjusted analyses
Adrie 2007*	Chronic respiratory failure; metastatic cancer; immunocompromised status; emergency surgery; acute respiratory failure and shock at hospital admission; urinary tract infection as a cause of sepsis; type of microorganism (*E coli, S pneumoniae*, and *Enterobacter* species)
Caceres 2013	Age; APACHE II; HCAP; white race; history of cardiac/renal/vascular/diabetes/respiratory disease; severe sepsis; hospital LOS; ICU LOS; MV after diagnosis of MRSA; CPIS at baseline
Dara 2012	APACHE II; age; site of infection; source of admission ; inappropriate antibiotics; other variables related to organ dysfunction
Luethi 2010	Illness severity (APACHE III score); pre-existing comorbidities (Charlson comorbidity index); cardiac arrhythmia; intravenous resuscitation fluid (per kilogram) administered before ICU admission
Madsen 2014	Age; race; SOFA; CHF; coagulopathy
Mahmood 2012	Acute physiology score; age; ethnicity; pre-ICU length of stay; pre-ICU location and hospital teaching status
Nachtigall 2011	Age; TISS-28 on admission (nursing workload); occurrence of pneumonia; septic shock; fungi detected; septic shock
Pietropaoli 2010	Age; dependent functional status at admission; African-American race; type of admittance; medical versus surgical patient; type of insurance; CPR within 24h of admission; comorbidities (chronic liver disease, active cancer within 5 years, chronic cardiovascular disease, chronic respiratory disease, immunocompromised status); illness severity (neurological dysfunction, cardiovascular dysfunction, elevated serum lactate, acute renal failure, hepatic dysfunction, hematologic dysfunction; SAPS II score); source of infection; processes of care; hospital characteristics
Sakr 2013	Age; comorbidities (renal failure with dialysis, chronic obstructive pulmonary disease); SAPS II; type of admission (elective surgery, emergency surgery, medical admission); initial SOFA sub-scores; referring facility; source of infection (abdominal)
Samuelsson 2015	Age; comorbidity (scored as in the Simplified Acute Physiology III); hospital LOS in days; location prior to ICU admission; therapy prior to ICU admission; reason for ICU admission; surgical status; presence of nosocomial or lower-airway infection; physiologic derangement (scored as in the Simplified Acute Physiology III); hospital characteristics
Sunden-Cullberg 2020	Temperature-adjusted SAPS3; body temperature; incorrect antibiotics; treatment limitations
van Vught 2017†	Age; body mass index; comorbidity; source of infection; acute physiology score
Xu 2019‡	Age; race; first ICU service; marital status; insurance; admission location; SAPS; SOFA

* Adrie 2007 reported adjusted analyses using a conditional logistic regression after matching on age, death propensity score, and centre.

† van Vught 2017 reported adjusted analyses only for 90-day mortality.

‡ Xu 2019 reported adjusted analyses using a Cox proportional hazard regression model.

Abbreviations: APACHE: Acute Physiology and Chronic Health Evaluation; CHF: Congestive heart failure; CPIS: Clinical Pulmonary Infection Score; CPR: Cardiopulmonary resuscitation; HCAP: Health care-associated pneumonia; ICU: Intensive care unit; MRSA: methicillin-resistant *Staphylococcus aereus;* MV: Mechanical ventilation; LOS: Length of stay; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment score; TISS-28: Therapeutic Intervention Scoring System-28.

Supplemental Table 9. Summary outcome estimates for each included study

Study	Unadjusted OR, 95%CI*				Adjusted OR, 95%CI*			
	Hospital mortality	28-day mortality	1-year mortality	ICU mortality	Hospital mortality	28-day mortality	1-year mortality	ICU mortality
Adrie 2007	0.88 (0.71-1.10)	N/A	N/A	0.87 (0.69-1.09)	0.75 (0.57-0.97)	N/A	N/A	0.75 (0.58-0.98)
Caceres 2013	1.35 (0.81-2.26)	1.35 (0.81-2.26)	N/A	N/A	0.99 (0.52-1.93)	0.99 (0.52-1.93)	N/A	N/A
Dara 2012	0.95 (0.87-1.04)	N/A	N/A	N/A	1.07 (0.96-1.19)	N/A	N/A	N/A
Luethi 2010	N/A	N/A	N/A	1.14 (0.82-1.58)	N/A	N/A	N/A	<50y: 1.18 (0.47-2.86) >50y: 1.33 (0.90-1.96)
Madsen 2014	1.10 (0.80-1.52)	N/A	N/A	N/A	"Multivariable analysis…Gender was not associated with in-hospital survival"	N/A	N/A	N/A
Mahmood 2012	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.07 (0.99-1.16)
Nachtigall 2011	N/A	N/A	N/A	1.89 (1.06-3.36)	N/A	N/A	N/A	1.91 (1.00-3.64)
Pietropaoli 2010	1.09 (1.02-1.16)	N/A	N/A	1.09 (1.02-1.17)	1.11 (1.04-1.19)	N/A	N/A	N/A
Sakr 2013	N/A	"Kaplan-Meier analysis showed reduced 28-day survival in female compared with male patients"	N/A	2.01 (1.20-3.37)	N/A	N/A	N/A	2.23 (1.17-4.24)

Samuelsson 2015	N/A	N/A	N/A	N/A	N/A	1.17 (1.06-1.29)†	N/A	N/A
Sunden-Cullberg 2020	N/A	1.11 (0.91-1.36)	N/A	N/A	N/A	1.28 (1.00-1.64)	N/A	N/A
van Vught 2017‡	1.02 (0.81-1.27)	1.13 (0.90-1.43)	0.92 (0.74-1.13)	1.14 (0.89-1.45)	N/A	N/A	N/A	N/A
Xu 2019	0.89 (0.80-0.99)	0.91 (0.82-1.01)	0.84 (0.76-0.93)	N/A	N/A	N/A	0.83 (0.68-0.98)§	N/A

***** Prognostic effect reported as OR (95% CI).

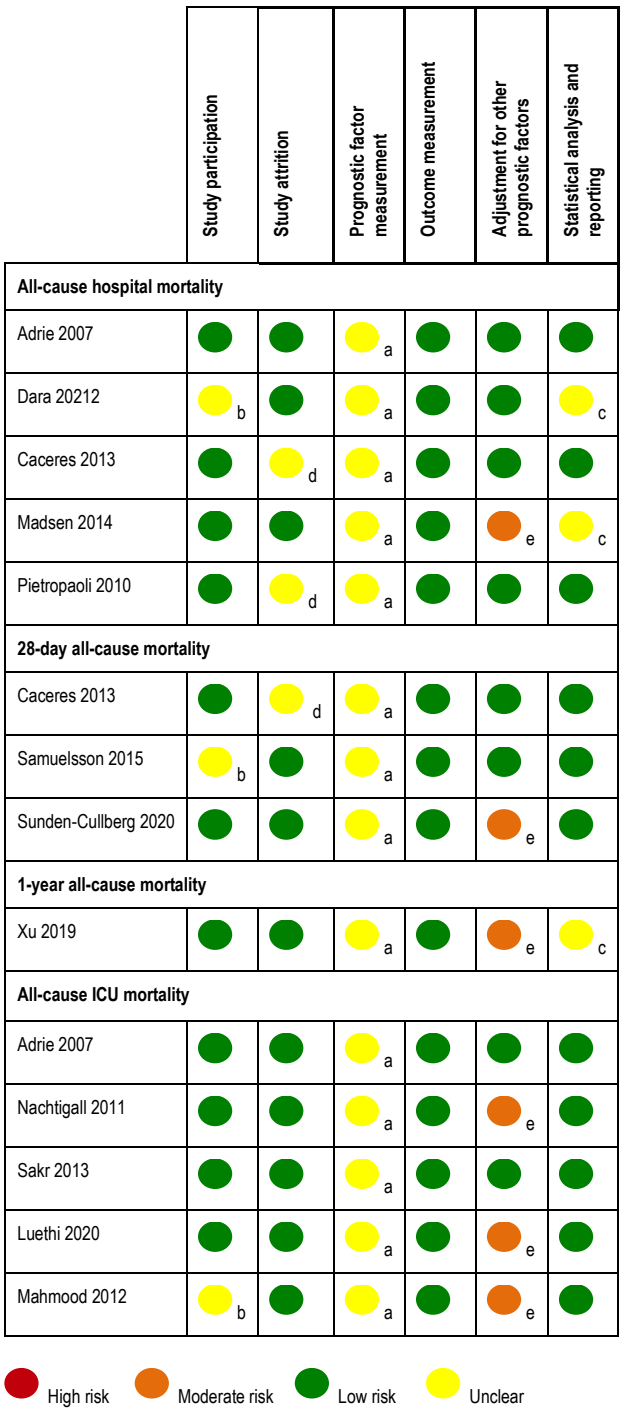
† Prognostic effect reported by the study authors as OR (99% CI), 1.17 (1.03- 1.33). We transformed it into OR (95% CI).

‡ van Vught 2017 reported adjusted analyses only for 90-day mortality.

§ Xu 2019 reported adjusted analyses using a Cox proportional hazard regression model as OR (95% CI), 1.08 (1.01-1.17), without additional clarifications. After contacting the study authors and no reply received, we assumed that they reported Cox analyses as hazard ratios (HR). We transformed HR into OR (95% CI)

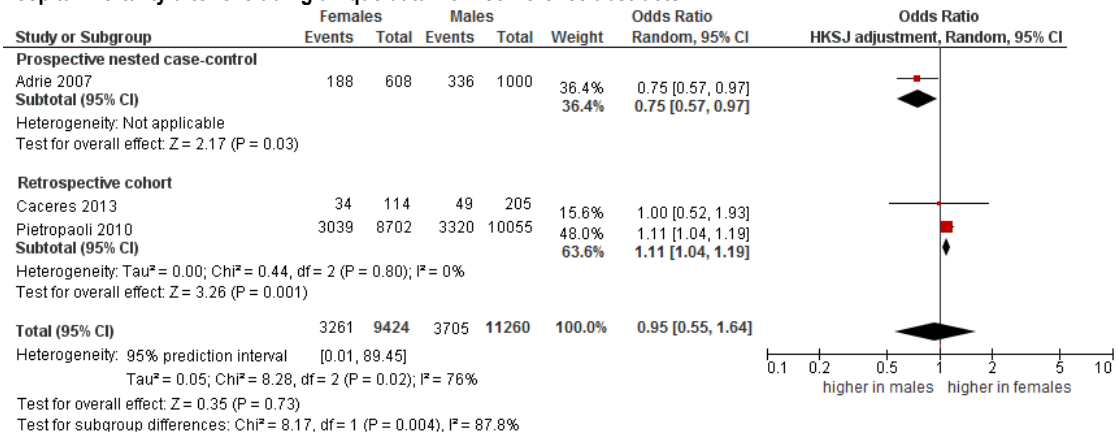
Abbreviations: CI: Confidence interval; N/A: Not available; OR: Odds ratio; Y: Years old.

Supplemental Figure 1. QUIPS Risk of bias domain summary by outcome

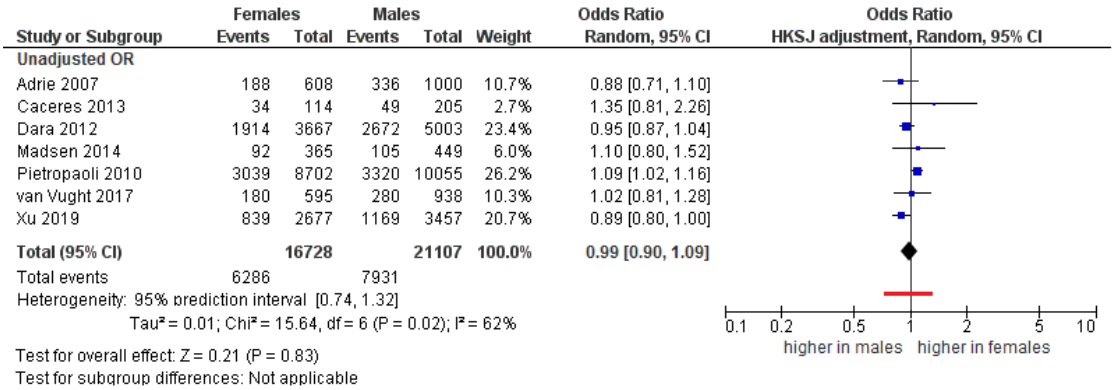


Explanations:
a. Unclear or not stated a definition of sex or gender.
b. Insufficient data on baseline description for sepsis subgroup.
c. Insufficient presentation of data to assess the adequacy of the analytic strategy.
d. Inadequate description of dropouts to judge the risk of important differences between participants analysed and those who were not.
e. Minimal adjustment for covariates as defined in our review core set of adjustment factors.

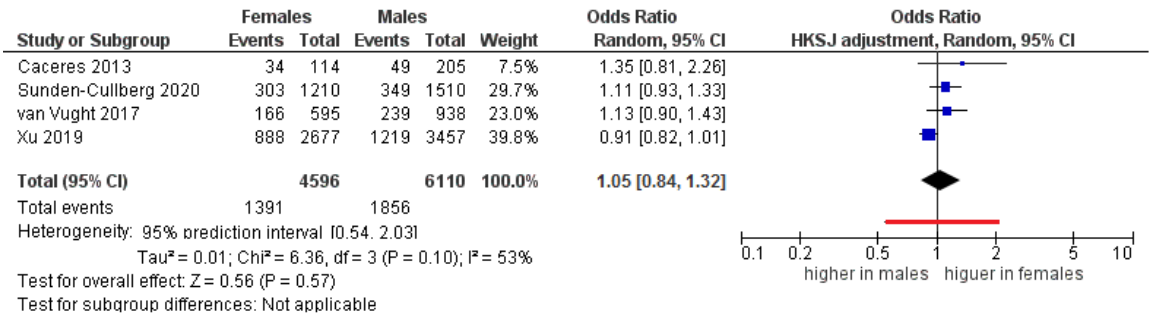
Supplemental Figure 2. Sensitivity analysis of adjusted analyses for association between sex and all-cause hospital mortality after excluding unique data from conference abstracts



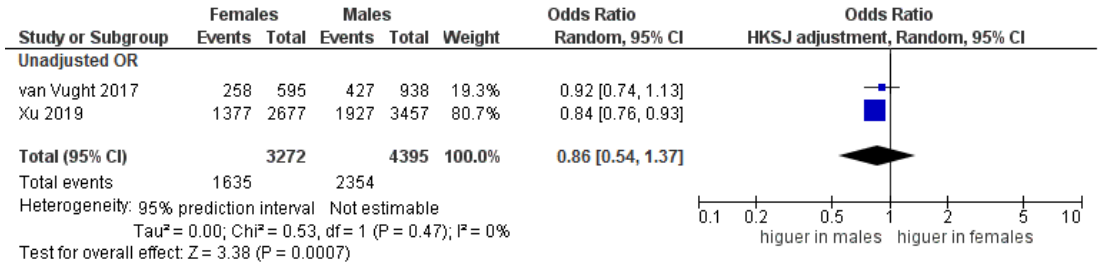
Supplemental Figure 3. Forest plot of unadjusted analyses for association between sex and all-cause hospital mortality



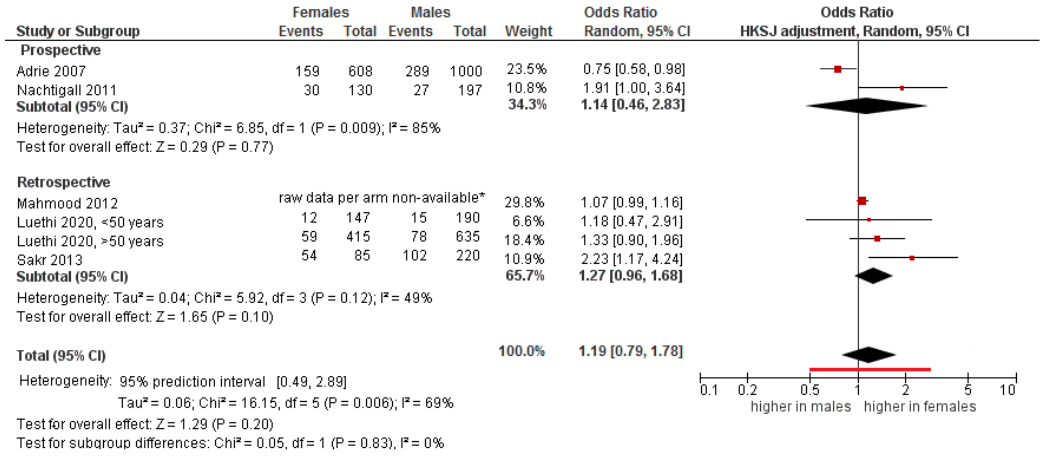
Supplemental Figure 4. Forest plot of unadjusted analyses for association between sex and 28-day all-cause mortality



Supplemental Figure 5. Forest plot of unadjusted analyses for association between sex and 1-year all-cause mortality

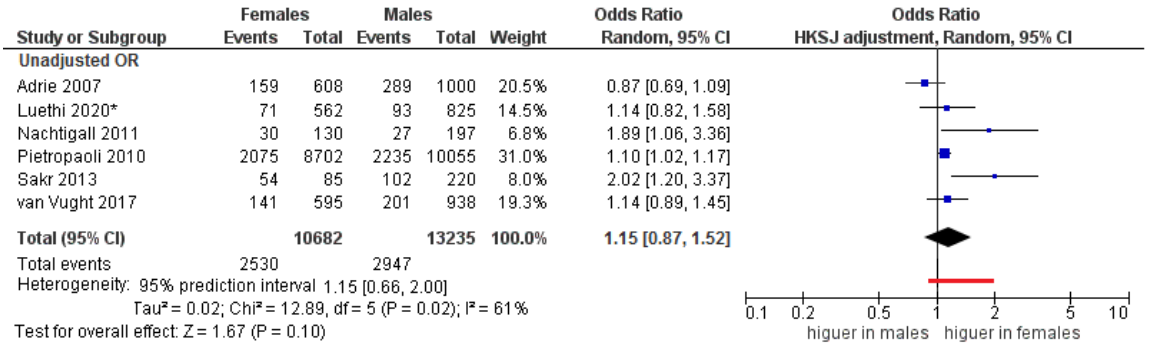


Supplemental Figure 6. Forest plot of adjusted analyses for association between sex and all-cause ICU mortality



* only provided the adjusted estimate

Supplemental Figure 7. Forest plot of unadjusted analyses for association between sex and all-cause ICU mortality



* Luethi 2020 reported an overall unadjusted odds ratio.