BMJ Open

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

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To cite: Antequera A, Lopez-Alcalde J, Stallings E, *et al*. Sex as a prognostic factor for mortality in critically ill adults with sepsis: a systematic review and meta-analysis. *BMJ Open* 2021;**11**:e048982. doi:10.1136/bmjopen-2021-048982

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-048982).

Received 13 January 2021
Accepted 30 July 2021

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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.

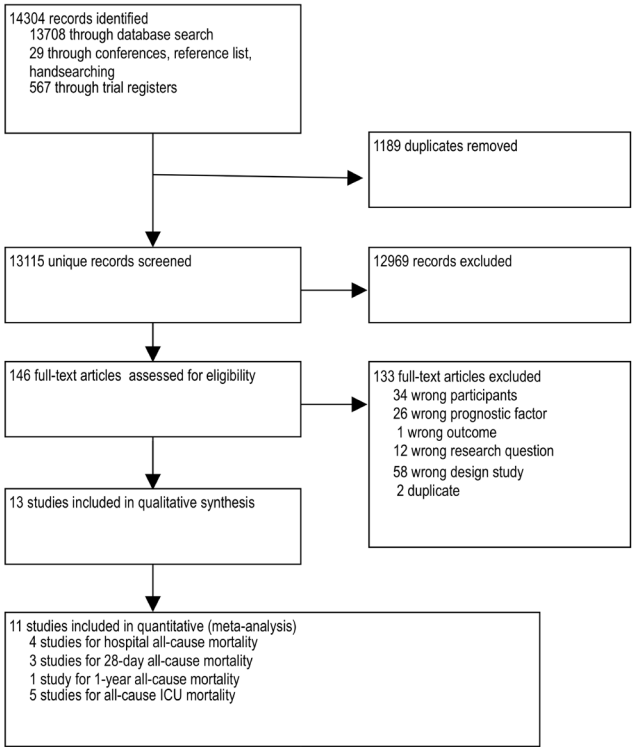

Figure 1 Flow diagram. ICU, intensive care unit.

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,

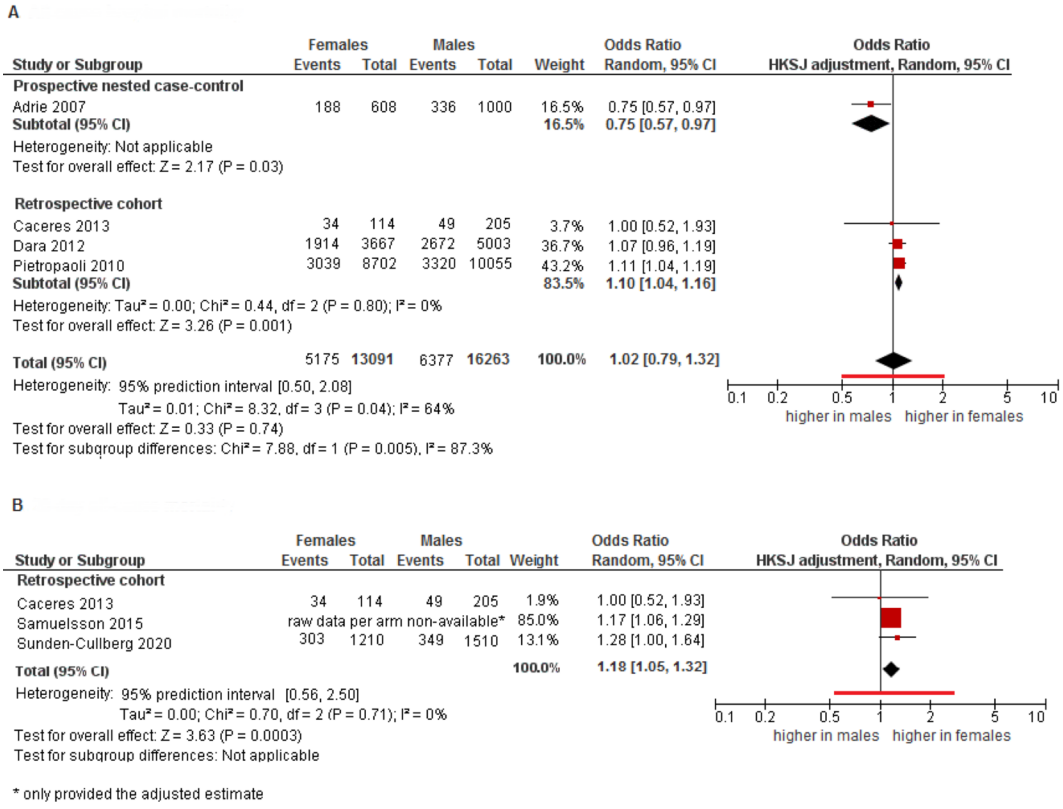

Figure 2 Forest plots of adjusted analyses for association between sex and all-cause hospital mortality (A) and 28-day all-cause mortality (B). HKSJ, Hartung-Knapp-Sidik-Jonkman.

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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Acknowledgements The authors thank colleagues contacted by email who provided further information regarding studies: Carolina Samuelsson (Skåne University Hospital and Halland Hospital, Sweden), Haibo Qui (Zhongda Hospital, Southeast University, China), Nora Luethi (Australian and New Zealand Intensive Care Research Centre, Monash University, Australia), and Yasser Sakr (Friedrich-Schiller University, Germany). The authors gratefully acknowledge the collaboration of Miriam Mateos on extracting declaration of interest of included studies. The authors gratefully acknowledge Professor Khalid S. Khan (Distinguished Investigator at the University of Granada, Spain) for his support and advice on the manuscript. Furthermore, the authors thank the Networking Biomedical Research Centre (CIBER) for its support. Lastly, the authors thank Dr Elizabeth Wilcox, Dr TM Scalea, Dr Bruno Besen for their insightful comments to improve the clarity of this manuscript during the peer-review process.

Contributors JL-A, JZ and AA conceived the systematic review. AA coordinated the systematic review. AA, JL-A, ES, JZ, and IS designed the systematic review. JL-A, NÁ-D, AA, and IS designed the search strategy. AA, ES, BFF, AVH, MP-A, PF, RdC, OM-P, AM, JZ and JL-A screened abstracts and full texts. AA, ES and OM-P extracted data and assessed. AA, JL-A, ES, AM and BFF elaborated the analysis plan. AA performed the statistical analyses. JL-A and AA conducted the GRADE assessment. AA, AVH, FG, PF, MP-A, RdC and OM-P provided clinical perspective. JL-A, AA, AM, IS, JZ, ES and GU provided methodological perspective. AA drafted the first version of the manuscript. All authors had the opportunity to read approved the final manuscript. JZ, JL-A and GU secured funding for the systematic review. AA is the guarantor. AA is a doctoral candidate in Methodology of Biomedical Research and Public Health, at the Department of Pediatrics, Obstetrics, Gynaecology and Preventive Medicine at Universitat Autònoma de Barcelona (Spain) and this work is part of her PhD.

Funding The SEXCOMPLEX project was supported by Instituto de Salud Carlos III (Plan Estatal de I+D + i 2013–2016) and cofinanced by the European Development Regional Fund 'A way to achieve Europe' (ERDF) grant number PIE16/00050. AA was funded by the Instituto de Salud Carlos III through the 'Acción Estratégica en Salud 2013–2016/Contratos Río Hortega call 2018/ CM18/00141' (Co-funded by European Social Fund 2014–2020, 'Investing in your future'). MP-A is also the recipient of a Río Hortega Contract (CM19/00069). CIBERESP funded BF-F.

Disclaimer These funding sources had no role in the design of this review, its execution, analyses, interpretation of the data, or decision to submit results.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The authors adhered to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines. Ethical committee approval and patient consent for publication were not required for this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. The study protocol is available online at http://dx.doi.org/10.1136/bmjopen-2019-035927 and PROSPERO CRD42019145054. Included studies are publicly available, main data supporting the conclusions of this systematic review are included in the article and supplemental material.

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