

Evaluation of the role of sex as a prognostic factor in critically ill adults with sepsis: a systematic review and meta-analysis

Alba Antequera (✉ alba.antequera.martin@gmail.com)

Fundacio Institut de Recerca Hospital de la Santa Creu i Sant Pau: Hospital de la Santa Creu i Sant Pau
Institut de Recerca <https://orcid.org/0000-0002-1670-6302>

Jesús López-Alcalde

Faculty of Health Sciences, Universidad Francisco Vitoria. Clinical Biostatistics Unit, Instituto Ramón y Cajal de Investigación Sanitaria. CIBER Epidemiología y Salud Pública (CIBERESP). Institute for Complementary and Integrative Medicine, University Hospital Zurich and University Zurich,

Elena Stallings

Clinical Biostatistics Unit, Instituto Ramón y Cajal de Investigación Sanitaria. CIBER Epidemiología y Salud Pública (CIBERESP)

Alfonso Muriel

University of Leon Nursing and Physiotherapy Department: Universidad de Leon Departamento de Enfermería y Fisioterapia

Borja Manuel Fernández-Félix

Clinical Biostatistics Unit, Instituto Ramón y Cajal de Investigación Sanitaria. CIBER Epidemiología y Salud Pública (CIBERESP)

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Department of Microbiology, Hospital Universitario Ramón y Cajal

Pilar Fidalgo

Universidad Francisco de Vitoria

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Ivan Solà

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Federico Gordo

Faculty of Health Sciences, Universidad Francisco Vitoria. Department of Intensive Care, Hospital Universitario del Henares

Gerard Urrútia

Iberoamerican Cochrane Centre, Biomedical Research Institute Sant Pau, Hospital de la Santa Creu i Sant Pau. CIBER Epidemiología y Salud Pública (CIBERESP)

Javier Zamora

Clinical Biostatistic Unit, Instituto Ramón y Cajal de Investigación Sanitaria. CIBER Epidemiología y Salud Pública (CIBERESP). Women's Health Research Unit, Queen Mary University of London (UK)

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Abstract

Background: Incidence and sepsis-related mortality are failing, but sepsis continues to be a leading cause of admission and death in intensive care units (ICUs). Although the preceding evidence suggests sex-related risk differences for developing sepsis, the influence of sex on mortality outcomes remains unclear as previous studies showed discordant results. This systematic review assessed the independent effect of sex for mortality among critically ill patients with sepsis.

Methods: Electronic databases were searched up to 17th July 2020 for studies that examined independent associations between sex and mortality outcomes in critically ill adults with sepsis while controlling for covariates. Primary meta-analyses were performed by pooling adjusted estimates for a pre-specified core set of adjustment factors. The primary outcomes included all-cause hospital mortality and 28-day all-cause hospital mortality. The secondary outcomes included 7-day all-cause hospital mortality, 1-year all-cause mortality, and all-cause ICU mortality.

Results: Among the 14304 records identified, 12 studies (71850 participants) were included. Meta-analysis showed inconclusive results on sex-based differences in hospital mortality (OR 0.95, 95% CI 0.55 to 1.64; very low-certainty evidence) and ICU mortality (OR 1.19, 95% CI 0.79 to 1.78; very low-certainty evidence). Meta-analysis found higher 28-day hospital mortality in the female group (OR 1.18, 95% CI 1.05 to 1.32; very low-certainty evidence). No studies reported on 7-day hospital mortality. A single study provided adjusted estimates on 1-year mortality reporting lower risk in the female group (OR 0.83 95% CI 0.68 to 0.98; low-certainty of evidence). The main reasons for assessing the certainty of evidence as very low were inconsistency and imprecision while downgrading to low-certainty was risk of bias and imprecision.

Conclusions: The prognostic independent effect of sex on hospital mortality, 28-day hospital mortality, and ICU mortality for critically ill adults with sepsis is uncertain. Female sex may be associated with decreased 1-year mortality. No included studies reported on 7-day all-cause hospital mortality.

Background

Sepsis is a life-threatening organ dysfunction produced by a dysregulated host response to inflammation [1]. Sepsis, accounting for one of year five deaths worldwide and leading cause of death in intensive care units (ICUs), remains to be a global health problem [2–4]. Sepsis is a heterogeneous illness affecting both male and female individuals [5]. Prior evidence suggests sex-related risk differences for developing sepsis. However, the prognostic effect of sex on sepsis outcomes remains uncertain, as previous studies reported inconsistent findings [6–8].

Research on prognostic factors pretends to identify factors, including patient characteristics such as sex, associated with clinical outcomes in people with a particular condition [9]. To determine the role of sex as a prognostic factor in patients with sepsis may help to stratify these patients according to different risk profiles and contribute to reducing morbidity and mortality. Likewise, to define the prognostic effect of

sex may support the decision-making process in clinical settings for which the benefit-risk balance of an intervention is unclear. For example, open-ended questions remained about whether buffered solutions reduce acute kidney injury or the prophylactic use of low-molecular-weight heparin in patients with renal failure [10, 11]. Furthermore, combining independent prognostic factors within a prognostic model may help to tailor to the goal of reducing morbidity and mortality [9]. 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 a peer-reviewed journal [12]. Supplementary Table 1 (Additional File 1) details the differences between the protocol and the review. We reported this study according to the PRISMA statement [13].

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 while controlling for covariates (called phase 2 studies) [14]. 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 [15]. We accepted any assessment of sex as a biological characteristic, which, when applicable, we also appraised operational concepts of sex and gender provided by the study authors using the classification detailed in Supplementary Table 2 (Additional File 1) [16]. We pre-specified the following core set of adjustment factors: age, severity score [Sequential Organ Failure Assessment score (SOFA), Simplified Acute Physiology Score II (SAPS II) or Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II)], comorbidities (immunosuppression, pulmonary diseases, cancer, liver diseases, or alcohol dependence), non-urinary source of infection, and inappropriate or late antibiotic coverage. The primary outcomes were all-cause hospital mortality (the longest follow-up provided by the study authors) and 28-day all-cause hospital mortality. Secondary outcomes were 7-day all-cause hospital mortality, 1-year all-cause mortality, and all-cause ICU mortality.

Search Strategy And Selection Process

We searched MEDLINE Ovid, Embase Elsevier, and Web of Science for studies published any time up to 17th July 2020. We based the search string on terms related to the population (sepsis), the outcome (mortality), prognostic study methods [17], as well as the prognostic factor (sex) for which we used a search string adapted from previous studies [18–21]. We applied no language restrictions. We checked the bibliographic references of the key publications and the included studies for additional relevant studies. We also searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform for unpublished and ongoing studies. Furthermore, we handsearched conference

proceedings from 2010 to 2019 of the foremost critical care and infectious diseases symposia (See Supplementary Table 3, Additional File 1).

We used the online software EPPI-Reviewer 4 to manage the study selection process [22]. Pairs of review authors (from AA, AVH, MP-A, OMP, RdC, PF) 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 (from AM, BF-F, JL-A, JZ) if disagreement remained.

Data Collection And Risk Of Bias Assessment

Two authors (from AA, ES, OMP) independently extracted data and reached consensus using electronic extraction templates in EPPI-Reviewer 4. We used the CHARMS-PF (checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies for prognostic factors) guidance for data collection [23]. For each included study, we extracted the following data: general study characteristics, participant characteristics, sepsis definition, prognostic factor, outcomes assessed, missing data, analysis, and all unadjusted and adjusted estimates of the association between the prognostic factor and each review outcome, with details on any covariate used for adjusted ones. If a study provided several estimates for the same outcome, each of them adjusted for different covariates, we extracted the estimate adjusted for the maximum number of covariates from the core of adjustment factors. We contacted the study authors for clarification. Two authors (from AA, ES, OMP) independently assessed the risk of bias of the included studies, agreed on ratings, and a third author (JL-A) participated when required. We applied an outcome-level approach and amended the QUIPS (quality in prognosis studies) tool using four categories (low, moderate, high, or unclear risk) [23–25]. 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 [26]. 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 [24].

Data Synthesis

For each study and prognostic factor estimate, we extracted the measures of associations alongside its confidence intervals (CIs). We transformed association measures into an odds ratio (OR) with its 95% CIs to allow statistical pooling whenever adequate [27]. We estimated no data from Kaplan-Meier curves because of the risk of overestimation of events and censorship concerns [28]. 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 evaluated the censoring mechanisms assumed in the studies that have been analysed using time-to-event procedures (i.e., Cox proportional hazard models). We performed random-effects meta-analyses applying the Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment [29], using RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and the template for conversion provided by IntHout [30].

We examined heterogeneity computing prediction intervals when the meta-analysis contained at least three studies [29, 31]. We planned to undertake subgroup analyses based on study design characteristics: cohort studies versus case-control studies, and prospective studies versus retrospective studies. We foresaw to compare differences between subgroups by performing a test of interaction [32].

We conducted sensitivity analyses accounting for the risk of bias. We considered the following QUIPS domains as key domains for the analyses: study attrition, prognostic factor measurement, outcome measurement, and adjustment for other prognostic factors. Firstly, we planned to exclude studies with a high risk of bias in at least one key domain. Secondly, we excluded studies with either a high or moderate risk of bias in at least one key domain. In other sensitivity analyses, we foresaw to exclude studies that adjusted for a set of adjustment factors entirely different from ours. Additionally, we explored potential differences between meta-analyses based on unadjusted (crude) and adjusted estimates.

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 [33].

Assessing The Certainty Of The Evidence

We assessed the certainty of the evidence using the GRADE (grading of recommendations assessment, development, and evaluation) approach and guidance for prognosis studies (See Supplementary Table 4, Additional File 1) [26, 34–39]. We summarised our results for each outcome in a “Summary of findings” table using the GRADEpro GDT software [37]. We described results for prognostic effect estimate considering the certainty of the 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 on an absolute risk difference of at least $\pm 10\%$ as clinically important difference.

Results

Studies research and characteristics

Our searches threw a total of 14304 records. After removing duplicates, we screened 13115 titles and abstracts and identified 146 full texts for further examination. Out of these studies, two are awaiting classification [40, 41], and another one is ongoing [42] (See Supplementary Tables 5 and 6, Additional File 1, respectively). Finally, the review included 12 studies [43–54] (Fig. 1).

The included studies involved a total of 7850 adult participants (45.67% females). Table 1 and Supplementary Table 7 (Additional File 1) display their characteristics.

Table 1: Characteristics of included studies

| Study | Study dates | Study design | Sites | Population | Primary outcome |
|-----------------------------|---------------------------------|--|-----------------|---|--|
| Adrie 2007 | 1997-2005 | Prospective nested case-control | 12 | Adults admitted to the ICU for severe community-acquired sepsis | ICU mortality Post-ICU mortality |
| Caceres 2013 | 2006-2007 | Retrospective cohort | 4 | Adults admitted to the ICU for hospital-acquired pneumonia | All-cause mortality |
| Luethi 2010 | 2008-2014 | <i>Post-hoc</i> analysis of a RCT | 51 | Adults presented to the ED with septic shock. Data were available for ICU setting | 90-day all-cause illness severity-adjusted mortality |
| Madsen 2014 | 2005-2012 | Retrospective cohort | 1 | Adults admitted to the ICU for severe sepsis or septic shock | SSC resuscitation bundle completion |
| Mahmood 2012 | 2004-2008 | Retrospective cohort | NS ^a | Adults admitted to the ICU (sepsis subgroup) | ICU mortality |
| Nachtigall 2011 | Jan/March 2006; Feb/May 2007 | Prospective cohort | 1 | Adults admitted to mixed ICUs with a special focus on sepsis patients (sepsis subgroup) | ICU mortality |
| Pietropaoli 2010 | 2003-2006 | Retrospective cohort | 98 | Adults admitted to the ICU for severe sepsis or septic shock | Hospital mortality |
| Sakr 2013 | April/Sep 2006 | <i>Post-hoc</i> analysis of a prospective cohort | 24 | Adults admitted to the medical and/or surgical ICU for severe sepsis | ICU mortality |
| Samuelsson 2015 | 2008-2012 | Retrospective cohort | 65 | Adults admitted to the ICU (sepsis subgroup) | 30-day mortality |
| Sunden-Cullberg 2020 | 2008-2015 | Retrospective cohort | 42 | Adults admitted to the ICU for sepsis or shock septic via the ED within 24 h | Sepsis bundle completion; 30-day mortality |
| van Vught 2017 | 2011-2014 | Prospective cohort | 2 | Adults admitted to the ICU for sepsis | 90-day mortality |
| Xu 2019 | 2001-2012 | Retrospective cohort | 1 | Adults admitted to the ICU for sepsis | 1-year mortality |

| Sample size N of study participants (N with outcome) | Inclusion criteria | Exclusion criteria |
|--|---|---|
| 1692 (1608) | > 16 years old; ICU stays > 24 hours; community-acquired severe sepsis | NS |
| 416 (319) | ≥ 18 years old; ICU admission; clinical suspicion of pneumonia | None |
| 1387 (1387) | ≥ 18 years old; septic shock | NS |
| 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 |
| 27935 (27935) | Consecutive adults in the APACHE IV database; sepsis subgroup | Readmission to the ICU |
| 327 (327) | Consecutive adult (≥ 18 years); ICU stays > 36 hours; sepsis criteria for at least 1 day during the ICU stay | NS |
| 18757 (18318) | ≥ 16 years old; severe sepsis/septic shock patients; data from the first ICU admission | If gender, age, or hospital mortality was missing |
| 305 (305) | > 18 years old; severe sepsis; data from the first ICU admission | NS |
| 9830 (9830) | Consecutive SAPS III-scored adults ICU (>15 years old); validated mortality data in the registry; sepsis subgroup | Reasons for not being able to obtain mortality data: non-Swedish residency and patients with concealed identity |
| 2720 (2430) | ≥ 18 years old; ICU admission within 24 h 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. |
| 1533 (1815 admissions ^b) | Consecutive patients >18 years old; sepsis; expected ICUs stay > 24 hours; data from multiple ICU admission† | Transfer from other ICUs |
| 6134 (6134) | All adults diagnosed with sepsis, severe sepsis, or septic shock in the database | < 18 years old |

Supplementary Table 8 (Additional File 1) shows covariates included in the adjusted models of each included study. Although four studies [49, 50, 53, 54] were phase 2 designs and provided adjusted data on mortality, their timeframes differed from ours and/or reported unadjusted estimates for some of the review outcomes. Hence, we only used those data for sensitivity analyses.

Risk Of Bias Assessment

Supplementary Fig. 1 (Additional File 1) depicts the risk of bias assessment at outcome level of each included study using the QUIPS tool. We rated over half of the studies [43, 45, 46, 48, 50, 53] as having low risk in study participation, study attrition, and outcome measurement domains. We assessed all

studies as having unclear risk in the prognosis factor domain, given that none provided any definition or adequate description of the sex/gender variable. The risk of bias for the adjustment for other prognosis factors domain was moderate for over half of the studies [45–48, 52, 53] and low for the others [43, 44, 49–51] because of a minimal or acceptable adjustment, respectively. We penalised two studies [46, 53] that provided insufficient data presentation as moderate risk in the statistical analysis and reporting domain, while we classified the remaining studies as low risk of bias.

Results Of Synthesis

Supplementary Table 9 (Additional File 1) presents the summary outcome estimates for each study. Table 2 displays “Summary of findings” for each review outcome.

Table 2: Summary of findings

| Outcomes | Anticipated absolute prognostic effects* | | | Effect estimate (95% CI) [95% prediction interval] | № 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 (the longest follow-up provided by the study authors; median observed length of stay ranged from 6 to 26 days) | 299 per 1 000 ^a | 288 per 1 000 (190 to 412) | 11 fewer per 1000 (109 fewer to 113 more) | OR 0.95 (0.55 to 1.64) [0.01 to 89.45] | 20245 (3 observational phase 2 studies) | ⊕●●● VERY LOW ^{b,c,d} |
| 28-day all-cause hospital mortality | 240 per 1 000 ^a | 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] | 12579 (3 observational phase 2 studies) | ⊕●●● VERY LOW ^{b,d,e,f} |
| 7-day all-cause hospital mortality - not reported | - | - | - | - | - | - |
| 1-year all-cause mortality | 505 per 1 000 ^a | 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 ^{d,e,g,h} |
| All-cause ICU mortality (median observed length of stay ranged from 2.7 to 13 days) | 200 per 1 000 ^a | 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] | 31562 (5 observational phase 2 studies) | ⊕●●● VERY LOW ^{b,c,d} |

Abbreviations: ARD: Absolute risk difference; ARI: Absolute risk increase; ARR: Absolute risk reduction; CI: Confidence interval; ICU: Intensive care unit; N/M: Not meaningful; OIS: Optimal information size; OR: Odds ratio; OSS: Observed sample size.

*The risk in the female group (and its 95% confidence interval) 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 $\pm 10\%$ 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 ($10\% < ARR \leq 5\%$), minimal or no effect ($-5\% < ARD < 5\%$), slight worsening ($5\% \leq ARI < 10\%$), and important worsening (ARI of at least 10%).

Not meaningful: < 3 studies for computing of the 95% prediction interval a meaningful estimate.

Explanations

- a. The assumed risk in male participants is based on the median risk amongst the male participants in the included studies. We consider this risk reflects the context of ICUs in high-resource countries adequately.
- b. 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.
- c. Downgraded by two levels for very serious imprecision because the CI 95% 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.
- d. Publication bias not assessed because of the scarce number of included studies (< 10).
- e. 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 (i.e., it is compatible with an important or a slight prognostic effect). The OSS was greater than the OIS.
- f. Downgraded by one level for serious indirectness because one study was responsible for 85% of the weight reported in- and out-hospital mortality.[51]
- g. 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.
- h. Inconsistency not assessed because a single study was considered.

Not meaningful: < 3 studies for computing of the 95% prediction interval a meaningful estimate.

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- a. The assumed risk in male participants is based on the median risk amongst the male participants in the included studies. We consider this risk reflects the context of ICUs in high-resource countries adequately.
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- e. 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 (i.e., it is compatible with an important or a slight prognostic effect). The OSS was greater than the OIS.
- f. Downgraded by one level for serious indirectness because one study was responsible for 85% of the weight reported in- and out-hospital mortality.[51]
- g. 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.
- h. Inconsistency not assessed because a single study was considered.

Primary outcomes

We investigated the independent prognostic effect of sex on all-cause hospital mortality. We found six studies [43, 44, 46, 49, 53, 54] (29346 recruited participants) addressing this question. Among the four studies [43, 44, 46, 49] (21059 analysed participants) that provided adjusted results, three of them [43, 44, 49] (20245 analysed participants) presented sufficiently similar data allowing quantitative synthesis. Meta-analysis showed inconclusive results on sex-based differences in all-cause hospital mortality (OR 0.95, 95% CI 0.55 to 1.64; $I^2 = 76\%$; 3 studies; very low-certainty evidence) (Fig. 2). Heterogeneity was substantial (95% prediction interval ranging from 0.01 to 89.45). We performed no subgroup analyses based on study characteristics because there were insufficient studies. Sensitivity analysis results using unadjusted estimates remained unaltered (OR 1.00, 95% CI 0.88 to 1.14) (See Supplementary Fig. 2, Additional File 1). We conducted no other pre-specified analyses as no other comparisons met the predefined criteria.

We examined sex-based differences in 28-day all-cause hospital mortality. We found six studies [44, 50–54] (20930 recruited participants) addressing this question. Three studies [44, 51, 52] (12579 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; $I^2 = 0\%$; 3 studies; very low-certainty evidence) (Fig. 3). 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 to male patients. Heterogeneity was substantial (95% prediction interval ranging from 0.56 to 2.5). Sensitivity analysis results pooling either 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 were inconclusive (OR 1.05, 95% CI 0.84 to 1.32) (See Supplementary Fig. 3, Additional File 1). We undertook no additional analyses as no other comparisons met the predefined criteria.

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 [53, 54] investigating this question, only one [53] (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 hazard ratio) 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 to male patients. Sensitivity analysis results using unadjusted estimates were inconclusive (OR 0.86, 95% CI 0.54 to 1.37) (See Supplementary Fig. 4, Additional File 1). We performed no other pre-specified analyses due to absence of data.

We evaluated sex-related all-cause ICU mortality. We found seven studies [43, 45, 47–50, 54] (51936 recruited participants) addressing this topic. Five studies [43, 45, 47, 48, 50] (31562 analysed participants) provided adjusted estimates. One of them [45] 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; $I^2 = 69\%$; 5 studies; very low-certainty evidence) (Fig. 4). Heterogeneity was substantial (95% prediction interval ranging 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 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) (See Supplementary Fig. 5, Additional File 1). We conducted no further pre-specified analyses as no other comparisons met the predefined criteria.

Publication Bias

No meta-analysis included more than 10 studies; therefore, we explored the risk of publication bias by neither funnel plot nor Peter's test.

Discussion

We conducted a systematic review to assess the role of sex as an independent prognostic factor for mortality amongst critically ill patients with sepsis. We are uncertain of the role of sex as an independent prognostic factor for all-cause hospital mortality, 28-day all-cause hospital mortality, and all-cause ICU mortality in patients with sepsis managed in the ICU, as the certainty of the evidence was assessed as very low. These inconclusive results should be interpreted as a lack of evidence supporting sex as an independent prognostic factor in these patients, and not as the evidence of a lack of prognostic effect. Adjusted analysis based on a single study found that female sex may be associated with an important reduction in 1-year all-cause mortality (low-certainty evidence). However, the confidence interval of the absolute reduction is also compatible with a slight protective effect. No studies reported on 7-day all-cause mortality.

Existing research has investigated the association between sex and mortality in sepsis patients with conflicting findings. We are aware of two systematic reviews that examined the influence of sex on outcomes in critically ill adults with sepsis and found a small disadvantage for survival amongst female patients alongside other unclear results that highlighted the complexity of the subject [55, 56]. Notwithstanding, our review makes an additional contribution to the current knowledge with some

methodological aspects, outlining those related to inclusion criteria, risk of bias assessment, and the use of GRADE, not considered in any of these previous reviews. The hypothesis of mortality outcomes associated with sex in sepsis rests upon possible sex-based differences in illness severity and provision of care. Several underlying mechanisms may explain sexual dimorphism in the host response related to immune response and the effect and metabolism of sexual hormones [57–59], while various studies suggest that raised oestrogen and adrenal hormone concentrations in critically ill patients are associated with poor outcomes [60, 61]. In our review, we observed that among those studies that found sex-based mortality risk-adjusted, only three reported significantly higher severity scores for the mortality disadvantaged group [43, 48, 53]. The most common prognostic scores were based on physiological measures [62–64], which usually differ between sexes. Therefore, these scoring models may require sex adjustments for a reliable prediction of illness severity. Moreover, some studies showed female patients were less likely to receive recommended care for sepsis [65], including invasive procedures during ICU admission [66]. In this review, most of the included studies that provided data on care delivered found similar coverage rates [43–46], while a single study pointed to differential management between both sexes, although not accounting for a higher likelihood of mortality for the female group [49].

This review has several major strengths. Two experienced librarians designed and conducted a comprehensive and non-language-restricted search strategy. We included observational phase 2 explanatory studies, which initially provide high certainty of the evidence for prognosis, and pre-specified a core set of adjustment factors based on a literature review, the consensus amongst clinician review authors, and inputs from reviewers during the protocol publication process. We also performed the HKSJ procedure, which yields a wider and more rigorous confidence interval [29]. When few studies contributed to the meta-analysis (i.e., hospital mortality and 28-day hospital mortality), the HKSJ method may lead to substantial and uninformative adjustment [29, 67]. Nevertheless, the interpretation of these pooled estimates remained virtually unaffected regarding standard DerSimonian-Laird method. Moreover, we followed the GRADE framework adaptations for prognostic factor research to interpret our results based on their certainty [23, 36–38]. We further attempted to contact all corresponding authors of included and awaiting classification studies to request additional data and clarifications, but we received a poor response. We noted some limitations of this review arising from poor reporting in the included studies. Firstly, the included studies provided no a clear and adequate definition of the sex variable. Although we anticipated poor biological assessments, we expected at least a statement based on sexual dimorphism observed by healthcare staff. 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- and out-hospital events or omitted further details. After requesting additional clarifications, only Samuelsson replied [51]. We pooled these studies and downgraded evidence certainty for indirectness. Another limitation is the substantial clinical and statistical heterogeneity between studies. Included studies differed in regard to illness severity measurements and score ratings, comorbidity burden, as well as in clinical practice. We addressed statistical heterogeneity using 95% prediction intervals, which illustrate the distribution range of prognostic effects over study populations, including the true effect expected in future settings, and help to assess the inconsistency criteria in GRADE, where usually large

study sample sizes may result in narrow CIs alongside high I^2 [37, 68, 69]. However, these intervals are still imprecise when meta-analysis includes few studies [69], as in this review. 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, and we may need to seek other factors associated with this variation [29, 68]. Moreover, most pre-specified subgroup analyses were not feasible because of the scarcity of studies. A potential objection might point out to our established clinical thresholds. We considered that, as sex is a non-modifiable factor that affects the entire population, an absolute risk difference of 10‰ on mortality may lead to a clinically important impact. Besides, a most demanding threshold (e.g., $\pm 20\%$) would not modify the certainty of evidence assessment. A further limitation is that we could not investigate asymmetry for publication bias given that meta-analyses contained less than 10 studies, which may hamper the reliability of the test and funnel plot [70, 71]. Nevertheless, we should note that for the 28-day mortality outcome, none of the included studies were statistically significant, thus suggesting that preferential inclusion of studies with significant results has skewed our sample may be inappropriate [71]. We also attempted to explore a possible small-study effect using cumulative analyses for ICU mortality. We observed a shift towards higher mortality in the female group that indicates that the effect size tends to increase in the smaller studies, but the rationale remains unexplained. Importantly, this shift does not alter the findings of the meta-analysis. However, given the absence of standardised registers for prognostic research, the issue also jeopardises the selective outcome reporting. We unsuccessfully searched for protocols and registers, examined the primary publication of the main cohort where appropriate, and assessed methods descriptions. This may have biased if the authors removed outcomes or pre-specified covariates from the methods section. Lastly, included studies were mainly conducted in North America and Western Europe, poorly reported on race participants, and none provided socioeconomic data, while previous studies found different mortality rates associated with these features [72, 73].

The research question of whether sex is an independent prognostic factor for mortality in critically ill patients with sepsis is set to continue. First, assessment of the certainty of the evidence of review findings was low or very low, and heterogeneity was substantial for the review outcomes appraised. We would advise further prospective, well-designed research to address this question. Besides, some studies evaluated the impact of pre-menopausal status based on the estrogenic protective effect hypothesis using different cut-off times defined by data from the literature [45, 51], instead of direct hormone level measurement. Sex is a complex, hormone dynamic throughout life, biological variable, and at the same time, like age or race, has some permeability to social components. For example, several studies suggest that smoking and low socioeconomic status are associated with earlier natural menopause [74, 75]. Moreover, 1-year mortality data was available from a single study; hence, there is room to foster research on testing the possible independent association between sex and long-term mortality. Lastly, the architecture for tracking of prognosis research is poorly assembled. Academics, journals, editors, and librarians may boost pre-registering 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

We are uncertain whether sex has an independent prognostic impact on all-cause hospital mortality, 28-day all-cause hospital mortality, and all-cause ICU mortality amongst critically ill adults with sepsis since we assessed the certainty of the evidence as very low. Female sex may be associated with decreased 1-year all-cause mortality (low-certainty evidence). No included studies looked at 7-day all-cause mortality.

Abbreviations

APACHE: Acute physiologic assessment and chronic health evaluation

ARD: Absolute risk difference

ARI: Absolute risk increase

ARR: Absolute risk reduction

CHARMS-PF: Checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies for prognostic factors

CI: Confidence intervals

ED: Emergency department;

GRADE: Grading of recommendations assessment, development, and evaluation

HKSJ adjustment: Hartung-Knapp-Sidik-Jonkman adjustment

ICU: Intensive care units

NS: Not stated

N/M: Not meaningful

OIS: Optimal information size

OR: Odds ratio

OSS: Observed sample size

QUIPS: Quality in prognosis studies

RCT: Randomised clinical trial

SAPS: Simplified acute physiology score

SOFA: Sequential organ failure assessment score

SSC: Surviving sepsis campaign

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The study protocol is available online at <http://dx.doi.org/10.1136/bmjopen-2019-035927> and PROSPERO [CRD42019145054](https://doi.org/10.1136/bmjopen-2019-035927). Included studies are publicly available, main data supporting the conclusions of this systematic review are included in the article and further data are detailed in its information file.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

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, NA-D, AA, and IS designed the search strategy. AA, ES, BF-F, AH, 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 BF-F elaborated the analysis plan. AA performed the statistical analyses. JL-A and AA conducted the GRADE assessment. AA, FG, PF, MP-A, RdC, and OM-P provided clinical perspective. AA drafted the first version of the manuscript. All authors had the opportunity to read

approved the final manuscript. JZ and JL-A secured funding for the systematic review. AA is the guarantor.

Alba Antequera is a doctoral candidate in Public Health and Methodology of Biomedical Research, at the Department of Pediatrics, Obstetrics, Gynaecology and Preventive Medicine at Universitat Autònoma de Barcelona (Spain) and this work is part of her PhD.

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Figures

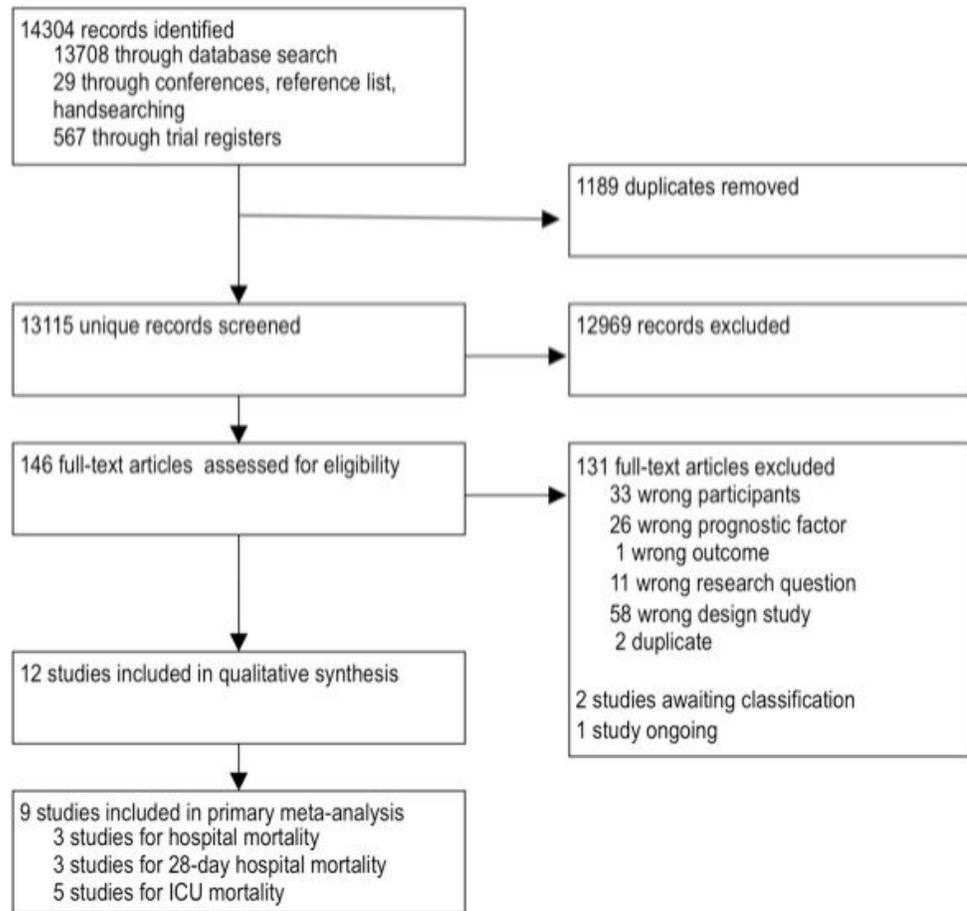


Figure 1

Flow diagram

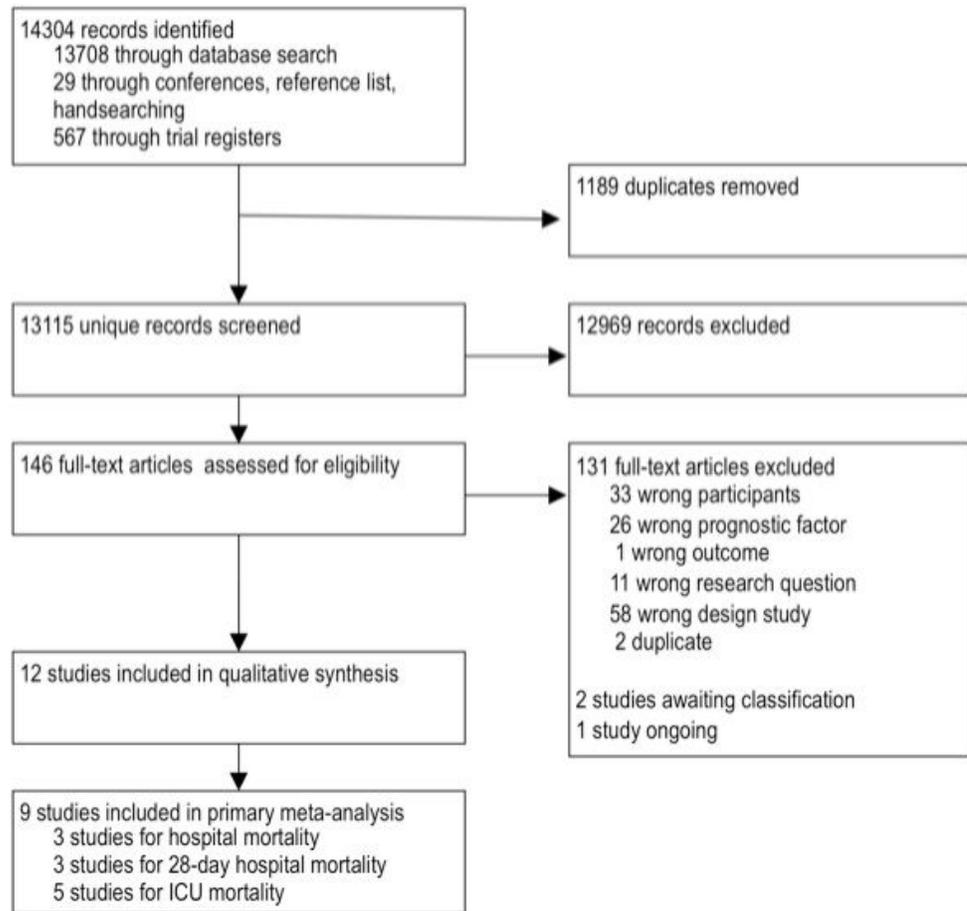


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Flow diagram

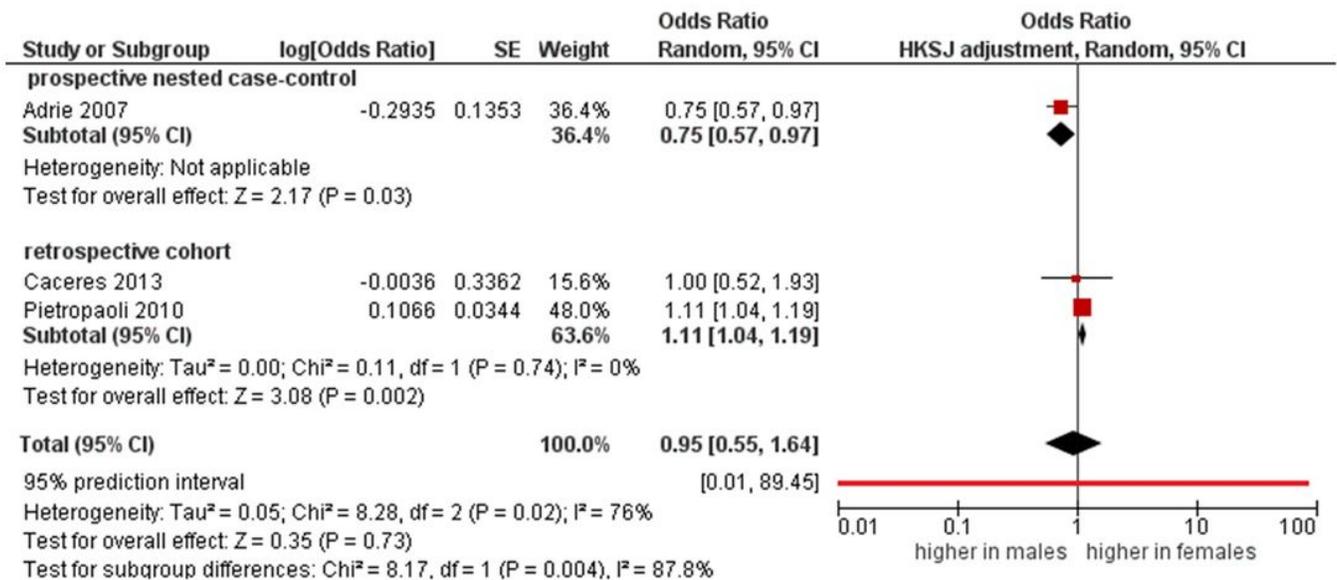


Figure 2

Forest plot of adjusted analyses for association between sex and all-cause hospital mortality (the longest follow-up provided by the study authors)

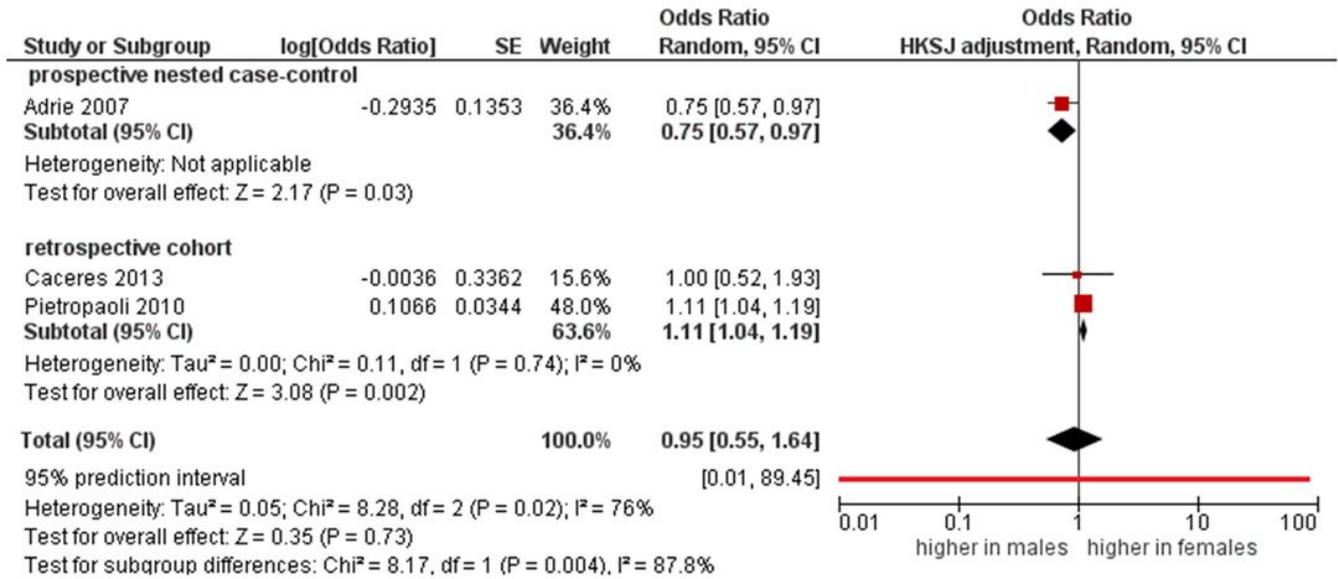


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Forest plot of adjusted analyses for association between sex and all-cause hospital mortality (the longest follow-up provided by the study authors)

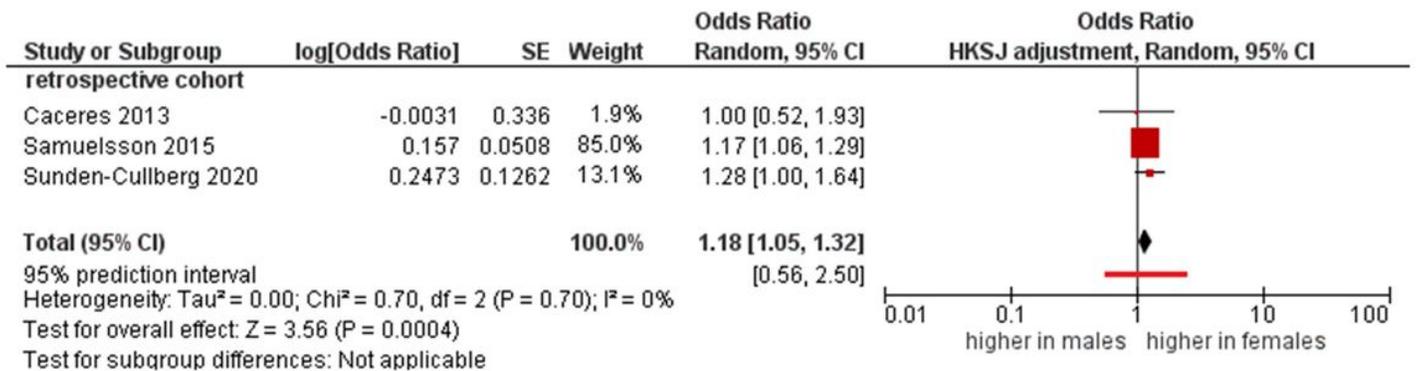


Figure 3

Forest plot of adjusted analyses for association between sex and 28-day all-cause hospital mortality

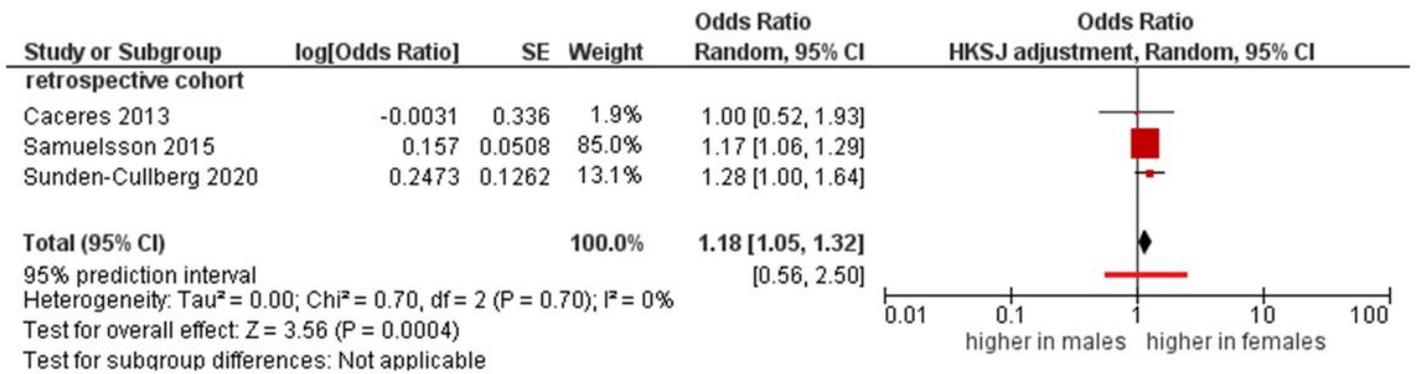


Figure 3

Forest plot of adjusted analyses for association between sex and 28-day all-cause hospital mortality

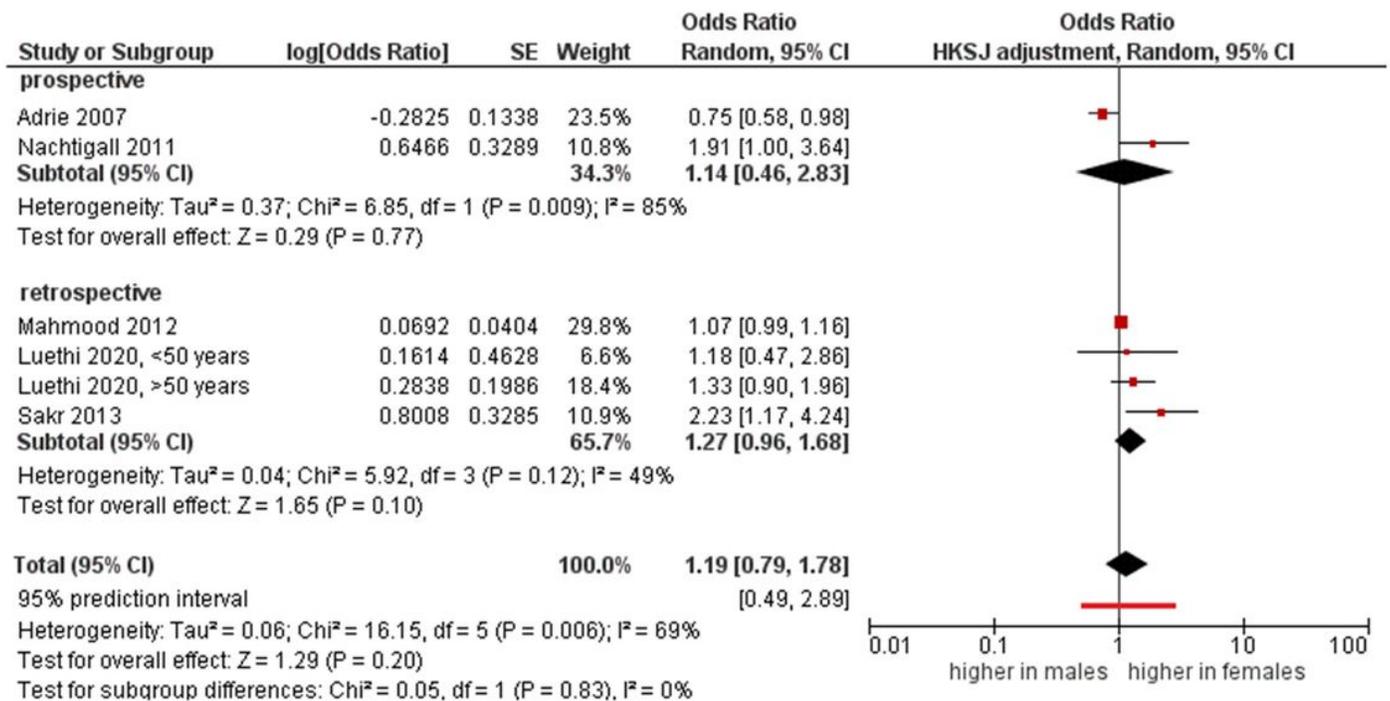


Figure 4

Forest plot of adjusted analyses for association between sex and all-cause ICU mortality

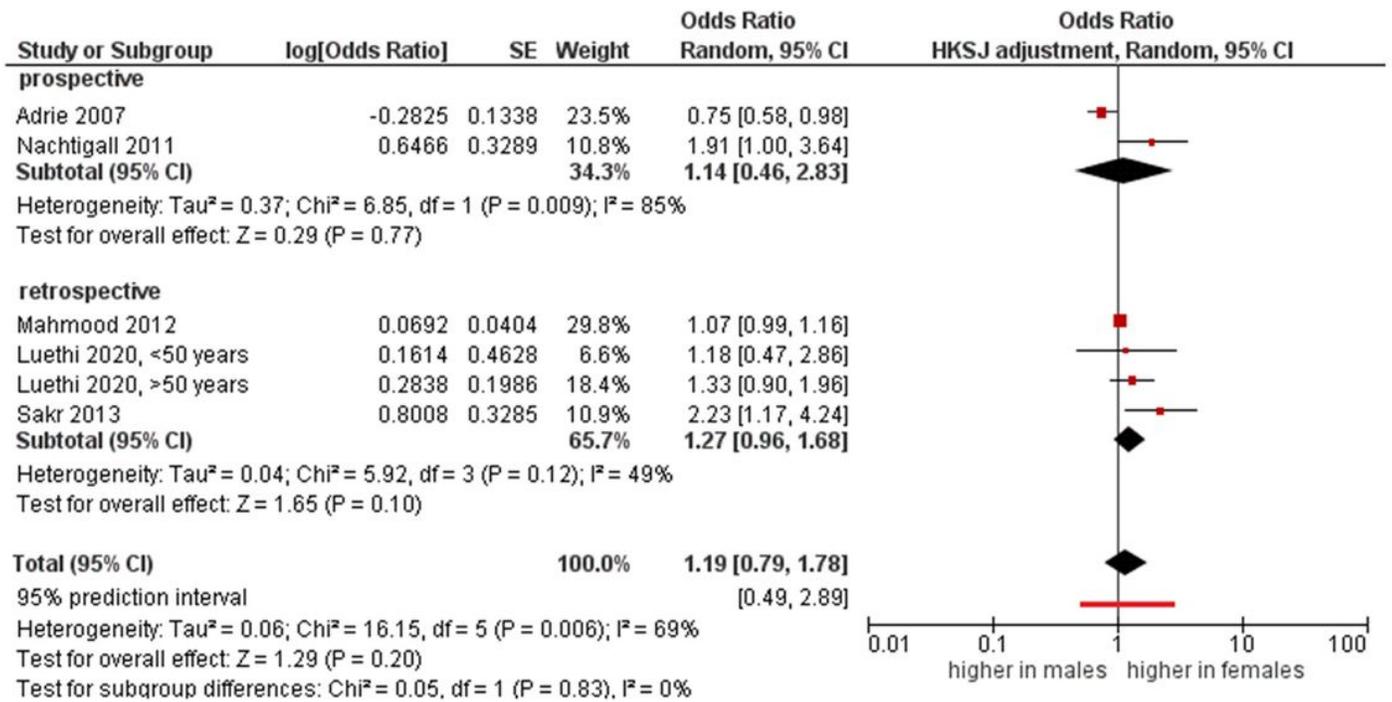


Figure 4

Forest plot of adjusted analyses for association between sex and all-cause ICU mortality

Supplementary Files

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