Supplemental material

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

Alba Antequera, Jesús López-Alcalde, Elena Stallings, Alfonso Muriel, Borja Manuel Fernández-Félix, Rosa del Campo, Manuel Ponce-Alonso, Pilar Fidalgo, Ana Verónica Halperin, Olaya Madrid-Pascual, Noelia Álvarez-Díaz, Ivan Solà, Federico Gordo, Gerard Urrútia, Javier Zamora.

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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-subsidy 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 estimate 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 biological characteristics. |
| - Gender for socially constructed roles, behaviours, and identities. | - Sex for socially constructed roles, behaviours, and identities. |
| - Females or males for sex. | - Females or males for gender. |
| - Women or men 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. 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 cholesterol  
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    | We considered factors included in the SOFA prognostic model | 1. PaO2  
2. FiO2  
3. On mechanical ventilation  
4. Platelets, ×10³/µL  
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    | 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. (septicemia or "systemic inflammatory response syndrome" or pyemia).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.                             |   |
**Full search string for Embase Elsevier (consulted 17th July 2020)**

| String 1 | String 2 | String 3 | String 4 | String 5 | String 6 | String 7 | String 8 | String 9 | String 10 | String 11 | String 12 | String 13 | String 14 | String 15 | String 16 | String 17 | String 18 | String 19 | String 20 | String 21 | String 22 | String 23 | String 24 | String 25 | String 26 | String 27 | String 28 | String 29 | String 30 | String 31 | String 32 | String 33 | String 34 | String 35 | String 36 | String 37 | String 38 | String 39 | String 40 | String 41 | String 42 | String 43 | String 44 | String 45 | String 46 | String 47 | String 48 |
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| #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 septicemia: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 diagnosis: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' |
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: (septicemia) OR TITLE: (pyemia) 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: (incidence 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

| Factor                        | Details                                                                                                                                                                                                 |
|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **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 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

| Methods          | Adrie 2017 | Caceres 2013 | Dara 2012 | Luethi 2020 | Madsen 2014 | Mahmood 2012 | Nachtigall 2011 |
|------------------|------------|--------------|-----------|--------------|--------------|---------------|-----------------|
| **Study design** | Nested case-control | Cohort IMPACT-HAP | Cohort CATSS | Post-hoc analysis ARISE | Cohort SSC Database | Cohort APACHE IV | Cohort Not reported |
| **Database**     | OutcomeRea | Not reported | Not reported | Not reported | Reported | Not reported | Not reported |
| **Sample size calculation** | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| **Participants** | Females; Males | Age 69 (57-77); 65 (51-75) | Age 62.4 (16.9); 55.7 (16.5) | Age 62.8 (15.9); 62.3 (16.6) | Age 62 (17.1); 63.5 (15.8) | Age 66.2 (18); 66.3 (16.2) | Age 284 (78.5); 370 (82.4) |
| **Sociodemographics** | Not reported | Ethnicity | Caucasian 123 (19.5); 266 (25) | African-American 71 (11.2); 123 (11.6) | Race 31 (21.4); 45 (16.9) | Race 28 (10); 41 (15.9) | Race 31 (21.4); 45 (16.9) |
| **Comorbidities** | Not reported | Respiratory | Respiratory 37 (25.5); 54 (20.2) | Respiratory 32 (22.1); 58 (21.6) | Respiratory 46 (31.7); 74 (27.6) | Respiratory 28 (4.4); 66 (8.2) | Respiratory 28 (4.4); 66 (8.2) |
| **Severity score** | APACHE II 119 (18.9); 207 (19.5) | Cardiac | Cardiac 132 (19.5); 206 (25) | Cardiac 71 (11.2); 123 (11.6) | Cardiac 31 (21.4); 45 (16.9) | Cardiac 28 (4.4); 66 (8.2) | Cardiac 28 (4.4); 66 (8.2) |
| **Infection site** | SIRS II 6 (4-9); 6 (4-9) | Immunosuppression | Immunosuppression 60 (41.4); 101 (37.8) | Immunosuppression 60 (41.4); 101 (37.8) | Immunosuppression 26 (4.1); 57 (6) | Immunosuppression 26 (4.1); 57 (6) | Immunosuppression 26 (4.1); 57 (6) |
| **Prognosis factor** | Gender 68 (10.8); 51 (4.8) | Liver disease | Liver disease 28 (4.4); 66 (8.2) | Liver disease 28 (4.4); 66 (8.2) | Liver disease 28 (4.4); 66 (8.2) | Liver disease 28 (4.4); 66 (8.2) | Liver disease 28 (4.4); 66 (8.2) |
| **Independent variable** | Gender | Other/unknown | Other/unknown 6 (4-9); 6 (4-9) | Other/unknown 6 (4-9); 6 (4-9) | Other/unknown 6 (4-9); 6 (4-9) | Other/unknown 6 (4-9); 6 (4-9) | Other/unknown 6 (4-9); 6 (4-9) |
| **Sex/ gender definition** | Not reported | Sex | Sex 21 (7.6); 19 (7.2) | Sex 25.9 (8.2); 25.5 (8.1) | Sex 25.9 (8.2); 25.5 (8.1) | Sex 25.9 (8.2); 25.5 (8.1) | Sex 25.9 (8.2); 25.5 (8.1) |
| **Terms used** | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported |
| **Inadequate** | Inadequate | Inadequate | Inadequate | Inadequate | Inadequate | Inadequate | Inadequate |
| **Unclear** | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |

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### Extracted outcomes

| Primary outcomes | All-cause hospital mortality | 28-day all-cause mortality | Secondary outcomes | 7-day all-cause hospital mortality | 1-year all-cause mortality | All-cause ICU mortality |
|------------------|-----------------------------|---------------------------|-------------------|-----------------------------------|---------------------------|------------------------|
|                  | Yes                         | No                        | No                | No                                | No                        | No                     |
|                  | Yes                         | Yes                       | No                | No                                | No                        | No                     |
|                  | No                          | No                        | No                | No                                | No                        | No                     |
|                  | No                          | No                        | No                | No                                | No                        | No                     |
| Follow-up        | Not reported                | Hospital discharge, death or 28 days after pneumonia diagnosis, whichever occurred first | 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 Louisville Foundation responsible for project oversight | Unrestricted grants from Eli-Lilly, Pfizer, Bayer, Astellas, Merck, Manitoba 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

| Identifier or protocol | None | Declared | Not reported | None | Declared | Not reported | None | Declared | 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. | Email sent to study authors in March 2020; no reply received. | Baseline data available only for main cohort (N=1,281,255 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=1,281,255 participants). Email sent to study authors in June 2020; no reply received. | Email sent to study authors in May 2020; no reply received. |
### Continued

| Methods          | Pietropaoli 2010 | Sakr 2013 | Samuelsson 2015 | Sunden-Cullberg 2020 | van Vught 2017 | Xu 2019 |
|------------------|------------------|-----------|------------------|----------------------|----------------|---------|
| Study design     | Cohort           | Cohort    | Cohort           | Cohort               | Cohort         | Cohort  |
| Database         | Cerner Project IMPACT | Piademont Intensive Care Unit Network | Not reported | Not reported | Not reported | Not reported |
| 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) | 1,210 (44.5); 1,510 (55.5) | 595 (38.8); 936 (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) | 68 (56–77); 68(58–77) | 59.4 (16.2); 60.8 (14.8) | 65-89 (50.4); 85-89 (51.1) |
|                  | Caucasian        | 6,439 (74); 7,541 (75) | Not reported | Not reported | 510 (85.7); 839 (89.4) | 1,915 (71.5); 2,597 (75.1) |
|                  | African-American | 1,218 (14); 1,207 (12) | Not reported | Not reported | 870 (10); 1005 (10) | 369 (13.8);273 (7.9) |
|                  | Latin            | 435 (5); 603 (6) | Not reported | Not reported | 432 (14.5); 131 (14) | 70 (2.6); 143 (4.1) |
|                  | Other/Unknown    | 610 (7); 704 (7) | Not reported | Not reported | 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    | Respiratory      | 870 (10); 1005 (10) | 3 (3.5); 18 (8.2) | 72 (12.1); 138 (14.7) | 72 (12.1); 138 (14.7) | 136 (22.9); 245 (28.1) |
|                  | Cardiac          | 522 (6); 704 (7) | 8 (8.4); 17 (7.7) | 131 (22); 232 (24.7) | 131 (22); 232 (24.7) | 124 (20.8); 153 (19.5) |
|                  | Renal            | 522 (6); 603 (6) | 16 (18.8); 40 (18.2) | 86 (14.5); 131 (14) | 86 (14.5); 131 (14) | 124 (20.8); 153 (19.5) |
|                  | Diabetes         | 1,131 (13); 1,307 (13) | 18 (21.2); 34 (15.5) | 124 (20.8); 153 (19.5) | 124 (20.8); 153 (19.5) | Not reported |
|                  | Immunosuppression| Not reported | Not reported | Not reported | Not reported | Not reported |
|                  | Liver disease    | 281 (3); 402 (4) | Not reported | Not reported | 72 (12.1); 138 (14.7) | 136 (22.9); 245 (28.1) |
|                  | Cancer           | 1,218 (14); 1,709 (17) | 4 (4.7); 6 (2.7) | Not reported | Not reported | Not reported |
| Severity score   | APACHE II        | 21 (15-27); 21 (15-27) | Not reported | Not reported | 79 (62-99); 76 (58-98)† | 21.39 (5.73); 21.06 (5.6) |
|                  | SAPS II          | 35 (15-64); 33 (14-64) | Not reported | Not reported | 79 (62-99); 76 (58-98)† | 6.97 (3.52); 7.29 (3.75) |
|                  | SOFA             | Not reported | 55 (18.8); 55.3 (17.5) | Not reported | 7 (5-9); 7 (4-9) | 7 (5-9); 7 (4-9) |
|                  | Infection site   | 2,688 (31); 1,910 (19) | 9.1 (3.3); 9.8 (3.7) | Not reported | Not reported | Not reported |
|                  | Urinary source of infection | 5 (5.9); 13 (5.9) | Not reported | Not reported | 5 (5.9); 13 (5.9) | 5 (5.9); 13 (5.9) |
|                  | Prognosis factor | 2,688 (31); 1,910 (19) | 258 (21.3); 301 (19.9) | Not reported | Not reported | Not reported |
|                  | Independent variable | Gender | Gender | Gender | Sex | Gender | Sex |
| Terms used       | Sex/ gender definition | Reported | Not reported | Not reported | Not reported | Not reported | Not reported |
|                  | 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 | Yes | Yes |
| 28-day all-cause mortality | Secondary outcomes | 7-day all-cause hospital mortality | 1-year all-cause mortality | All-cause ICU mortality | Follow-up | Identification | Country | Funding source | Conflict of interest | Notes |
|---------------------------|-------------------|----------------------------------|--------------------------|------------------------|-----------|---------------|---------|---------------|------------------|-------|
| No                        | No                | No                               | Yes                      | Yes                    | Yes       | Brazil, Canada, US National Heart, Lung and Blood Institute | Italy Regione Piamonte, progetti finalizzati di ricerca | None | Email sent to study authors in April 2020; no reply received. |
| Yes                       | Yes               | Yes                              | Yes                      | Yes                    | Yes       | Sweden Regional Health Care Authorities in the Halland and Skåne regions of Sweden | Sweden Karolinska Institute, Swedish Government Funds for Clinical Research | None | 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. |
| Yes                       | Yes               | Yes                              | Yes                      | Yes                    | Yes       | Netherlands Center for Translational Molecular Medicine, project MARS | Sweden Karolinska Institute, Swedish Government Funds for Clinical Research | None | 30-day mortality reported, authors were contacted for clarification in June 2020; no reply received. |
| Yes                       | Yes               | Yes                              | Yes                      | Yes                    | Yes       | United States 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 | United States 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 | None | 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 \(<90\) mmHg or a mean arterial pressure of \(65\) mmHg after an intravenous fluid challenge), or hyperlactatemia (blood lactate level of \(\geq 4.0\) 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, requiring 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; 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 aureus; 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) | N/A | 0.75 (0.57-0.97) | 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) | N/A | 0.99 (0.52-1.93) | N/A |
| Dara 2012  | 0.95 (0.87-1.04)      | 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) | N/A | 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) |
| Study                  | Year | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
|-----------------------|------|-------------|-------------|-------------|-------------|-------------|
| Samuelsson 2015       |      | N/A         | N/A         | N/A         | 1.17 (1.06-1.29)† | N/A         |
| Sunden-Cullberg 2020  |      | N/A         | 1.11 (0.91-1.36) | N/A         | N/A         | 1.28 (1.00-1.64) | 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         |
| Xu 2019               |      | 0.89 (0.80-0.99) | 0.91 (0.82-1.01) | 0.84 (0.76-0.93) | 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

| Study participation | Study attrition | Prognostic factor measurement | Outcome measurement | Adjustment for other prognostic factors | Statistical analysis and reporting |
|---------------------|----------------|-----------------------------|---------------------|---------------------------------------|----------------------------------|
| **All-cause hospital mortality** | | | | | |
| Adrie 2007          |               |                             |                     |                                       |                                  |
| Dara 2021           | b             |                             |                     |                                       |                                  |
| Caceres 2013        |               |                             |                     |                                       |                                  |
| Madsen 2014         |               |                             |                     |                                       |                                  |
| Pietropaoli 2010    |               | d                           |                     |                                       |                                  |

| **28-day all-cause mortality** | | | | | |
| Caceres 2013          |               | d                           |                     |                                       |                                  |
| Samuelsson 2015       | b             |                             |                     |                                       |                                  |
| Sunden-Culberg 2020  |               |                             |                     |                                       |                                  |

| **1-year all-cause mortality** | | | | | |
| Xu 2019               |               |                             |                     |                                       |                                  |

| **All-cause ICU mortality** | | | | | |
| Adrie 2007          |               |                             |                     |                                       |                                  |
| Nachtigall 2011    |               |                             |                     |                                       |                                  |
| Sakr 2013          |               |                             |                     |                                       |                                  |
| Luethi 2020       |               |                             |                     |                                       |                                  |
| Mahmood 2012      | b             |                             |                     |                                       |                                  |

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

| Study or Subgroup               | Females | Males | Total | Random. | 95% CI       | Odds Ratio |
|---------------------------------|---------|-------|-------|---------|--------------|------------|
| Prospective nested case-control |         |       |       |         |              |            |
| Adult 2002                      | 108     | 166   | 274   | 0.64    | 0.42 [0.28, 0.92] | 0.67       |
| Subtotal (95% CI)               |         |       |       |         |              |            |
| Heterogeneity                   | Not applicable |   |       |         |              |            |
| Test for overall effect         | Z = 2.17 (P = 0.03) |   |       |         |              |            |
| Retrospective cohort            |         |       |       |         |              |            |
| CECAC 2013                      | 34      | 114   | 148   | 0.05    | 0.00 [0.00, 0.33] | 0.03       |
| Subtotal (95% CI)               | 332     | 332   | 664   | 0.00    | 0.00 [0.00, 0.33] | 0.03       |
| Heterogeneity                   | Tau^2 = 0.00, I^2 = 100% |   |       |         |              |            |
| Test for overall effect         | Z = 3.15 (P = 0.00) |   |       |         |              |            |
| Total (95% CI)                  | 3261    | 9424  | 12685 | 0.00    | 0.00 [0.00, 0.33] | 0.03       |
| Heterogeneity                   | Tau^2 = 0.00, I^2 = 100% |   |       |         |              |            |
| Test for subgroup differences   | Z = 0.36 (P = 0.72) |   |       |         |              |            |

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

| Study or Subgroup               | Females | Males | Total | Random. | 95% CI       | Odds Ratio |
|---------------------------------|---------|-------|-------|---------|--------------|------------|
| Unadjusted OR                   |         |       |       |         |              |            |
| Adult 2007                      | 168     | 608   | 776   | 0.69    | 0.71 [0.60, 0.84] | 0.69       |
| CECAC 2013                      | 34      | 114   | 148   | 1.35    | 1.26 [1.12, 1.40] | 1.26       |
| Dora 2012                       | 1914    | 2872  | 4786  | 0.95    | 0.92 [0.89, 0.99] | 0.92       |
| Madrid 2014                     | 62      | 564   | 626   | 1.10    | 1.08 [1.06, 1.10] | 1.08       |
| Pfeiffer 2014                   | 3039    | 8702  | 11741 | 1.69    | 1.62 [1.57, 1.74] | 1.62       |
| van Vaugh 2017                  | 103     | 595   | 715   | 1.62    | 1.51 [1.42, 1.60] | 1.51       |
| Xia 2019                        | 939     | 2677  | 3616  | 0.69    | 0.60 [0.50, 0.73] | 0.60       |
| Total (95% CI)                  | 16728   | 21107 | 37835 | 0.09    | 0.09 [0.07, 0.11] | 0.09       |
| Heterogeneity                   | Tau^2 = 0.01, I^2 = 99.9% |   |       |         |              |            |
| Test for overall effect         | Z = 0.21 (P = 0.83) |   |       |         |              |            |

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

| Study or Subgroup               | Females | Males | Total | Random. | 95% CI       | Odds Ratio |
|---------------------------------|---------|-------|-------|---------|--------------|------------|
| Unadjusted OR                   |         |       |       |         |              |            |
| CECAC 2013                      | 34      | 114   | 148   | 1.39    | 1.29 [1.19, 1.60] | 1.29       |
| Bundred-Culbing 2020            | 307     | 1210  | 1517  | 1.11    | 1.03 [1.00, 1.06] | 1.03       |
| van Vaugh 2017                  | 196     | 659   | 855   | 1.13    | 1.00 [0.95, 1.05] | 1.00       |
| Xia 2019                        | 939     | 2677  | 3616  | 0.91    | 0.82 [0.73, 0.93] | 0.82       |
| Total (95% CI)                  | 4596    | 6110  | 10706 | 1.05    | 1.04 [0.98, 1.10] | 1.04       |
| Heterogeneity                   | Tau^2 = 0.01, I^2 = 99.9% |   |       |         |              |            |
| Test for overall effect         | Z = 0.66 (P = 0.51) |   |       |         |              |            |

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

| Study or Subgroup | Females | Males | Odds Ratio | Odds Ratio |
|-------------------|---------|-------|------------|------------|
|                   | Events  | Total |            | Random, 95% CI |
|                   | Events  | Total |            | HKSJ adjustment, Random, 95% CI |
| van Vught 2017    | 256     | 596   | 0.92       | 0.84       |
| Xu 2015           | 137     | 2877  | 1347       | 0.84 [0.74, 1.13] |
| Total (95% CI)    | 3272    | 4395  | 100.0%     | 0.86 [0.54, 1.37] |
|                  | 1635    | 2384  |            |             |

Heterogeneity: 95% prediction interval Not estimable

Test for overall effect: Z = 3.38 (P = 0.0007)

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

| Study or Subgroup | Females | Males | Odds Ratio | Odds Ratio |
|-------------------|---------|-------|------------|------------|
|                   | Events  | Total |            | Random, 95% CI |
|                   | Events  | Total |            | HKSJ adjustment, Random, 95% CI |
| Prospective       |         |       |            |             |
| Adibe 2007        | 150     | 609   | 0.75       | 1.31       |
| Backergardt 2011  | 31      | 219   | 1.96       | 1.91 [0.68, 3.44] |
| Subtotal (95% CI)  |         |       | 34.3%      | 1.14 [0.46, 2.83] |
| Test for overall effect: Z = 0.29 (P = 0.77) |

| Retrospective     |         |       |            |             |
| Mahmoud 2002      |         |       | 1.97       | 1.97 [0.69, 6.18] |
| Lusti 2000<60 years| 91      | 295   | 1.14       | 1.14 [0.47, 2.94] |
| Lusti 2000>60 years| 50     | 183   | 1.30       | 1.30 [0.60, 2.69] |
| Sall 2012         | 54      | 212   | 2.23       | 2.23 [1.17, 4.24] |
| Subtotal (95% CI)  |         |       | 65.7%      | 1.27 [0.56, 2.98] |
| Test for overall effect: Z = 1.65 (P = 0.10) |

| Total (95% CI)    |         |       | 100.0%     | 1.19 [0.79, 1.78] |

Heterogeneity: 95% prediction interval (0.49, 2.39)

Test for overall effect: Z = 1.29 (P = 0.20)

Test for subgroup differences: Chi² = 0.05, df = 1, P = 0.99

* only provided the adjusted estimate
Supplemental Figure 7. Forest plot of unadjusted analyses for association between sex and all-cause ICU mortality

| Study or Subgroup   | Females Events | Total Events | Males Events | Total Events | Odds Ratio Random, 95% CI | Odds Ratio HRSJ adjustment, Random, 95% CI |
|---------------------|----------------|--------------|--------------|--------------|---------------------------|------------------------------------------|
| Luethi 2017         | 159            | 908          | 209          | 1080         | 0.87 [0.69, 1.08]         |                                          |
| Luethi 2020*        | 71             | 962          | 03           | 835          | 1.14 [0.82, 1.59]         |                                          |
| Nachigall 2011      | 30             | 139          | 27           | 197          | 1.89 [1.06, 3.39]         |                                          |
| Pittiripiti 2010     | 2075           | 8702         | 2336         | 10055        | 1.19 [1.03, 1.37]         |                                          |
| Saida 2013          | 54             | 65           | 102          | 220          | 2.02 [1.20, 3.37]         |                                          |
| van Vugt 2017       | 141            | 565          | 201          | 838          | 1.14 [0.88, 1.49]         |                                          |
| Total (95% CI)       | 10802          | 13235        |              |              | 1.15 [0.87, 1.52]         |                                          |
| Total events        | 2630           | 2947         |              |              |                           |                                          |
| Heterogeneity        | 95% prediction interval: 1.15 [0.68, 2.00] |
| Tau² = 0.02; Chi² = 12.08; df = 5 (P = 0.02); P = 61% |
| Test for overall effect: Z = 1.87 (P = 0.10) |

* Luethi 2020 reported an overall unadjusted odds ratio.

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