Universiteit Leiden
The Netherlands

Staphylococcus aureus colonization and infection: optimizing MRSA decolonization and addressing challenges in S. aureus bacteremia management

Westgeest, A.C.

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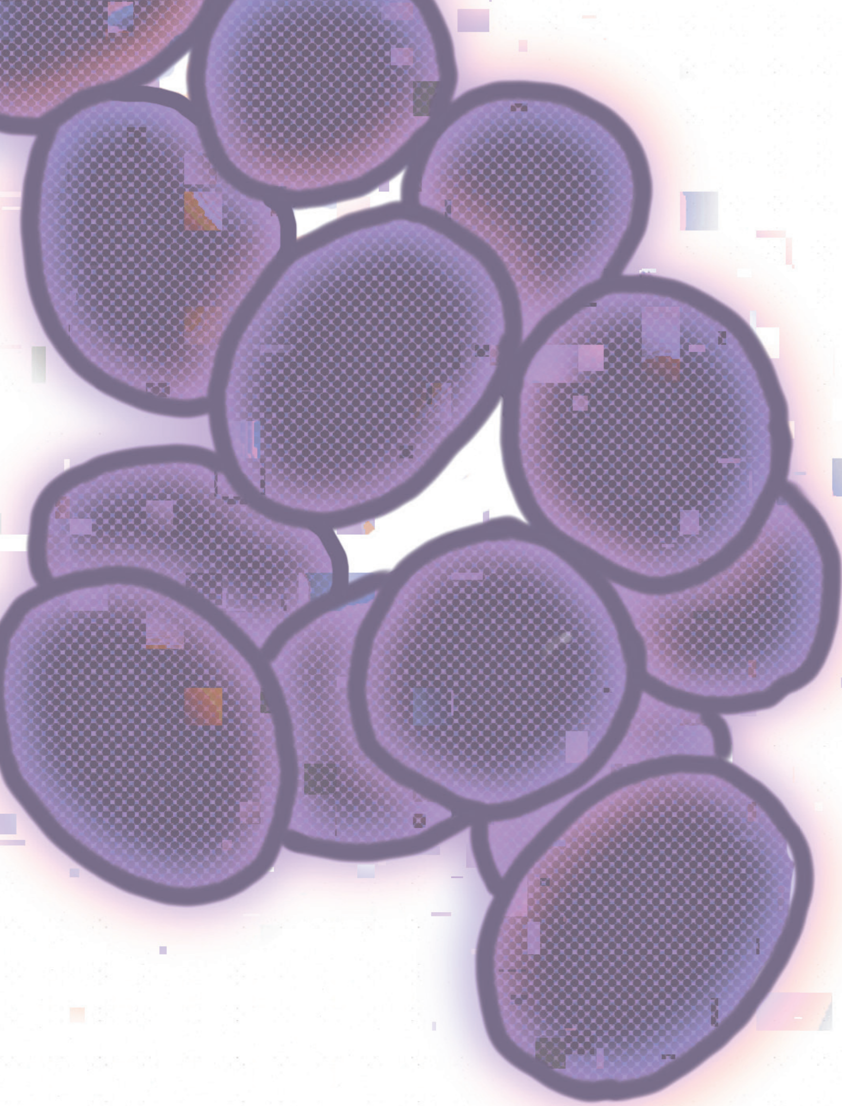

Chapter 10

Female sex and mortality in patients with *Staphylococcus aureus* bacteremia: a systematic review and meta-analysis

Annette C. Westgeest, Merel M.C. Lambregts, Felicia Ruffin, Rachel E. Korn, Maren E. Webster, Jackson L. Kair, Joshua B. Parsons, Stacey A. Maskarinec, Samantha Kaplan, Olaf M. Dekkers, Mark G.J. de Boer, Vance G. Fowler Jr., Joshua T. Thaden

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Abstract

Importance. *Staphylococcus aureus* is the leading cause of death due to bacterial bloodstream infection. Female sex has been identified as a risk factor for mortality in *S aureus* bacteremia (SAB) in some studies, but not in others.

Objective. To determine whether female sex is associated with increased mortality risk in SAB.

Data sources. MEDLINE, Embase, and Web of Science were searched from inception to April 26, 2023.

Study selection. Included studies met the following criteria: (1) randomized or observational studies evaluating adults with SAB, (2) included 200 or more patients, (3) reported mortality at or before 90 days following SAB, and (4) reported mortality stratified by sex. Studies on specific subpopulations (eg, dialysis, intensive care units, cancer patients) and studies that included patients with bacteremia by various microorganisms that did not report SAB-specific data were excluded.

Data extraction and synthesis. Data extraction and quality assessment were performed by 1 reviewer and verified by a second reviewer. Risk of bias and quality were assessed with the Newcastle-Ottawa Quality Assessment Scale. Mortality data were combined as odds ratios (ORs).

Main outcome and measures. Mortality at or before 90-day following SAB, stratified by sex.

Results. From 5339 studies retrieved, 89 were included (132 582 patients; 50 258 female [37.9%], 82 324 male [62.1%]). Unadjusted mortality data were available from 81 studies (109 828 patients) and showed increased mortality in female patients compared with male patients (pooled OR, 1.12; 95% CI, 1.06-1.18). Adjusted mortality data accounting for additional patient characteristics and treatment variables were available from 32 studies (95 469 patients) and revealed a similarly increased mortality risk in female relative to male patients (pooled adjusted OR, 1.18; 95% CI, 1.11-1.27). No evidence of publication bias was encountered.

Conclusions and relevance. In this systematic review and meta-analysis, female patients with SAB had higher mortality risk than males in both unadjusted and adjusted analyses. Further research is needed to study the potential underlying mechanisms.

Introduction

Staphylococcus aureus is the leading cause of death due to bacterial bloodstream infection [1]. Previously identified risk factors for mortality in patients with *Staphylococcus aureus* bacteremia (SAB) have included increasing age, infective endocarditis, hemodialysis dependence, and persistent bacteremia, among others [2]. Female sex has been suggested as risk factor for mortality in SAB in several studies, with an increase of mortality of up to 30% relative to male patients [3-5]. However, other studies found no sex inequality in outcome of SAB [6,7], or even a higher mortality in male individuals in a subgroup of patients with a higher comorbidity score [8]. Thus, the impact of female sex in SAB remains unclear. The aim of this systematic review and meta-analysis was to determine whether female sex is associated with mortality in SAB.

Methods

The key question of this systematic review was: is female sex associated with increased mortality risk in patients with SAB? The study protocol was registered on Prospero (CRD42022373176). We followed the meta-analysis of observational studies in epidemiology Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline as the included studies involved observational data.

Search strategy

We conducted a literature search of MEDLINE via PubMed, Embase via Elsevier, and Web of Science Core Collection (1900 to present) via Clarivate from inception to October 31, 2022, using a combination of key words to capture *S aureus*, bacteremia, mortality, and sex (eAppendix 1 in Supplement 1). An experienced medical librarian (S.K.) devised, developed, and executed the search with input from the entire team. The search was peer reviewed by a second medical librarian according to a modified Peer Review of Electronic Search Strategies (PRESS) checklist [9]. No limitations were placed on language in the initial search, but studies published in languages other than English were excluded in the full-text review phase. A search update was conducted on April 26, 2023, to identify newly published studies. In addition, we hand-searched key references to identify citations not captured in the electronic database searches. All results were compiled in EndNote and imported into Covidence, a web-based data synthesis software program [10], for deduplication and screening.

Study selection, data extraction, and quality assessment

We included studies that met the following conditions: (1) randomized or observational study evaluating outcomes in adults with SAB, (2) included 200 or more patients, (3) reported mortality at or before 90 days following SAB, and (4) reported mortality stratified by sex. Exclusion criteria were studies on specific subpopulations (eg, dialysis, intensive care unit, hematological or oncological patients), studies that included SAB patients as a subgroup (eg, patients with bacteremia by any microorganism) that did not report SAB-specific data, and studies using (partially) the same cohort as another study included in this review. In this latter scenario, the study with the largest cohort was included. Titles and abstracts of articles (with authors and institutions visible) identified through our primary search were screened independently by two reviewers (A.W. reviewed all; R.K., M.W., J.K., F.R., J.P., S.M., S.K., M.L., V.F., and J.T. were second reviewers). Conflicts at this stage were resolved by a third person. Articles marked for full-text review underwent full-text screening by two independent reviewers. Conflicts at this stage were resolved by consensus or by obtaining a third reviewer's opinion when consensus could not be reached. Data extraction and quality assessment was done by one reviewer and verified by a second reviewer. Extracted variables included lead author, journal, year of publication, start and end year of inclusion, country, aim of study, study design, number of hospitals, number of patients, population description, and whether methicillin-resistant *S aureus* (MRSA), methicillin-susceptible *S aureus* (MSSA), or both were addressed. Unadjusted mortality stratified by sex was extracted, as well as adjusted mortality when reported, the statistical model and the covariates for which mortality was adjusted. If a study described mortality for two subgroups (eg, for MSSA and MRSA bacteremia separately), both were included. Risk of bias and quality were assessed with the Newcastle-Ottawa Quality Assessment Scale [11] (eAppendix 2 in Supplement 1) because only observational studies were identified.

Statistical analysis

Mortality data were combined as odds ratios (ORs). If ORs were not reported in a study, we calculated ORs from raw mortality by sex if such data was available. If raw data was not available either, then ORs were calculated from the provided risk ratio (RR) or hazard ratio (HR) values based on previously published methods [12,13]. In the single study that reported a rate ratio [14], this rate ratio was used to estimate the OR [15]. Sensitivity analyses involving only studies that directly reported an OR (as opposed to estimating OR based on HR or RR) were conducted. ORs were combined using inverse variance with random effects models. We used the Knapp and Hartung method to adjust the standard errors of the estimated coefficients [16,17]. Robustness of findings were assessed through influence and sensitivity analyses as detailed in the

text. We evaluated statistical heterogeneity with the Cochran Q and I2 statistics. To explore potential sources of heterogeneity, we performed meta-analyses on subsets of studies to determine if variation in factors such as mortality time point (eg, 30-day vs 90-day mortality), bacterial groups (eg, MSSA only, MRSA only, both MSSA and MRSA), or geographic location between studies could be contributing. Statistical analyses were performed with RStudio version 2022.02.0 (R Project for Statistical Computing). Publication bias was assessed using funnel plots with the Egger test [18] when ten or more studies were included in the analysis. We used the Evidence-based Practice Center (EPC) model from the US Agency for Healthcare Research and Quality (AHRQ) to grade overall strength of evidence [19]. A full description of the EPC approach is detailed in eAppendix 3 in Supplement 1.

Results

We screened the title and abstract of 5339 studies, and 4778 were deemed irrelevant (Figure 1). A full-text assessment was performed on 561 studies, and 472 of these were excluded. We included 89 studies in the analysis, with a total of 132 582 patients (50 258 female [37.9%], 82 324 male [62.1%]) (Table) [3-8,14,20-101]. All data on mortality by sex were from observational studies: 88 of 89 cohort studies and one post hoc analysis of a randomized clinical trial. Mortality was most frequently assessed at 28 to 30 days (54 of 89 studies [61%]). The majority of studies were conducted in Europe (36 [40%]), Asia (24 [28%]) and North America (20 [22%]). The majority of studies were published after 2010 (68 [76%]). Thirty-two studies (36%) were rated as having low risk of bias, and 57 studies (64%) as having high risk of bias (detailed quality assessment of each study in eTable 1 in Supplement 1).

Mortality by sex

Unadjusted mortality data was available from 81 studies (109 828 patients) and revealed an increased mortality risk in female compared with male patients (pooled OR, 1.12; 95% CI, 1.06-1.18) (Figure 2). Moderate heterogeneity was observed in this analysis ($Q = 130.17$; $P < .001$; $I2 = 37\%$). An influence analysis revealed that exclusion of any single study did not significantly alter the findings from the overall cohort (eAppendix 4 in Supplement 1). A sensitivity analysis with only studies that had an OR that was either reported or could be directly calculated (ie, excluding 14 studies in which RR or HR were reported) similarly did not change the overall findings (eFigure 1 in Supplement 1). Exclusion of single-center studies did not change the overall findings. No funnel plot asymmetry was found (eFigure 2 in Supplement 1).

Figure 1. Search flow diagram of systematic review

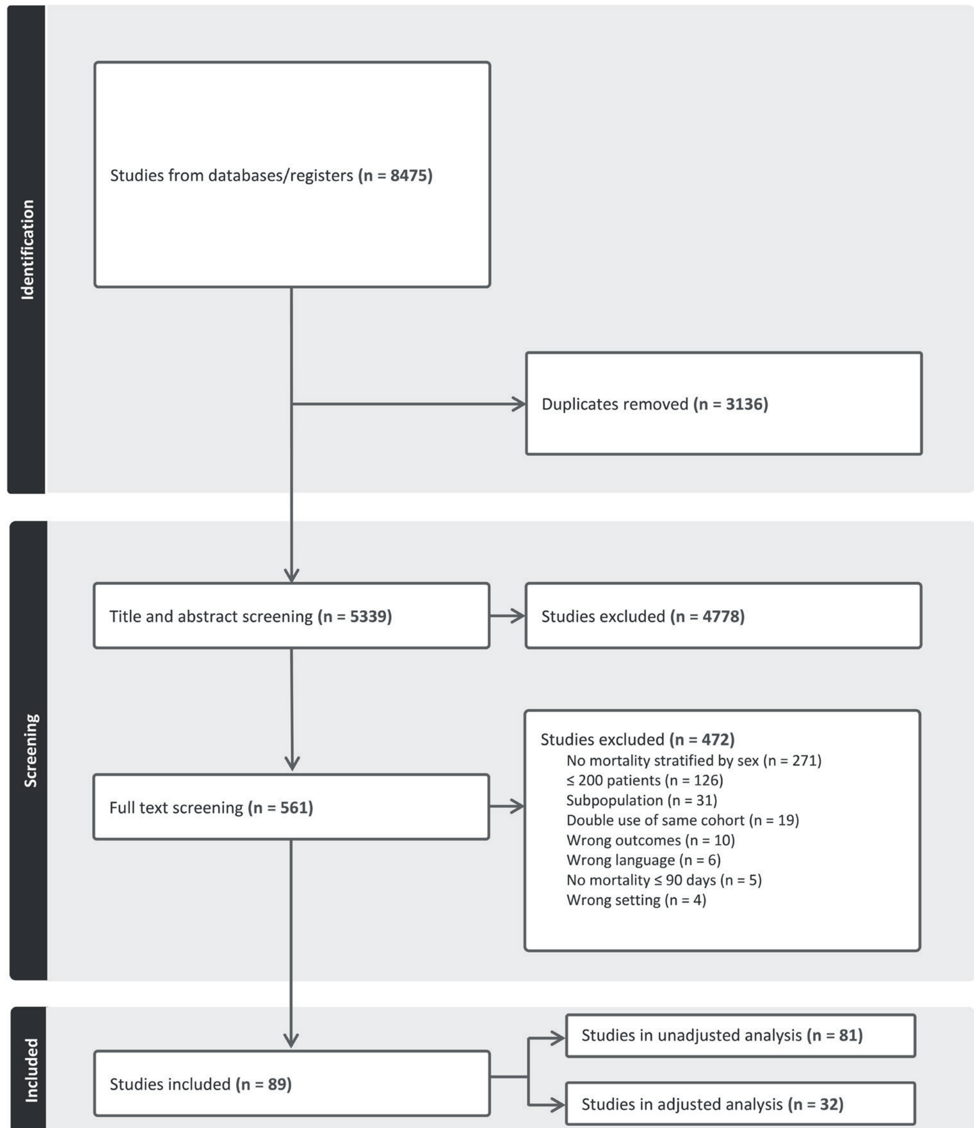


Table 1 (next page). Description of studies included in systematic review.

	Number of studies (%) N= 89
Publication year	
2000-2010	21 (24)
2011-2023	68 (76)
Study design	
Cohort study	88 (99)
Post-hoc analysis randomized trial	1 (1)
Continent	
Europe	36 (40)
Asia	24 (27)
North America	20 (22)
Oceania	5 (6)
South America	1 (1)
Africa	1 (1)
Multiple	2 (2)
Number of hospitals included	
1	44 (49)
2-20	33 (37)
>20	13 (15)
Number of patients included	
200 – 1,000	69 (78)
1,000 – 10,000	15 (17)
>10,000	4 (4)
Population	
All SAB patients	82 (92)
Healthcare/hospital-associated SAB	3 (3)
Community-acquired SAB	4 (4)
Outcome measure	
7 day mortality	1 (1)
14 day mortality	4 (4)
28-30 day mortality	54 (61)
90 day mortality	9 (10)
In-hospital mortality	16 (18)
Attributable mortality	5 (6)
MRSA vs MSSA	
Both MRSA and MSSA	59 (66)
Only MRSA	20 (22)
Only MSSA	10 (11)

Figure 2. Forest Plot of Unadjusted Mortality in Female vs Male Patients With *Staphylococcus aureus* Bacteremia

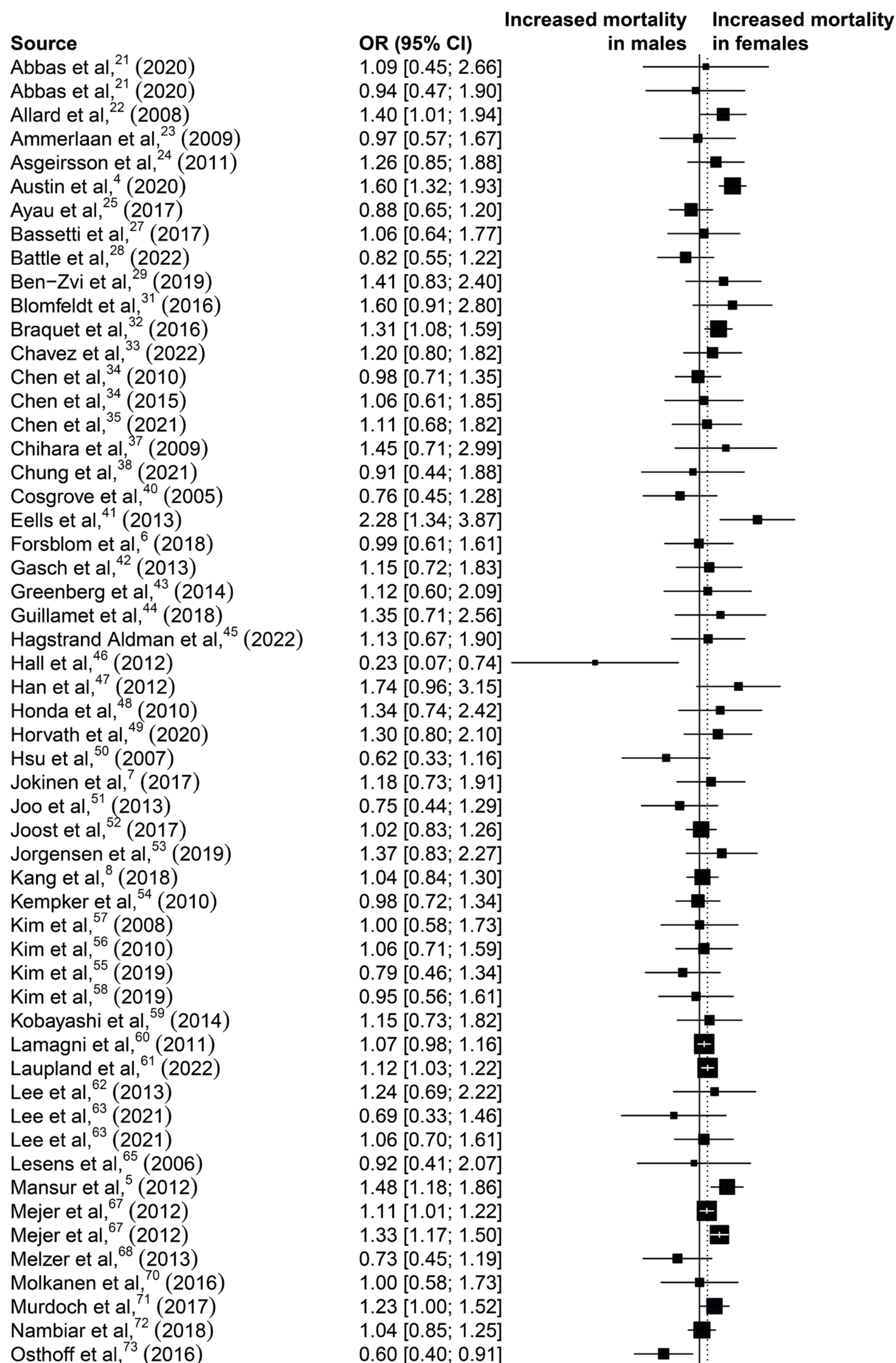
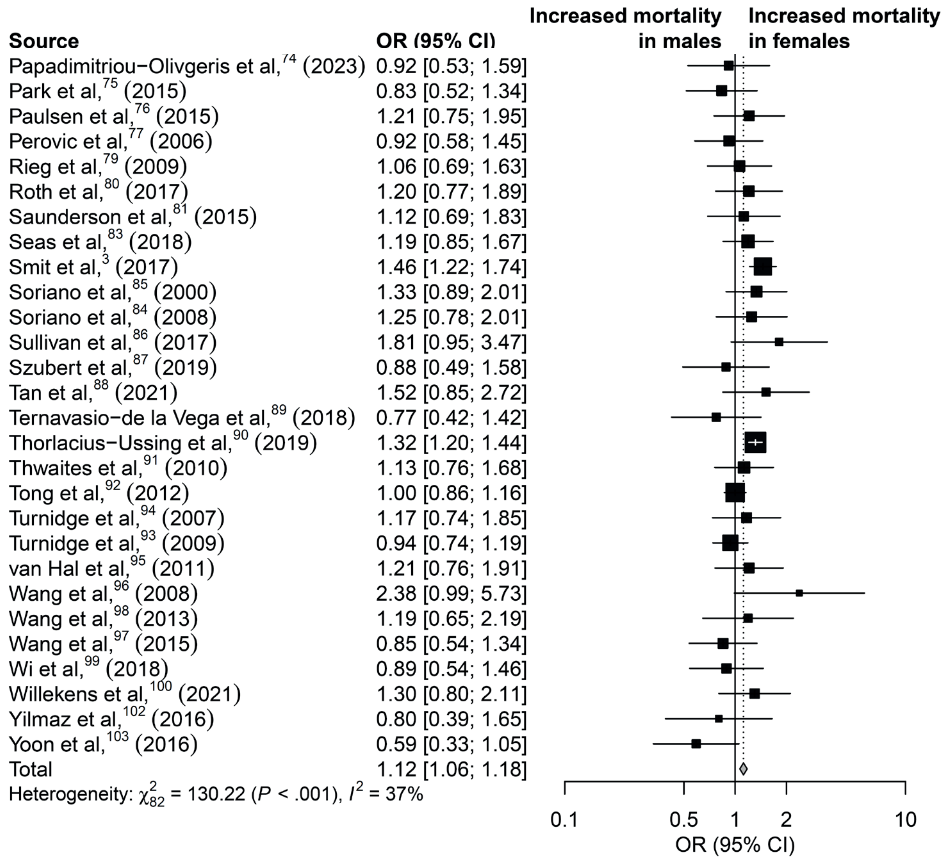


Figure 2 - continued



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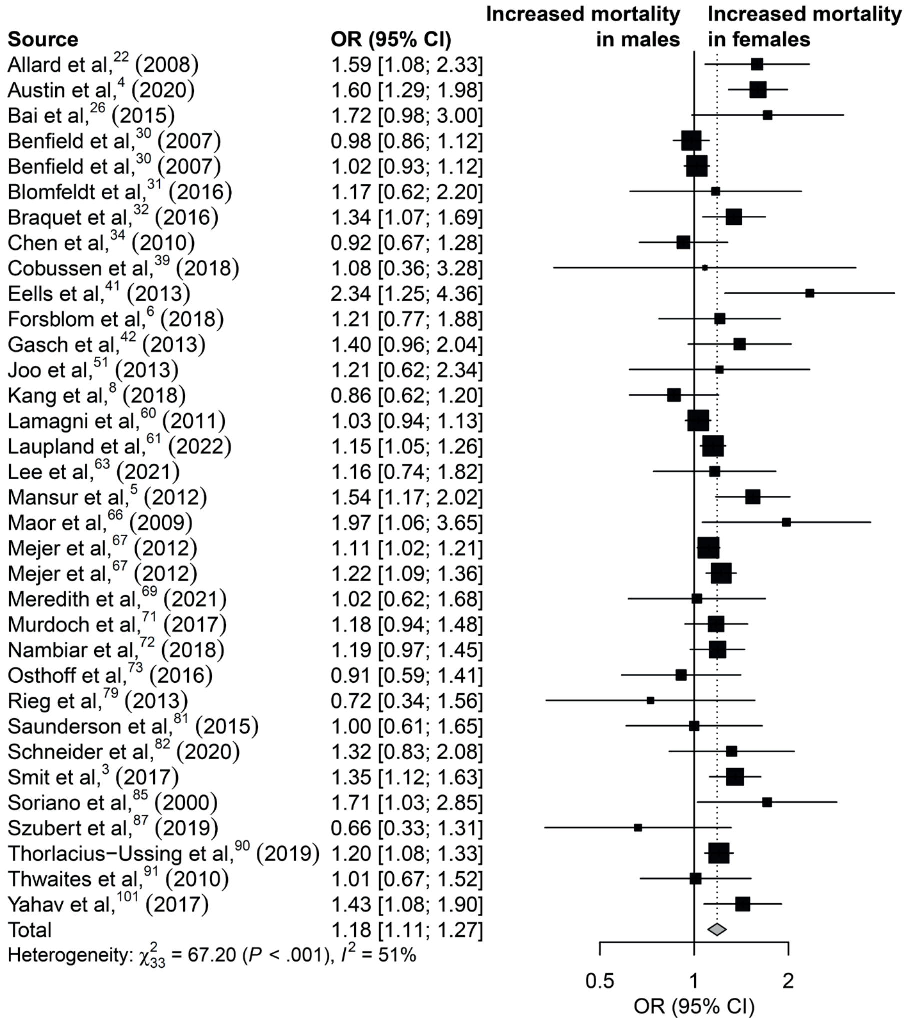
Adjusted mortality data that accounted for patient characteristics and treatment variables was available from 32 studies (95 469 patients) and revealed a similarly increased mortality risk in female relative to male patients (pooled adjusted OR [aOR], 1.18; 95% CI, 1.11-1.27) (Figure 3). An influence analysis revealed that exclusion of any single study did not significantly alter the findings from the overall cohort (eAppendix 5 in Supplement 1). A sensitivity analysis with only studies that had an OR that was either reported or could be directly calculated (ie, excluding 14 studies in which RR or HR were reported) similarly did not change the overall findings (eFigure 3 in Supplement 1). No funnel plot asymmetry was found (eFigure 4 in Supplement 1). Substantial heterogeneity was observed in this analysis of adjusted mortality data ($Q = 66.98$; $P < .001$; $I2 = 51\%$). Meta-analyses on subsets of studies showed that variation in the geographic location of the study impacted heterogeneity.

Meta-analyses of studies conducted in individual geographic regions all had lower observed heterogeneity than the overall cohort (overall I2 = 51%): Europe (19 studies; I2 = 41%), North America (5 studies; I2 = 12%), East Asia (4 studies; I2 = 0%), and Middle East (3 studies; I2 = 0%). The pooled aOR varied significantly based on geographic location of study and ranged from 0.96 (95% CI, 0.76-1.22) for studies conducted in East Asia to 1.57 (95% CI, 1.23-2.01) for studies conducted in North America. Stratification of studies by mortality time point or by methicillin resistance did not impact heterogeneity.

Evaluation of the evidence

Given that this systematic review contained observational studies that accounted for confounding through statistical adjustment (ie, the adjusted analysis), the baseline strength of evidence was moderate. The mortality effect estimate was downrated due to a serious risk of bias because studies without a sex-difference in a univariable analysis would likely not have included this variable in a multivariable analysis. We did not have serious concerns about inconsistency, indirectness, imprecision, or publication bias. Therefore, the overall strength of evidence for the association of female sex with increased mortality risk in patients with SAB was low (eTable 2 in Supplement 1).

Figure 3. Forest plot of adjusted mortality in female vs male patients with *Staphylococcus aureus* bacteremia



Discussion

In this systematic review and meta-analysis, we addressed the question of whether female sex is associated with increased mortality risk in patients with SAB. The included studies involved over 130 000 patients and identified an association between female sex and increased mortality risk in both unadjusted and adjusted analyses. Heterogeneity was observed, but substantially decreased with stratification by geographic region. This may reflect the large practice variations for SAB throughout the world, as recently described in a global survey [102].

This study sheds new light on sex differences in clinical outcomes of patients with SAB, which is an area of little clarity. Few studies have primarily focused on sex differences in outcome in SAB patients, and their results have been contradictory. Some studies reported higher mortality in female patients with SAB compared with male patient [3,5], while others did not report an overall sex-difference in mortality [6,8]. In this meta-analysis we identified a relatively large (18%) increased odds of death in female patients compared with male patients. This association was significant in both the unadjusted analysis and in an adjusted analysis that accounted for patient co-morbidities and treatment variables. Beyond patients with SAB, excess mortality has been reported in female patients with hospital-acquired bloodstream infection [103], severe sepsis [104-106], and endocarditis [107]; however, conflicting evidence has been reported as well [108].

The underlying causes of sex differences in clinical outcomes of patients with SAB were not addressed in this study. Sex-related differences in outcome may be due to a variety of social or biological factors. Firm data for a biological connection between sex differences in clinical outcomes from animal models has been elusive. Previous studies on sepsis have generally supported better outcomes in female patients relative to male [109]. This has been hypothesized to stem from the positive immunomodulatory properties of sex hormones on cell-mediated immune responses and cardiovascular functions in female patients [110,111] as well as the suppression of the anti-infective response by testosterone in male patients [112]. Even an ongoing immunological advantage in postmenopausal septic women has been reported [113]. In *S aureus* infections in particular, an animal study showed enhanced neutrophil bactericidal capacity in female mice [114]. However, females were more susceptible to lethal toxic shock caused by *S aureus* enterotoxin B in another mouse model [115]. Social factors could also be contributing to the observed differences in mortality between female and male patients with SAB. Analogous to acute myocardial infarction, where women waited longer before seeking treatment relative to men, gender-differences in health seeking behavior may exist in SAB patients [116]. Gender bias in health care delivery can potentially contribute to the difference in

outcome as well. Delays in antibiotic treatment and less invasive treatment have been reported in women with septic shock and critical illness [105,117-119], and women were less likely to receive the recommended quality of acute care compared with men in a US study on quality of care in sociodemographic subgroups [120]. In a 2023 cohort study from our research group [121], women with SAB received shorter durations of antimicrobial treatment and were less likely to undergo transesophageal echocardiography compared to men. Regional or cultural differences in health care delivery could be impacting the observed sex-based difference in patient outcomes. The association between female sex and mortality varied to some degree by location of study, and we have previously shown that there is considerable global variation in SAB treatment factors [102]. Finally, response to treatment can differ between female and male patients. Both pharmacokinetics and pharmacodynamics are generally subject to sex influences [122].

Limitations

This study had several limitations. First, sex difference was not the primary outcome of interest in the majority of the included studies. Therefore, a number of studies did not include adjusted data for mortality by sex, and inclusion of this data could have influenced the results. Second, reporting bias can exist as studies may not report mortality stratified by sex if there was no significant difference in mortality. Third, heterogeneity exists not only in study methodology but also in the disease itself.

The clinical presentation of SAB may vary from uncomplicated intravenous catheter-related bacteremia to complicated metastatic disease. Because all studies on SAB patients were included in our study, sex-based differences in outcome could not be stratified by infection severity. Lastly, whether reported sex represented sex assigned at birth or gender, was often not specified.

Conclusions

In this systematic review and meta-analysis, observational cohort studies demonstrated an association between female sex and increased mortality risk in adult patients with SAB. This association remained significant after including only studies that adjusted for patient clinical and treatment variables. Future research should focus on understanding the underlying causes and on promoting better outcomes in female patients with SAB. Fundamental research on biological sex differences in immune response or pharmacology, examinations of sex-based differences in management of SAB, and better reporting of sex-specific outcomes in randomized clinical trials are necessary to better understand the observed sex-specific differences in mortality among patients with SAB.

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eTable 2. Evidence profile for association of female sex and mortality in patients with *Staphylococcus aureus* bacteremia

eAppendix 1. Search Strategy Report: Original Search

Topic: Association of female sex with mortality in patients with *Staphylococcus aureus* bloodstream infections

Searcher: SJK

Date: 10.31.2022 Updated 4.26.2023

Database (including vendor/platform): MEDLINE (via PubMed)

Set #	Search Strategy	Results
#1 Staph	"Staphylococcus aureus"[Mesh] OR "staphylococcus aureus"[tiab] OR "s. aureus"[tiab] OR "s aureus"[tiab] OR "staph aureus"[tiab]	**150579**
#2 Infection	"Endocarditis, Bacterial"[Mesh] OR "Bacteremia"[Mesh] OR bacteremia[tiab] OR bacteraemia[tiab] OR bacteremias[tiab] OR bacteraemias[tiab] OR bacteremic[tiab] OR bacteraemic[tiab] OR ((bloodstream[tiab] OR "blood stream"[tiab] OR bloodstreams[tiab] OR "blood streams"[tiab]) AND (infection[tiab] OR infections[tiab] OR infected[tiab] OR infect[tiab] OR infects[tiab] OR infecting[tiab])) OR endocarditis[tiab]	**105361**
#3 Mortality	"Mortality"[sh] OR "Mortality"[Mesh] OR mortality[tiab] OR mortalities[tiab] OR fatal[tiab] OR fatality[tiab] OR fatalities[tiab] OR death[tiab] OR deaths[tiab] OR dying[tiab] OR die[tiab] OR died[tiab]	**2467469**
#4 Sex	"Female"[Mesh] OR "Male"[Mesh] OR "Sex Factors"[Mesh] OR female[tiab] OR females[tiab] OR male[tiab] OR males[tiab] OR women[tiab] OR woman[tiab] OR "womens" OR "womans" OR men[tiab] OR gender[tiab] OR genders[tiab] OR sex[tiab] OR sexes[tiab]	**13302123**
#5	1 AND 2 AND 3 AND 4	**3106**
#6	AND ("2022/01/01"[Date - MeSH] : "3000"[Date - MeSH])	**119**
Validation String	27343816 OR 26873381 OR 30194636 OR 29667110 OR 31185081 OR 23141419	**6/6**

Database (including vendor/platform): Embase via Elsevier

Set #	Search Strategy	Results
#1 Staph	'Staphylococcus aureus'/exp OR 'staphylococcus aureus':ti,ab OR 's. aureus':ti,ab OR 's aureus':ti,ab OR 'staph aureus':ti,ab	**249714**
#2 Infection	'bacteremia'/exp OR 'bacterial endocarditis'/exp OR bacteremia:ti,ab OR bacteraemia:ti,ab OR bacteremias:ti,ab OR bacteraemias:ti,ab OR bacteremic:ti,ab OR bacteraemic:ti,ab OR ((bloodstream:ti,ab OR 'blood stream':ti,ab OR bloodstreams:ti,ab OR 'blood streams':ti,ab) AND (infection:ti,ab OR infections:ti,ab OR infected:ti,ab OR infect:ti,ab OR infects:ti,ab OR infecting:ti,ab)) OR endocarditis:ti,ab	**153847**

#3 Mortality	'mortality'/de OR 'mortality rate'/exp OR mortality:ti,ab OR mor-talities:ti,ab OR fatal:ti,ab OR fatality:ti,ab OR fatalities:ti,ab OR death:ti,ab OR deaths:ti,ab OR dying:ti,ab OR die:ti,ab OR died:ti,ab	**3345439**
#4 Sex	'female'/exp OR 'male'/exp OR 'sex difference'/exp OR female:ti,ab OR females:ti,ab OR male:ti,ab OR males:ti,ab OR women:ti,ab OR woman:ti,ab OR womens OR womans OR men:ti,ab OR gender:ti,ab OR genders:ti,ab OR sex:ti,ab OR sexes:ti,ab	**16110857**
#5	#1 AND #2 AND #3 AND #4	**6105**
#6	#1 AND #2 AND #3 AND #4 AND [humans]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim)	**4138**
#7	#1 AND #2 AND #3 AND #4 AND [humans]/lim AND ([article]/lim OR [article in press]/lim OR [conference paper]/lim) AND [01-09-2022]/sd NOT [27-04-2023]/sd	**334**

Database (including vendor/platform): Web of Science Core Collection (1900-present) via Clarivate

Set #	Search Strategy	Results
#1 Staph	TS=("staphylococcus aureus" OR "s. aureus" OR "s aureus" OR "staph aureus")	**179081**
#2 Infection	TS=(bacteremia OR bacteraemia OR bacteremias OR bacteraemias OR bacteremic OR bacteraemic OR ((bloodstream OR "blood stream" OR bloodstreams OR "blood streams") AND (infection OR infections OR infected OR infect OR infects OR infecting)) OR endocarditis)	**102399**
#3 Mortality	TS=(mortality OR mortalities OR fatal OR fatality OR fatalities OR death OR deaths OR dying OR die OR died)	**2964183**
#4 Sex	TS=(female OR females OR male OR males OR women OR woman OR womens OR womans OR men OR gender OR genders OR sex OR sexes)	**4924618**
#5	1 AND 2 AND 3 AND 4	**936**
#6	Refined by Publication Years: 2022 or 2023	**101**

eAppendix 2. Newcastle-Ottawa Quality Assessment Scale for assessing risk of bias in observational studies. Risk of bias was assessed with the Newcastle-Ottawa Assessment Scale using the questions below. The procedure for converting the responses to an overall risk of bias assessment (i.e., low, medium, or high risk of bias) is detailed here as well.

Selection

1. Representativeness of the exposed cohort

a. Truly representative of the average patient with *S. aureus* bloodstream infection in the community (*)

b. Somewhat representative of the average patient with *S. aureus* bloodstream infection in the community (*)

c. Selected group of patients

d. No description of the derivation of the cohort

2. Selection of the non-exposed cohort

a. Drawn from the same community as the exposed cohort (*)

b. Drawn from a different source

c. No description of the derivation of the non-exposed cohort

3. Ascertainment of exposure

a. Secure record (e.g. medical records) (*)

b. Structured interview (*)

c. Written self-report

d. No description

4. Demonstration that outcome of interest was not present at start of study

a. Yes (*)

b. No

Comparability of cohorts on basis of design or analysis

1. Study controls for level of acute illness

a. Yes (*)

b. No

2. Study controls for any additional factor.

a. Yes (*)

b. No

Outcome

1. Assessment of outcome

a. Independent blind assessment (*)

b. Record linkage (*)

c. Self-report

d. No description

2. Was follow-up long enough for outcomes to occur

a. Yes (*)

b. No

3. Adequacy of follow up of cohorts

a. Complete follow up (all subjects accounted for) (*)

b. Subjects lost to follow up unlikely to introduce bias (≤10% lost to follow-up, or description provided of those lost) (*)

c. Follow up rate < 90% and no description of those lost

d. No statement

Thresholds used to convert the Newcastle-Ottawa scale to categories (good, fair, and poor):

Good quality/low risk of bias: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality/medium risk of bias: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.

Poor quality/high risk of bias: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

eAppendix 3. Description of EPC approach.

We used the Evidence-based Practice Center (EPC) model from the U.S. Agency for Healthcare Research and Quality (AHRQ) to grade the overall strength of evidence [20]. The EPC approach evaluates the following domains: study limitations/risk of bias, consistency, directness, precision, and reporting bias. In brief, the EPC classification system applies an overall strength of evidence grade rating to an estimate effect from a body of evidence: high (we are very confident that the estimate of effect lies close to the true effect for this outcome), moderate (we are moderately confident that the estimate of effect lies close to the true effect for this outcome), low (we have limited confidence that the estimate of effect lies close to the true effect for this outcome), or insufficient (we have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome). The initial strength of evidence grade was moderate given that the included observational studies in the primary adjusted analysis reduced bias from confounding through matching or statistical adjustment [20]. This baseline category could be rated down if the included studies demonstrated high risk of bias, imprecision, inconsistency, indirectness, or reporting bias.

eTable 1 (next page). Newcastle-Ottawa quality assessment of individual studies

The Newcastle-Ottawa Quality Assessment Scale determines a study's risk of bias through nine questions (detailed in Appendix 2). For each study, the grades for the nine questions are shown below. Grades that receive a star are highlighted in green, while those that do not are highlighted in red. Based on the grades from each question in the Newcastle-Ottawa Scale, an overall risk of bias (high, medium, low) can be assigned (detailed in Appendix 2).

Study	**Selection:** Representativeness of the exposed cohort	**Selection:** Selection of the non-exposed cohort	**Selection:** Ascertainment of exposure	**Selection:** Outcome of interest not present at start	**Comparability:** Study controls for level of acute illness	**Comparability:** Study controls for any additional factor	**Outcome:** Assessment of outcome	**Outcome:** Follow-up long enough for outcomes to occur	**Outcome:** Adequacy of follow up of cohorts	**Risk of bias**
Abbas 2020	b	a	a	a	b	b	b	a	a	Poor
Allard 2008	b	a	a	a	b	a	b	a	a	Good
Ammerlaan 2009	a	a	a	a	b	b	b	a	a	Poor
Asgeirsson 2011	b	a	a	a	b	b	b	a	a	Poor
Austin 2020	b	a	a	a	a	a	b	a	a	Good
Ayau 2017	c	a	a	a	b	b	b	a	a	Poor
Bai 2015	c	a	a	a	a	a	b	a	a	Good
Bassetti 2017	b	a	a	a	b	b	b	a	a	Poor
Battle 2022	b	a	a	a	b	b	b	a	a	Poor
Ben-Zvi 2019	b	a	a	a	b	b	b	a	a	Poor
Benfield 2007	b	a	a	a	b	a	b	a	b	Good
Blomfeldt 2016	b	a	a	a	b	a	b	a	d	Good
Braquet 2016	b	a	a	a	a	a	b	a	b	Good
Chavez 2022	b	a	a	a	b	b	b	a	d	Poor
Chen 2010	b	a	a	a	a	a	b	a	a	Good
Chen 2015	b	a	a	a	b	b	b	a	b	Poor
Chen 2021	c	a	a	a	b	b	b	a	a	Poor
Chihara 2009	c	a	a	a	b	b	b	a	a	Poor
Chung 2021	c	a	a	a	b	b	b	a	a	Poor
Cobussen 2018	b	a	a	a	a	a	b	a	a	Good

Cosgrove 2005	b	a	a	a	b	b	b	a	a	Poor
Eells 2013	c	a	a	a	a	a	b	a	a	Good
Forsblom 2018	c	a	a	a	a	a	b	a	b	Good
Gasch 2013	c	a	a	a	a	a	b	a	b	Good
Greenberg 2014	b	a	a	a	b	b	b	a	a	Poor
Guillamet 2018	c	a	a	a	b	b	b	a	b	Poor
HagstrandAldman 2022	c	a	a	a	b	b	b	a	a	Poor
Hallli 2012	c	a	a	a	b	b	b	a	a	Poor
Han 2012	b	a	a	a	b	b	b	a	a	Poor
Honda 2010	b	a	a	a	b	b	b	a	a	Poor
Horváth 2020	b	a	a	a	b	b	b	a	a	Poor
Hsu 2007	c	a	a	a	b	b	b	a	a	Poor
Jokinen 2017	b	a	a	a	b	b	b	a	c	Poor
Joo 2013	c	a	a	a	a	a	b	a	a	Good
Joost 2017	b	a	a	a	b	b	b	a	d	Poor
Jorgensen 2019	c	a	a	a	b	b	b	a	a	Poor
Kang 2018	b	a	a	a	a	a	b	a	d	Good
Kempker 2010	c	a	a	a	b	b	b	a	a	Poor
Kim 2008	b	a	a	a	b	b	b	a	a	Poor
Kim 2010	b	a	a	a	b	b	b	a	a	Poor
Kim 2019	b	a	a	a	b	b	b	a	d	Poor
Kim 2019	b	a	a	a	b	b	b	a	a	Poor
Kobayashi 2014	b	a	a	a	b	b	b	a	a	Poor
Lamagni 2011	c	a	a	a	a	a	b	a	a	Good
Laupland 2022	b	a	a	a	a	a	b	a	d	Good
Lee 2013	c	a	a	a	b	b	b	a	a	Poor
Lee 2021	c	a	a	a	b	a	b	a	a	Good
Lee 2021	c	a	a	a	b	b	b	a	a	Poor
Lesens 2006	a	a	a	a	b	b	b	a	a	Poor
Mansur 2012	b	a	a	a	a	a	b	a	a	Good
Maor 2009	c	a	a	a	b	a	b	a	d	Good
Mejer 2012	b	a	a	a	b	a	b	a	b	Good
Melzer 2013	c	a	a	a	b	b	b	a	a	Poor
Meredith 2021	b	a	a	a	a	a	b	a	d	Good
Mölkänen 2016	b	a	a	a	b	b	b	a	d	Poor
Murdoch 2017	b	a	a	a	b	a	b	a	d	Good

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Nambiar 2018	a	a	a	a	a	a	b	a	d	Good
Osthoff 2016	b	a	a	a	b	a	b	a	d	Good
Papadimitriou-Olivgeris	b	a	a	a	b	b	b	a	d	Poor
Park 2015	b	a	a	a	b	b	b	a	d	Poor
Paulsen 2015	b	a	a	a	b	b	b	a	a	Poor
Perovic 2006	b	a	a	a	b	b	b	a	b	Poor
Rieg 2009	b	a	a	a	b	b	b	a	a	Poor
Rieg 2013	b	a	a	a	b	a	b	a	d	Good
Roth 2017	b	a	a	a	b	b	b	a	b	Poor
Saunderson 2015	b	a	a	a	b	a	b	a	a	Good
Schneider 2020	b	a	a	a	b	a	b	a	a	Good
Seas 2018	a	a	a	a	b	b	b	a	b	Poor
Smit 2017	b	a	a	a	a	a	b	a	a	Good
Soriano 2000	b	a	a	a	a	a	b	a	a	Good
Soriano 2008	c	a	a	a	b	b	b	a	a	Poor
Sullivan 2017	c	a	a	a	b	b	b	a	d	Poor
Szubert 2019	b	a	a	a	a	a	b	a	d	Good
Tan 2021	b	a	a	a	b	b	b	a	d	Poor
Ternavasio-delaVega 2018	b	a	a	a	b	b	b	a	a	Poor
Thorlacius-Ussing 2019	b	a	a	a	b	a	b	a	a	Good
Thwaites 2010	a	a	a	a	b	a	b	a	b	Good
Tong 2012	b	a	a	a	b	b	b	a	a	Poor
Turnidge 2007	b	a	a	a	b	b	b	a	c	Poor
Turnidge 2009	b	a	a	a	b	b	b	a	a	Poor
vanHal 2011	b	a	a	a	b	b	b	a	a	Poor
Wang 2008	c	a	a	a	b	b	b	a	a	Poor
Wang 2013	b	c	a	a	b	b	b	a	a	Poor
Wang 2015	c	a	a	a	b	b	b	a	a	Poor
Wi 2018	a	c	a	a	b	b	b	a	d	Poor
Willekens 2021	b	a	a	a	b	b	b	a	a	Poor
Yahav 2017	b	c	a	a	b	a	b	a	a	Good
Yilmaz 2016	b	a	a	a	b	b	b	a	d	Poor
Yoon 2016	b	a	a	a	b	b	b	a	d	Poor

eAppendix 4. Influence analysis of unadjusted mortality in patients with *Staphylococcus aureus* bacteremia. An influence analysis showed that the overall results of the meta-analysis (i.e., association of female sex with increased mortality) did not change with removal of individual studies.

	OR	95%-CI	p-value	tau^2	tau	I^2
Omitting Abbas 2020	1.1193	[1.0648; 1.1766]	< 0.0001	0.0139	0.1178	37.8%
Omitting Abbas 2020	1.1201	[1.0656; 1.1774]	< 0.0001	0.0138	0.1177	37.6%
Omitting Allard 2008	1.1153	[1.0611; 1.1724]	< 0.0001	0.0139	0.1178	37.0%
Omitting Ammerlaan 2009	1.1203	[1.0657; 1.1777]	< 0.0001	0.0139	0.1179	37.6%
Omitting Asgeirsson 2011	1.1174	[1.0627; 1.1748]	< 0.0001	0.0141	0.1189	37.6%
Omitting Austin 2020	1.1119	[1.0605; 1.1659]	< 0.0001	0.0101	0.1007	31.3%
Omitting Ayau 2017	1.1242	[1.0697; 1.1814]	< 0.0001	0.0133	0.1153	36.4%
Omitting Bassetti 2017	1.1195	[1.0648; 1.1770]	< 0.0001	0.0140	0.1183	37.7%
Omitting Battle 2022	1.1238	[1.0696; 1.1807]	< 0.0001	0.0133	0.1153	36.4%
Omitting Ben-Zvi 2019	1.1172	[1.0629; 1.1744]	< 0.0001	0.0140	0.1182	37.5%
Omitting Blomfeldt 2016	1.1166	[1.0625; 1.1733]	< 0.0001	0.0138	0.1177	37.1%
Omitting Braquet 2016	1.1143	[1.0597; 1.1717]	< 0.0001	0.0139	0.1181	36.8%
Omitting Chavez 2022	1.1180	[1.0633; 1.1755]	< 0.0001	0.0142	0.1190	37.7%
Omitting Chen 2010	1.1215	[1.0667; 1.1791]	< 0.0001	0.0139	0.1180	37.3%
Omitting Chen 2015	1.1195	[1.0648; 1.1769]	< 0.0001	0.0140	0.1182	37.7%
Omitting Chen 2021	1.1191	[1.0644; 1.1766]	< 0.0001	0.0140	0.1185	37.8%
Omitting Chihara 2009	1.1179	[1.0636; 1.1750]	< 0.0001	0.0139	0.1180	37.6%
Omitting Chung 2021	1.1202	[1.0657; 1.1775]	< 0.0001	0.0138	0.1176	37.6%
Omitting Cosgrove 2005	1.1229	[1.0688; 1.1797]	< 0.0001	0.0134	0.1159	36.6%
Omitting Eells 2013	1.1144	[1.0622; 1.1691]	< 0.0001	0.0130	0.1140	34.5%
Omitting Forsblom 2018	1.1203	[1.0656; 1.1778]	< 0.0001	0.0139	0.1181	37.6%
Omitting Gasch 2013	1.1181	[1.0633; 1.1757]	< 0.0001	0.0142	0.1192	37.7%
Omitting Greenberg 2014	1.1191	[1.0645; 1.1765]	< 0.0001	0.0140	0.1182	37.8%
Omitting Guillamet 2018	1.1180	[1.0636; 1.1753]	< 0.0001	0.0140	0.1181	37.6%
Omitting Hagstrand Aldman 2022	1.1190	[1.0643; 1.1764]	< 0.0001	0.0140	0.1184	37.8%
Omitting HallIi 2012	1.1227	[1.0705; 1.1775]	< 0.0001	0.0133	0.1155	34.1%
Omitting Han 2012	1.1163	[1.0625; 1.1729]	< 0.0001	0.0138	0.1174	36.8%
Omitting Honda 2010	1.1181	[1.0635; 1.1754]	< 0.0001	0.0140	0.1183	37.7%
Omitting Horvath 2020	1.1176	[1.0630; 1.1749]	< 0.0001	0.0141	0.1185	37.6%
Omitting Hsu 2007	1.1234	[1.0698; 1.1797]	< 0.0001	0.0132	0.1151	35.9%
Omitting Jokinen 2017	1.1185	[1.0638; 1.1760]	< 0.0001	0.0141	0.1186	37.8%
Omitting Joo 2013	1.1227	[1.0687; 1.1795]	< 0.0001	0.0134	0.1160	36.6%
Omitting Joost 2017	1.1214	[1.0662; 1.1795]	< 0.0001	0.0142	0.1191	37.2%
Omitting Jorgensen 2019	1.1172	[1.0628; 1.1744]	< 0.0001	0.0140	0.1183	37.5%
Omitting Kang 2018	1.1207	[1.0655; 1.1787]	< 0.0001	0.0143	0.1196	37.4%
Omitting Kempker 2010	1.1216	[1.0668; 1.1793]	< 0.0001	0.0139	0.1180	37.3%
Omitting Kim 2008	1.1200	[1.0654; 1.1774]	< 0.0001	0.0139	0.1180	37.6%
Omitting Kim 2010	1.1196	[1.0648; 1.1772]	< 0.0001	0.0141	0.1188	37.7%
Omitting Kim 2019	1.1224	[1.0682; 1.1793]	< 0.0001	0.0135	0.1163	36.8%
Omitting Kim 2019	1.1205	[1.0659; 1.1779]	< 0.0001	0.0139	0.1178	37.5%
Omitting Kobayashi 2014	1.1187	[1.0640; 1.1762]	< 0.0001	0.0141	0.1187	37.8%
Omitting Lamagni 2011	1.1204	[1.0646; 1.1791]	< 0.0001	0.0148	0.1215	36.4%
Omitting Laupland 2022	1.1179	[1.0621; 1.1766]	< 0.0001	0.0151	0.1228	37.6%
Omitting Lee 2013	1.1184	[1.0638; 1.1757]	< 0.0001	0.0140	0.1183	37.7%
Omitting Lee 2021	1.1216	[1.0675; 1.1784]	< 0.0001	0.0136	0.1167	36.9%
Omitting Lee 2021	1.1196	[1.0648; 1.1772]	< 0.0001	0.0141	0.1187	37.7%
Omitting Lesens 2006	1.1200	[1.0655; 1.1772]	< 0.0001	0.0138	0.1176	37.6%
Omitting Mansur 2012	1.1130	[1.0596; 1.1691]	< 0.0001	0.0127	0.1127	35.3%
Omitting Mejer 2012	1.1185	[1.0628; 1.1772]	< 0.0001	0.0150	0.1225	37.5%
Omitting Mejer 2012	1.1128	[1.0585; 1.1699]	< 0.0001	0.0133	0.1152	34.9%
Omitting Melzer 2013	1.1239	[1.0700; 1.1805]	< 0.0001	0.0132	0.1149	36.1%
Omitting Molkanen 2016	1.1200	[1.0654; 1.1774]	< 0.0001	0.0139	0.1180	37.6%
Omitting Murdoch 2017	1.1158	[1.0609; 1.1737]	< 0.0001	0.0144	0.1201	37.5%
Omitting Nambiar 2018	1.1212	[1.0659; 1.1793]	< 0.0001	0.0143	0.1196	37.2%
Omitting Osthoff 2016	1.1292	[1.0770; 1.1838]	< 0.0001	0.0116	0.1075	32.8%
Omitting Papadimitriou-Olivgeris 2023	1.1208	[1.0662; 1.1781]	< 0.0001	0.0138	0.1176	37.5%
Omitting Park 2015	1.1224	[1.0680; 1.1794]	< 0.0001	0.0136	0.1165	36.9%
Omitting Paulsen 2015	1.1182	[1.0636; 1.1757]	< 0.0001	0.0141	0.1187	37.7%
Omitting Perovic 2006	1.1213	[1.0668; 1.1787]	< 0.0001	0.0138	0.1175	37.3%
Omitting Rieg 2009	1.1196	[1.0648; 1.1772]	< 0.0001	0.0141	0.1186	37.7%
Omitting Roth 2017	1.1182	[1.0635; 1.1757]	< 0.0001	0.0141	0.1188	37.7%
Omitting Saunderson 2015	1.1190	[1.0643; 1.1765]	< 0.0001	0.0141	0.1186	37.8%
Omitting Seas 2018	1.1178	[1.0629; 1.1754]	< 0.0001	0.0143	0.1195	37.7%
Omitting Smit 2017	1.1124	[1.0591; 1.1682]	< 0.0001	0.0121	0.1101	34.2%
Omitting Soriano 2000	1.1168	[1.0623; 1.1741]	< 0.0001	0.0141	0.1186	37.5%
Omitting Soriano 2008	1.1179	[1.0633; 1.1753]	< 0.0001	0.0141	0.1186	37.7%
Omitting Sullivan 2017	1.1165	[1.0627; 1.1730]	< 0.0001	0.0138	0.1174	36.8%
Omitting Szubert 2019	1.1209	[1.0665; 1.1782]	< 0.0001	0.0138	0.1174	37.4%
Omitting Tan 2021	1.1170	[1.0628; 1.1740]	< 0.0001	0.0139	0.1179	37.3%
Omitting Ternavasio-de la Vega 2018	1.1219	[1.0676; 1.1788]	< 0.0001	0.0136	0.1167	37.0%
Omitting Thorlacius-Ussing 2019	1.1124	[1.0580; 1.1696]	< 0.0001	0.0131	0.1146	32.4%
Omitting Thwaites 2010	1.1187	[1.0639; 1.1763]	< 0.0001	0.0142	0.1190	37.8%
Omitting Tong 2012	1.1234	[1.0681; 1.1816]	< 0.0001	0.0139	0.1178	36.0%
Omitting Turnidge 2007	1.1185	[1.0638; 1.1761]	< 0.0001	0.0141	0.1187	37.8%
Omitting Turnidge 2009	1.1242	[1.0695; 1.1818]	< 0.0001	0.0134	0.1158	36.4%
Omitting vanHal 2011	1.1182	[1.0635; 1.1757]	< 0.0001	0.0141	0.1187	37.7%
Omitting Wang 2008	1.1168	[1.0634; 1.1730]	< 0.0001	0.0138	0.1173	36.5%
Omitting Wang 2013	1.1187	[1.0641; 1.1761]	< 0.0001	0.0140	0.1182	37.8%
Omitting Wang 2015	1.1224	[1.0680; 1.1795]	< 0.0001	0.0136	0.1166	37.0%
Omitting Wi 2018	1.1214	[1.0669; 1.1787]	< 0.0001	0.0138	0.1173	37.3%
Omitting Willekens 2021	1.1176	[1.0630; 1.1749]	< 0.0001	0.0140	0.1185	37.6%
Omitting Yilmaz 2016	1.1209	[1.0666; 1.1780]	< 0.0001	0.0137	0.1172	37.3%
Omitting Yoon 2016	1.1246	[1.0714; 1.1804]	< 0.0001	0.0130	0.1138	35.2%
Pooled estimate	1.1193	[1.0652; 1.1761]	< 0.0001	0.0138	0.1174	37.0%

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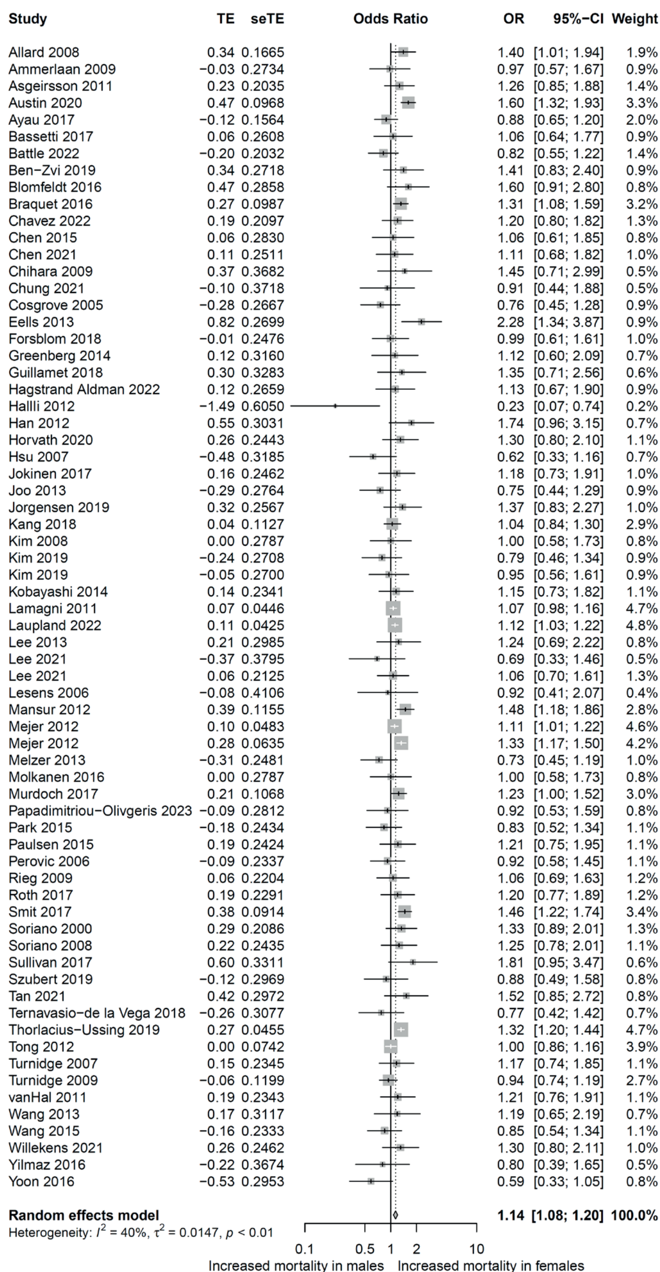
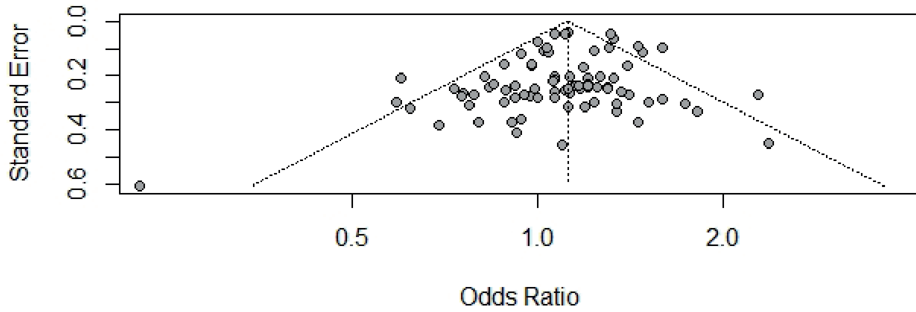
eFigure 1. Sensitivity analysis of unadjusted mortality. Only studies that either directly reported an odds ratio (OR) or contained raw mortality data such that ORs could be directly calculated are included here. Studies that reported a hazard ratio, relative risk, or mortality rate ratio were excluded.



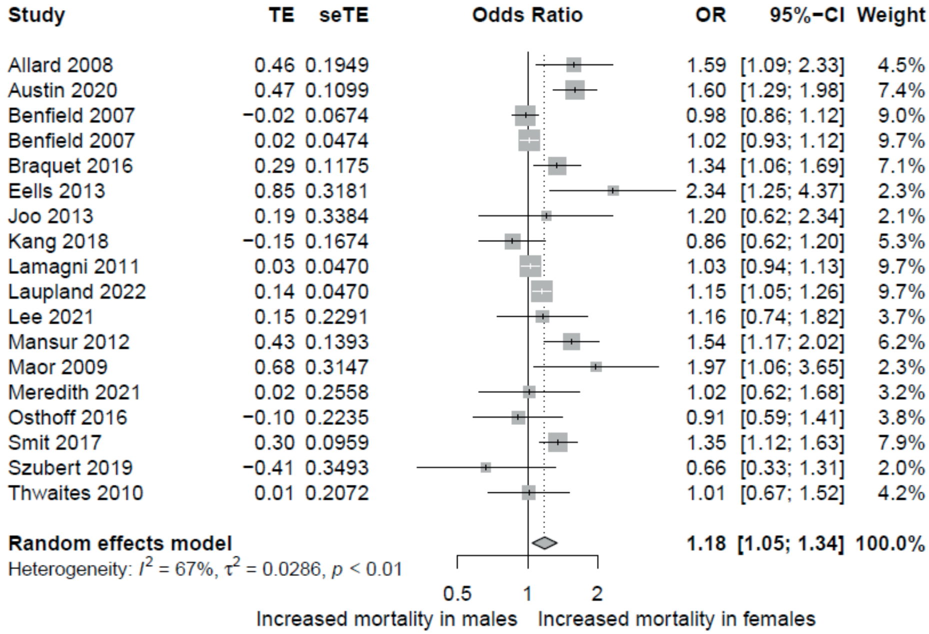
eFigure 2. Funnel plot of studies included in the analysis of unadjusted mortality. One study in particular had an effect size that was larger than expected based on the standard error (lower left corner of plot). This study demonstrated significantly lower mortality in females relative to males. Despite this, Egger's test did not reveal significant asymmetry in the funnel plot (p=0.06). Thus in total no clear evidence of publication bias was detected.



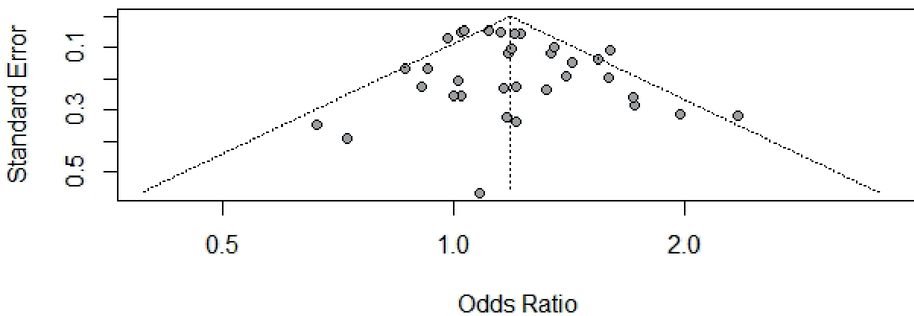
eAppendix 5. Influence analysis of adjusted mortality in patients with *Staphylococcus aureus* bacteremia. An influence analysis showed that the overall results of the meta-analysis (i.e., association of female sex with increased mortality) did not change with removal of individual studies.

	OR	95%-CI	p-value	tau^2	tau	I^2
Omitting Allard 2008	1.1757	[1.0998; 1.2568]	< 0.0001	0.0117	0.1084	50.0%
Omitting Austin 2020	1.1619	[1.0920; 1.2363]	< 0.0001	0.0081	0.0898	44.1%
Omitting Bai 2015	1.1784	[1.1021; 1.2600]	< 0.0001	0.0121	0.1102	50.7%
Omitting Benfield 2007	1.1956	[1.1181; 1.2785]	< 0.0001	0.0109	0.1045	48.1%
Omitting Benfield 2007	1.1956	[1.1164; 1.2805]	< 0.0001	0.0117	0.1084	47.4%
Omitting Blomfeldt 2016	1.1840	[1.1053; 1.2683]	< 0.0001	0.0128	0.1132	52.2%
Omitting Braquet 2016	1.1780	[1.0993; 1.2623]	< 0.0001	0.0127	0.1127	50.8%
Omitting Chen 2010	1.1911	[1.1132; 1.2744]	< 0.0001	0.0125	0.1119	51.1%
Omitting Cobussen 2018	1.1840	[1.1057; 1.2678]	< 0.0001	0.0126	0.1124	52.2%
Omitting Eells 2013	1.1753	[1.1026; 1.2528]	< 0.0001	0.0114	0.1069	48.3%
Omitting Forsblom 2018	1.1838	[1.1047; 1.2685]	< 0.0001	0.0130	0.1140	52.2%
Omitting Gasch 2013	1.1796	[1.1016; 1.2632]	< 0.0001	0.0126	0.1123	51.4%
Omitting Joo 2013	1.1837	[1.1051; 1.2678]	< 0.0001	0.0128	0.1130	52.2%
Omitting Kang 2018	1.1923	[1.1158; 1.2740]	< 0.0001	0.0120	0.1094	50.1%
Omitting Lamagni 2011	1.1953	[1.1155; 1.2807]	< 0.0001	0.0122	0.1103	48.1%
Omitting Laupland 2022	1.1884	[1.1061; 1.2769]	< 0.0001	0.0146	0.1209	52.2%
Omitting Lee 2021	1.1845	[1.1054; 1.2693]	< 0.0001	0.0130	0.1142	52.2%
Omitting Mansur 2012	1.1715	[1.0967; 1.2514]	< 0.0001	0.0108	0.1041	48.6%
Omitting Maor 2009	1.1775	[1.1024; 1.2577]	< 0.0001	0.0119	0.1092	50.0%
Omitting Mejer 2012	1.1911	[1.1089; 1.2793]	< 0.0001	0.0143	0.1196	51.9%
Omitting Mejer 2012	1.1833	[1.1016; 1.2711]	< 0.0001	0.0143	0.1196	51.0%
Omitting Meredith 2021	1.1864	[1.1076; 1.2708]	< 0.0001	0.0129	0.1138	52.1%
Omitting Murdoch 2017	1.1853	[1.1047; 1.2718]	< 0.0001	0.0138	0.1174	52.2%
Omitting Nambiar 2018	1.1850	[1.1042; 1.2718]	< 0.0001	0.0139	0.1180	52.1%
Omitting Osthoff 2016	1.1890	[1.1110; 1.2725]	< 0.0001	0.0128	0.1129	51.5%
Omitting Rieg 2013	1.1873	[1.1102; 1.2697]	< 0.0001	0.0126	0.1124	51.2%
Omitting Saunderson 2015	1.1867	[1.1080; 1.2710]	< 0.0001	0.0129	0.1137	52.0%
Omitting Schneider 2020	1.1820	[1.1034; 1.2661]	< 0.0001	0.0128	0.1132	51.9%
Omitting Smit 2017	1.1757	[1.0974; 1.2596]	< 0.0001	0.0123	0.1110	49.8%
Omitting Soriano 2000	1.1776	[1.1015; 1.2588]	< 0.0001	0.0120	0.1096	50.4%
Omitting Szubert 2019	1.1887	[1.1127; 1.2698]	< 0.0001	0.0125	0.1117	50.4%
Omitting Thorlacius-Ussing 2019	1.1848	[1.1028; 1.2729]	< 0.0001	0.0145	0.1204	51.5%
Omitting Thwaites 2010	1.1876	[1.1087; 1.2722]	< 0.0001	0.0130	0.1142	52.0%
Omitting Yahav 2017	1.1762	[1.0989; 1.2589]	< 0.0001	0.0121	0.1100	50.4%
Pooled estimate	1.1836	[1.1067; 1.2658]	< 0.0001	0.0125	0.1119	50.7%

eFigure 3. Sensitivity analysis adjusted mortality. Only studies that either directly reported an odds ratio (OR) or contained raw mortality data such that ORs could be directly calculated are included here. Studies that reported a hazard ratio, relative risk, or mortality rate ratio were excluded.



eFigure 4. Funnel plot for studies included in analysis of adjusted mortality. Egger’s test did not reveal significant asymmetry in the funnel plot (p=0.10).



eTable 2. Evidence profile for association of female sex and mortality in patients with *Staphylococcus aureus* bacteremia.

Patient population	Patients with *Staphylococcus aureus* bacteremia
Setting	Hospital
Intervention	Female sex
Comparison	Male sex
Outcome	Mortality
Studies (participants)	89 (132,582)
Risk of bias	High
Consistency	Consistent
Precision	Precise
Directness	Direct
Other limitations	Sex-difference was not the primary outcome of interest in the majority of the studies that were included
Overall strength of evidence	Low
Conclusion	Female sex is associated with higher mortality in patients with SAB
Summary estimate	Unadjusted: 1.12 (95%CI 1.07-1.18) Adjusted: 1.18 (95%CI 1.11-1.27)