

# Meta-meta-analysis of the mortality risk associated with MRSA compared to MSSA bacteraemia

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## SUMMARY

*Staphylococcus aureus* bacteraemia (SAB) is a bloodstream infection that carries a high risk of exacerbating a diseased state and may result in an increased death rate. The aim of this study was to assess mortality risk in Methicillin Resistant *Staphylococcus aureus* (MRSA) bacteraemia compared to Methicillin Susceptible *Staphylococcus aureus* (MSSA) bacteraemia through meta-meta-analyses. The study followed PRISMA guidelines, conducting a comprehensive search in Scopus, PubMed, and Google Scholar. It included full-text systematic reviews and meta-analyses comparing MRSA vs. MSSA bacteraemia, excluding reviews without data pooling and unclear selection criteria. Validity was assessed using QUOROM and AMSTAR. Edwards' Venn diagrams were used to visualize overlaps between primary studies. Aggregated odds ratio (OR) and risk ratios with 95% confidence intervals were calculated using the random-effect model. Heterogeneity was evaluated using the Higgins I<sup>2</sup> statistic. The study included 3 meta-analysis studies, a total of 38,159 patients, with 9,056

having MRSA bacteraemia and 29,103 having MSSA bacteraemia. Data were collected from 46 different outcome studies published between 2001 and 2022. The meta-analyses used 7 to 33 primary studies from 1990 to 2020, with no overlap. Odds ratios (ORs) ranged from 1.78 to 2.92, while relative risks (RR) ranged from 1.57 to 2.37 for the included meta-analysis. The pooled analysis confirmed a higher risk of mortality in patients with MRSA bacteraemia (OR: 2.35, RR: 2.01, HR: 1.61) compared to MSSA bacteraemia. Heterogeneity among the studies was considerable (I<sup>2</sup>: 90-91%).

The study strongly supports that most patient deaths from SAB are linked to MRSA rather than MSSA. This highlights the significant public health problem posed by SAB, with difficult and often unsuccessful treatment leading to increased mortality and high healthcare costs.

**Keywords:** Evidence synthesis, meta-analyses, MRSA, MSSA, *Staphylococcus aureus* bacteraemia.

## INTRODUCTION

*Staphylococcus aureus* bacteraemia (SAB) is a bloodstream infection that carries a high risk of exacerbating a diseased state and may result in an

increased death rate [1]. MRSA-related deaths result from acute complications like septic shock, coagulation issues, or lung injury, as well as complications of endocarditis or underlying disease [2]. Treatment of Methicillin-Resistant *Staphylococcus aureus* (*S. aureus*) or MRSA infections can be challenging due to limited antibiotic options, and in some cases, the infection may not respond well to available treatments [3]. This resistance to com-

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mon antibiotics can lead to longer hospital stays, increased healthcare costs, and a higher risk of complications and death [4]. It's important to note that both MRSA and Methicillin-Susceptible *S. aureus* (MSSA) bacteraemia are serious conditions that require immediate medical attention [4]. Prompt diagnosis and appropriate treatment, including the use of effective antibiotics, are essential for improving outcomes and reducing the risk of severe complications or death [5]. The risk of death from MRSA bacteraemia is generally higher compared to MSSA bacteraemia [6]. MRSA strains are resistant to methicillin and related drugs, which makes them more difficult to treat, leading to increased mortality rates [6]. Several studies have shown that patients with MRSA bacteraemia have higher mortality rates compared to those with MSSA bacteraemia [7]. The exact difference in mortality rates can vary depending on factors such as the patient population, the severity of illness, and the presence of underlying health conditions [7].

The aim of this study was to assess the mortality risk in MRSA bacteraemia compared to MSSA bacteraemia through meta-meta-analyses with the goal of improving evidence-based decision-making regarding the associated mortality risk.

## ■ METHODS

*Criteria for inclusion and exclusion, along with the parsing of data*

The study followed the PRISMA guidelines in conducting a literature review. A comprehensive search in three databases were carried out: Scopus, PubMed, and Google Scholar [13]. The search terms

were; (“risk”[MeSH Terms] OR “risk”[All Fields]) AND “odds”[All Fields] AND (“death”[MeSH Terms] OR “death”[All Fields] OR “deaths”[All Fields]) AND (“mortality”[MeSH Terms] OR “mortality”[All Fields] OR “mortalities”[All Fields] OR “mortality”[MeSH Subheading]) AND (“methicillin resistant staphylococcus aureus”[MeSH Terms] OR (“methicillin resistant”[All Fields] AND “staphylococcus”[All Fields] AND “aureus”[All Fields]) OR “methicillin resistant staphylococcus aureus”[All Fields] OR “mrsa”[All Fields]) AND “MSSA”[All Fields] AND (“bacteraemia”[All Fields] OR “bacteremia”[MeSH Terms] OR “bacteremia”[All Fields] OR “bacteraemias”[All Fields] OR “bacteremias”[All Fields])) AND (clinical trial[Filter] OR meta-analysis[Filter] OR randomized controlled trial[Filter] OR review[Filter] OR systematic review[Filter]).

This review focused on systematic reviews and meta-analyses that compared MRSA and MSSA bacteraemia using pooled data. Two authors (SA and AI) conducted a thorough assessment of potential studies, identifying relevant titles and abstracts with no disagreements between them. The review had no limitations based on the setting type or year of publication. The review included only full-text systematic reviews and meta-analyses of randomized controlled trials (RCT) that provided pooled data on MRSA vs MSSA bacteraemia. Excluded studies were reviews without data pooling, specified search algorithms, and clear selection criteria for included studies. The study protocol is registered with the open science framework (osf.io/dw8xm).

Data extracted from the included meta-analyses covered the study name, publication year, dichot-

**Table 1 - Characteristics of included meta-analysis.**

References	Number of databases searched	Outcomes	Number of primary studies	MRSA		MSSA		OR/RR	Lower	Upper	Review (year range)
				Events	Total	Events	Total				
Bai D. et al. [11]	3	Mortality ( <i>S. aureus</i> bacteraemia)	33	2188	8087	4692	27196	1.56	1.41	1.73	2008 to 2020
Park et al. [12]	8	Mortality ( <i>S. aureus</i> bacteraemia)	7	40	191	43	476	2.33	1.42	3.82	2007 to 2010
Whitby et al. [13]	4	Mortality ( <i>S. aureus</i> bacteraemia)	9	223	778	173	1431	2.12	1.76	2.57	1990 to 2000

omous number of events in each group, effect size data (Risk Ratio or Odds Ratio), number of databases searched, and review year range [8]. The validity and robustness of the included meta-analyses were assessed using the Quality of Reporting of Meta-analyses (QUOROM) checklist and Assessment of Multiple Systematic Reviews (AMSTAR) [9].

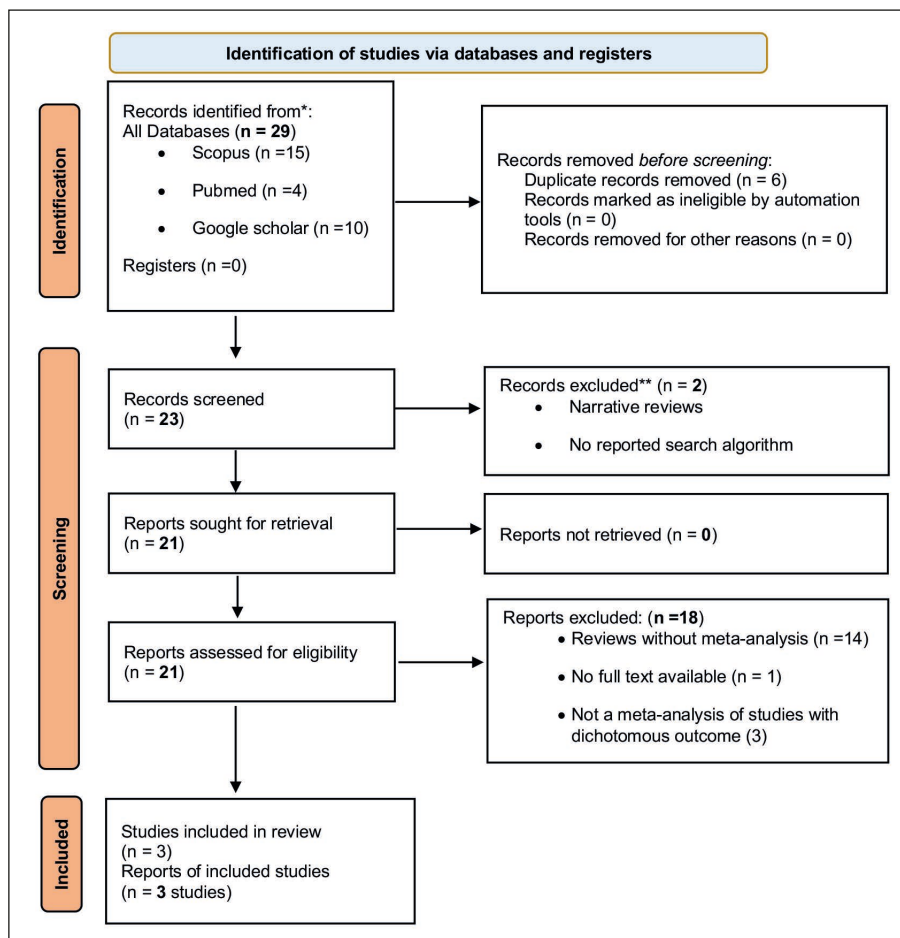
To visualize overlaps between primary studies, Edwards' Venn diagrams were employed with the intervene shiny package in R studio (Version II). The aggregated odds ratio (OR) and risk ratios, along with their corresponding 95% confidence intervals (CI), were calculated using the random-effect model of DerSimonian and Laird, utilizing the 'metafor' package and Comprehensive meta-analysis software (version 3.0). Heterogeneity was assessed using the Higgins I2 statistic, with values

below 25% indicating low heterogeneity and values above 75% indicating high heterogeneity [10].

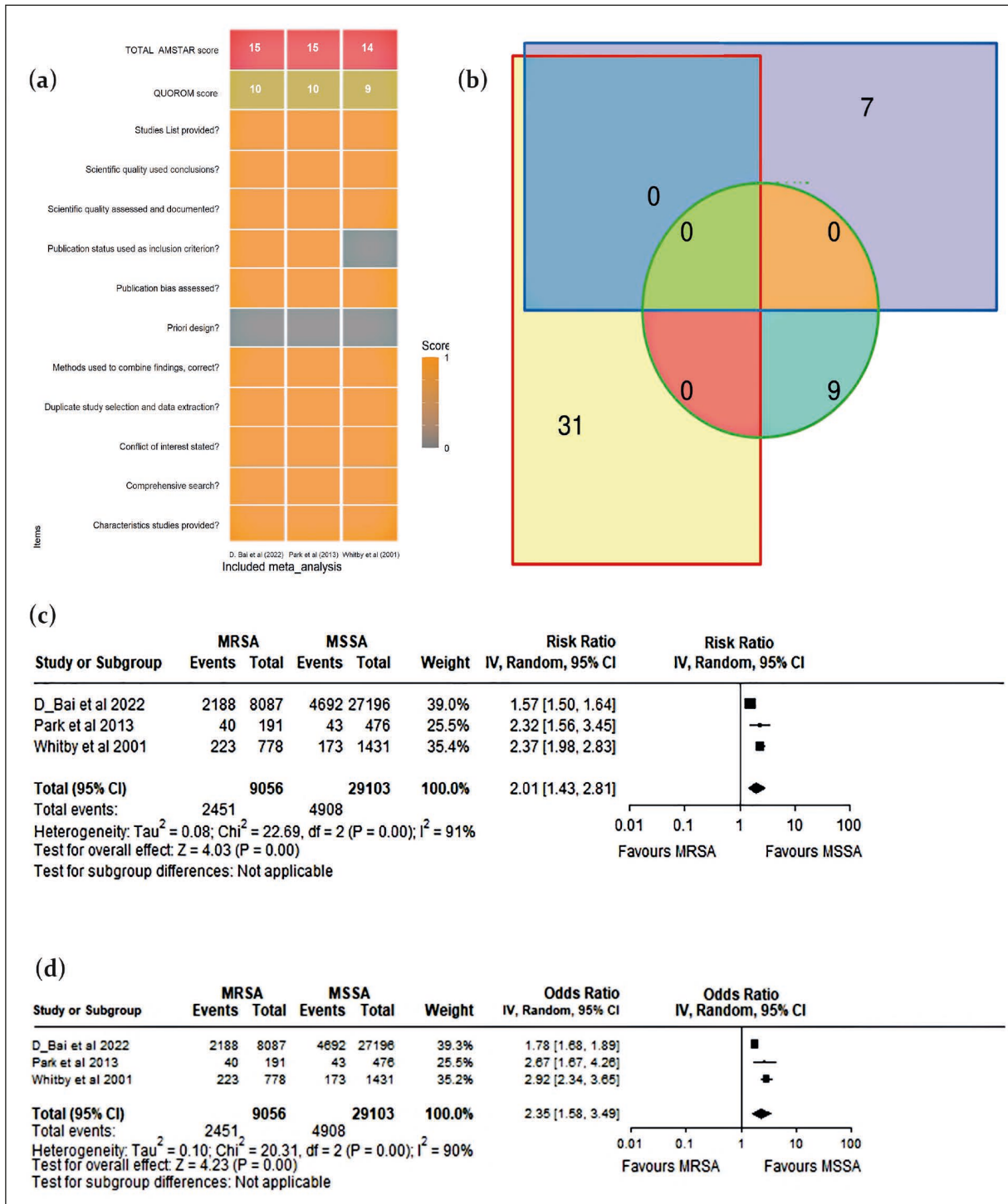
## RESULTS

Three meta-analysis were included in this study comprising a total of 38,159 patients [11-13]. These patients were divided into two groups: 9,056 patients with MRSA bacteraemia and 29,103 with MSSA bacteraemia. The data were collected from 46 different dichotomous outcome studies published between 2001 and 2022. The primary studies included in these meta-analyses were spanned from 1990 to 2020, with each meta-analysis comprising seven to thirty-three primary studies. There was no overlap in the primary studies used across the included meta-analyses.

The odds ratios (ORs) in the meta-analyses ranged



**Figure 1**  
PRISMA flow diagram  
of article selection  
for inclusion.



**Figure 2 -** (a) QUOROM and AMSTAR scores for the meta-analyses that were included in the study. (b) Edwards' Venn diagrams, which illustrate the overlap of studies in the analysis. (c) A forest plot of the Risk Ratio (RR) of MRSA (Methicillin-resistant *Staphylococcus aureus*) versus MSSA (Methicillin-sensitive *Staphylococcus aureus*) bacteremia. (d) Another forest plot presenting the Odds Ratio (OR) of MRSA versus MSSA bacteremia.

mostly from 1.78 (95% CI, 1.68-1.89) to 2.92 (95% CI, 2.34-3.65), while the calculated relative risks (RR) ranged from 1.57 (95% CI, 1.50-1.64) to 2.37 (95% CI, 1.98-2.38). The AMSTAR score ranged from 14 to 15, and the QUOROM score ranged from 9-10.

The combined odds ratio (OR) from the pooled analysis was 2.35 (95% CI, 1.58-3.49,  $p=0.00$ ), indicating a significantly higher odds of mortality in patients with MRSA bacteraemia compared to MSSA bacteraemia. Similarly, the pooled relative risk (RR) was 2.01 (95% CI, 1.43-2.81,  $p=0.00$ ), suggesting a significantly higher risk of mortality in patients with MRSA bacteraemia compared to MSSA bacteraemia. Further, a pooled hazard ratio (HR) of 1.61 (95% CI, 1.53-1.70,  $p=0.00$ ) was calculated.

The pooled analysis revealed considerable heterogeneity between the studies, with a  $\chi^2$  value of 22.69 ( $p=0.00$ ) and an  $I^2$  value of 91% for RR, and a  $\chi^2$  value of 20.31 ( $p=0.00$ ) and an  $I^2$  value of 90% for OR.

## ■ DISCUSSION

The aim of this study was to systematically compile the evidence from multiple meta-analyses regarding mortality risk associated with MRSA compared to MSSA bacteraemia into an accessible up-to-date source. Three meta-analyses were identified and included in the review, [11-13]. The consistent finding across all three meta-analyses was a significantly higher mortality risk in MRSA bacteraemia compared to MSSA bacteraemia. The primary variation among the meta-analyses was in the magnitude of risk and odds. Combining the results of these meta-analyses yielded an overall substantial relative risk (RR) of 2.01 and an odds ratio (OR) of 2.35. These results demonstrate the consistency of conclusions across each individual meta-analysis.

Furthermore, two studies have reported RRs and ORs that align with our findings or fall within the range of the 95% confidence interval reported here [14, 15]. The increased mortality risk associated with MRSA bacteraemia is attributed to several factors, including limited treatment options: MRSA's resistance to multiple antibiotics makes it more difficult to treat effectively [16]. The standard first-line antibiotics used to treat MSSA infections, such as methicillin and penicillin, are ineffective against MRSA. As a result, clinicians must rely on alternative, often more toxic or less effective antibi-

otics, which may not completely eradicate the infection [17]. Identifying MRSA requires specific laboratory testing, and the results may not be available for a few days especially in low income countries. Patients may receive broad-spectrum antibiotics that do not target MRSA effectively [18]. Delayed administration of appropriate antibiotics can lead to worsened outcomes. Some studies suggest that certain MRSA strains might have increased virulence compared to MSSA strains [16]. These strains can cause more severe infections, leading to a higher risk of complications and mortality [16]. MRSA is often associated with healthcare settings, such as hospitals and long-term care facilities [19]. Patients in these settings may already have weakened immune systems or other underlying health issues, making them more susceptible to severe infections [20]. MRSA strains have also emerged in community settings, affecting otherwise healthy individuals [21]. Community-acquired MRSA can cause severe infections, such as skin and soft tissue infections, which can lead to bacteraemia and, in some cases, mortality [22]. Patients who acquire MRSA bacteraemia often have other underlying health conditions that can complicate treatment and increase the risk of mortality [23]. It's essential to recognize that while MRSA bacteraemia carries a higher risk of mortality compared to MSSA, the actual outcome can vary significantly depending on the patient's overall health, the virulence of the infecting strain, and timely and appropriate medical intervention [24]. Early detection, appropriate antimicrobial therapy, and supportive care play crucial roles in improving the prognosis for patients with MRSA bacteraemia [23].

This analysis has limitations that should be acknowledged. Being a meta-analysis based on previously published articles and observational data, it limits the transparency and reproducibility of the study. Relying on existing literature also restricts individual patient data analysis and may lead to variations and potential biases. The diverse healthcare settings of the selected studies result in heterogeneous patient care. Caution is necessary when interpreting the results. To improve reliability and strengthen the evidence, further research using well-planned randomized controlled trials, including studies from the previous meta-analysis and other published works not previously considered, is needed.



## ■ CONCLUSIONS

The combined findings from comparing mortality rates provide strong evidence (based on Risk, odds, and Hazard Ratio) that the majority of patient deaths related to SAB were associated with MRSA rather than MSSA. This study's evidence reinforces the notion that SAB poses a significant public health issue due to the challenging and often unsuccessful treatment, leading to increased mortality and imposing excessive costs on health-care services.

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None received.

### Conflict of interest

The authors declared that they have no conflict of interest.

### Authors contribution

S.A.S. played a key role in conceptualization, data curation, formal analysis, investigation, methodology and the original draft and subsequent revisions of the manuscript. A.I. contributed significantly to methodology development, resource allocation, software implementation, supervision, validation, and the critical review and editing of the manuscript.

### Data availability

The data supporting the results of this study are openly accessible in the Open Science Framework (OSF) registries ([osf.io/v7uz2](https://osf.io/v7uz2)), Supplementary documents, and available from the corresponding author upon request.

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