Original Article

Predictors of mortality in adult patients with methicillin-resistant *Staphylococcus aureus* bloodstream infection: a meta-analysis and systematic review

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Background: Cases of methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection have been increasing. Patients with MRSA bloodstream infection have a poor prognosis and high mortality rate. Identification of potential risk factors associated with MRSA bloodstream infection-related mortality may help improve patient outcomes.

Methods: Embase, PubMed, and the Cochrane Library databases were searched to identify articles describing predictors of mortality in patients with MRSA bloodstream infections. Two investigators independently assessed articles for inclusion and data extraction.

Results: Twenty observational studies were included in the analysis. Factors associated with higher mortality were development of severe sepsis or septic shock [odds ratio (OR): 4.56, 95% CI: 3.37–6.18], congestive heart failure (OR: 1.78, 95% CI: 1.27–2.50), liver cirrhosis (OR: 1.90, 95% CI: 1.27–2.65), malignancy (OR: 1.62, 95% CI: 1.33–1.98), infective endocarditis (OR: 2.05, 95% CI: 1.35–3.11), nosocomial infection (OR: 2.80, 95% CI: 1.41–5.55), intensive care unit admission (OR: 3.08, 95% CI: 1.49–6.36) and inappropriate empirical antimicrobial treatment (OR: 2.25, 95% CI: 1.16–4.36); removal of the eradicable foci was a protective factor (OR: 0.51, 95% CI: 0.40–0.63) The average APACHE II score at the time of diagnosis of MRSA bloodstream infection was considerably higher in patients who did not survive than in those who survived [weighted mean difference (WMD): 5.81, 95% CI: 3.03–8.59].

Discussion: Patient condition, appropriate timing of antimicrobial treatment, surgical intervention and disease severity according to the APACHE II score are the most important risk factors for death in patients with MRSA bloodstream infections.

Keywords: Methicillin-resistant *Staphylococcus aureus* (MRSA); bloodstream infection; mortality; risk factors

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Introduction

As an important opportunistic pathogen, nasal carriage of *Staphylococcus aureus* was reported in 20% of healthy individuals. With the widespread use of antimicrobial drugs, the level of bacterial resistance has changed greatly, and methicillin-resistant *Staphylococcus aureus* (MRSA) infection has become a serious clinical challenge and has attracted the attention of medical institutions worldwide. MRSA can cause nosocomial infections [such as hospital-acquired or ventilator-associated pneumonia (VAP)], skin and soft tissue infection, suppurative osteomyelitis and bacteremia among patients with critical illnesses. According to the data released by the China Antimicrobial Surveillance Network (CHINET), the proportion of *Staphylococcus aureus* isolates resistant to methicillin decreased from 51.7% in 2010 to 35.3% in 2017 in China (1). Nevertheless, because of the limited range of antibiotics available for treatment, the mortality rate of patients with MRSA bloodstream infections did not decrease parallelly. Previous studies have shown that methicillin resistance is an independent risk factor for mortality in *Staphylococcus aureus* bacteremia (2,3), so it is essential to identify potential risk factors associated with the mortality of MRSA bloodstream infections to help improve patient outcomes. Some risk factors, such as nosocomial acquisition, inappropriate antimicrobial treatment, and higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores (4,5), have been identified. The results of several studies remain controversial. For example, although some studies have revealed that a higher vancomycin minimum inhibitory concentration (MIC) is positively associated with fatality (6,7), other study failed to find the correlation between vancomycin MIC and the prognosis of MRSA bloodstream infection (8). Therefore, a meta-analysis was conducted to evaluate the predictors of mortality in patients with MRSA bacteremia. We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-932).

Methods

Search strategy

Two independent examiners (MHJ and YYH) conducted a comprehensive search in the PubMed, Embase, and Cochrane Library databases from their inception to October 31, 2020 for relevant articles. The search strategy used the following keywords: ("*Staphylococcus aureus*") AND ("methicillin" OR "meticillin") AND ("resistance" OR "resistant") OR ("MRSA") AND ("bloodstream" OR "bacteremia" OR "bacteraemia") AND ("mortality" OR "lethality" OR "fatality" OR "prognosis" OR "survival" OR "predictor") (Table S1). Furthermore, reference lists cited by eligible retrieved articles were also manually retrieved and reviewed to maximize the inclusion of studies. Only articles written in English were reviewed.

Selection criteria

This meta-analysis included studies reporting mortality and associated risk factors for patients with MRSA bloodstream infections. The primary outcome was mortality. After review by two independent examiners, nonoriginal articles such as reviews, meta-analyses, case reports, *in vitro* or experimental animal studies, or studies containing patients who were younger than 16 years old were not included. Studies in which MRSA status (infection/colonization) was not clarified were also excluded. The protocol for this systematic review was registered on INPLASY (Unique ID 202120082) and is available in full on inplasy.com (https://doi.org/10.37766/inplasy2021.2.0082).

Quality assessment and data extraction

The methodological quality of the articles included was assessed with the Newcastle-Ottawa Scale score (NOS) (9). Two independent examiners (MHJ and YYH) performed the NOS assessment for each study. Inconsistencies between the 2 investigators were extensively discussed until agreement was achieved. Studies with an NOS score of at least 5 underwent further analysis, while others were excluded because of the potential high risk of bias. Two investigators (MHJ and YYH) independently extracted the relevant data from each eligible article, including authors, date of publication, location, study design and period, sample size, patient population characteristics (such as age, sex, site of acquisition, and comorbidities), severity of diseases, microbiologic data and treatment variables. Variables examined in less than three eligible studies were excluded.

Statistical analysis

Review Manager (version 5.3 software) was used for statistical analyses. Heterogeneity was tested with the Q statistic (significant when P<0.10), and the extent of

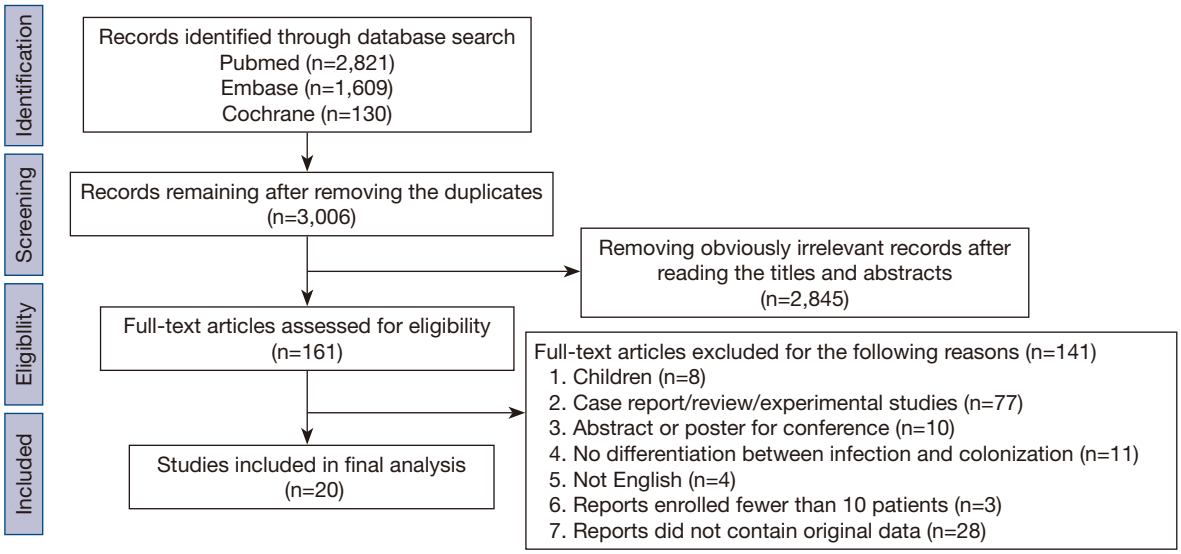

Figure 1 Meta-analysis on the forest plots of development of severe sepsis or septic shock.

heterogeneity was quantified with the I^2 statistic. I^2>50% was interpreted as substantial and significant heterogeneity or inconsistency. Pooled odds ratios (ORs) and 95% CIs were calculated to express binary outcome results, while the weighted mean difference (WMD) and 95% CIs were used to express continuous outcome results. Sensitivity analysis of the included literature was performed by omitting each study one at a time in the process of meta-analysis to inspect the change in the merging effect to demonstrate the stability and accuracy of the outcome. Publication bias was shown by a funnel plot.

Results

Results of study inclusion

The literature search identified a total of 3,116 publications. After duplicates were removed, 3,006 articles were screened. After reviewing abstracts and titles for obvious irrelevancy, 2,485 articles were excluded. After reviewing the full texts, we excluded other studies according to the eligibility criteria. Twenty studies (4,5,10-27) were included in the final analysis. The process of article selection is shown in *Figure 1*.

Study characteristics

The characteristics of the 20 included studies (4-5,10-27) are summarized (*Table 1*). Of the 20 studies, 5 were multicenter studies, and 15 were single-center studies. Most (17/20) had a retrospective design. The studies were from 7 countries and areas, including Taiwan (n=5), the USA (n=5), Korea (n=4), Japan (n=3), and Spain (n=1), and all were published between 2010 and 2020. Sample sizes ranged from 48 to 556, and 3,743 total adult patients with MRSA bloodstream infections were included in the systematic review. Among them, 1,050 (28.1%) cases were reported deaths. The average NOS score of the 20 studies was 6.95. Almost all studies explained the process of population selection clearly but failed to describe the comparability between groups coherently. Evaluation of exposure factors, especially the nonresponse rate, is scarcely reported in most studies.

Predictors of death in patients with MRSA bloodstream infections

Potential risk factors associated with death in patients with MRSA bloodstream infections were analyzed (*Table 2*). Notably, only factors mentioned in at least 3 studies were included. As shown in *Table 2*, factors such as patient comorbidities at admission, including presentation with severe sepsis or septic shock (OR: 4.56; 95% CI: 3.37–6.18) (*Figure 2*), infective endocarditis (OR: 2.05, 95% CI: 1.35–3.11), liver cirrhosis (OR: 1.90, 95% CI: 1.37–2.65), congestive heart failure (OR: 1.78, 95% CI: 1.27–2.50), and malignancy (OR: 1.62, 95% CI: 1.33–1.98), were considered to increase mortality. Moreover, inappropriate empirical antimicrobial treatment (OR: 2.25, 95% CI: 1.16–4.36) may

Table 1 General characteristics of the eligible studies

Study	Year	Country/ area	Study period	Design	Mortality day	Non-survivors/MRSA BSI patients (%)	NOS score
Lin *et al.* (10)	2010	Taiwan	January 2000 to December 2008	R, cohort/ SC	30 d	102/227 (44.9)	7
Honda *et al.* (11)	2011	United States	July 2005 to July 2007	P, cohort/ SC	28 d	35/163 (21.5)	7
Woods *et al.* (12)	2012	United States	January 2009 to December 2010	R, cohort/ SC	In-hospital	36/99 (36.4)	7
Hall II *et al.* (13)	2012	United States	July 2002 to June 2008	R, cohort/ MC	In-hospital	47/336 (14.0)	7
Wi *et al.* (14)	2012	Korea	2009 to 2010	R, cohort/ MC	30 d	31/137 (22.6)	7
Jang *et al.* (15)	2012	Korea	January 2005 to December 2008	R, cohort/ MC	30 d	98/307 (31.9)	7
Isobe *et al.* (16)	2012	Japan	January 2006 and December 2010	R, cohort/ SC	NA	46/115 (40.0)	6
Seah *et al.* (17)	2013	Singapore	January 2006 to December 2009	R, cohort/ SC	30 d	16/76 (21.1)	7
Takata *et al.* (18)	2013	Japan	1987 to 2007	R, cohort/ SC	30 d	34/93 (36.6)	7
Lee *et al.* (4)	2013	Taiwan	July 2006 and June 2009	R, cohort/ SC	14 d	56/339 (16.5)	7
Lee *et al.* (19)	2013	Taiwan	January 2010 to October 2010	P, cohort/ SC	30 d	15/55 (27.3)	7
Gasch *et al.* (20)	2013	Spain	June 2008 to December 2009	R, cohort/ MC	30 d	178/556 (32.0)	7
Lodise *et al.* (21)	2014	United States	Januray 2005 to June 2009	R, cohort/ SC	30 d	25/123 (20.3)	7
Lee *et al.* (5)	2015	Taiwan	January 2010 to December 2011	R, cohort/ SC	30 d	55/189 (29.1)	7
Hu *et al.* (22)	2015	Taiwan	January 2009 to December 2010	R, cohort/ SC	In-hospital	35/48 (72.9)	7
Britt *et al.* (23)	2016	United States	September 2012 to June 2014	R, cohort/ SC	30 d	11/53 (20.8)	7
Yoon *et al.* (24)	2016	Korea	February 2010 to July 2011	R, cohort/ MC	In-hospital	81/254 (31.9)	8
Kim *et al.* (25)	2019	Korea	August 2008 and June 2011	P, cohort/ SC	28 d	75/385 (19.5)	7
Kawasuji *et al.* (26)	2020	Japan	January 2011 to December 2018	R, cohort/ SC	In-hospital	18/55 (32.7)	7
Niek *et al.* (27)	2020	Malaysia	2013 to 2015	R, cohort/ SC	NA	56/133 (42.1)	6

MRSA, methicillin-resistant *Staphylococcus aureus*; BSI, bloodstream infection; NOS, Newcastle-Ottawa Scale; R, retrospective; P, prospective; SC, single center; MC, multicenter; NA, not available/not applicable.

lead to a higher mortality rate, while removing eradicable foci (OR: 0.51, 95% CI: 0.40–0.63) improved patient survival. In addition, our results show that nosocomial acquisition of infection (OR: 2.80, 95% CI: 1.41–5.55) and ICU admission (OR: 3.08, 95% CI: 1.49–6.36) were associated with a poorer clinical outcome.

Continuous risk factors for death in patients with MRSA bloodstream infections

Several important continuous variables were assessed for their association with mortality in patients with MRSA bacteremia (*Table 3*). As shown, quantitative analysis with a fixed- or random-effects model indicated that older age, symptom severity (evaluated with APACHE II score) and comorbidity (evaluated with Charlson comorbidity index) were significantly correlated with higher mortality. Notably, the APACHE II score, especially upon diagnosis of MRSA bloodstream infection, was much higher in the non-survival group than in the survival group (WMD, 5.81; 95% CI: 3.03–8.59).

Sensitivity analysis

In this research, sensitivity analysis was performed by eliminating each included study individually. We found that the OR value, 95% CI and P-value after omission were very close to the results when the study was not omitted for most of the risk factors. Nevertheless, when we removed the study of Gasch, the ORs and the corresponding 95% CIs for metastatic infection changed to 1.98 (95% CI: 1.30–3.02). When we removed the study by Kim, the ORs

Table 2 Risk factors for mortality in patients with MRSA BSI upon diagnosis

Type of factors	Number of studies	No. of patients in studies [non-survivors]	No. of patients in studies reporting specific data [non-survivors]	I^2 (%)	P value of heterogeneity	Pooled OR (95% CI)	P value
Characteristics							
Sex, male	16	3,034 [780]	1,972 [499]	36	0.07	1.00 (0.84, 1.19)	0.99
Comorbidities							
Diabetes mellitus	15	2,136 [635]	805 [237]	0	0.46	0.98 (0.80, 1.20)	0.86
End stage renal disease	4	1,050 [269]	224 [62]	58	0.07	0.84 (0.45, 1.56)	0.58
COPD	7	893 [254]	137 [43]	39	0.13	1.43 (0.95, 2.16)	0.09
Dialysis	7	933 [237]	202 [56]	43	0.1	1.08 (0.73, 1.60)	0.69
Infective endocarditis	8	1,426 [419]	111 [52]	28	0.2	2.05 (1.35, 3.11)	0.0008
Liver cirrhosis	10	1,769 [458]	203 [73]	0	0.71	1.90 (1.37, 2.65)	0.0001
Foreign body	3	866 [278]	278 [81]	68	0.04	1.23 (0.35, 4.31)	0.75
Malignancies	17	2,612 [769]	701 [241]	44	0.03	1.62 (1.33, 1.98)	<0.00001
Transplantation	3	415 [112]	22 [7]	0	0.74	1.42 (0.56, 3.65)	0.46
Cerebrovascular disease	8	1,085 [352]	193 [65]	60	0.01	0.91 (0.48, 1.70)	0.76
Cardiovascular diseases	6	1,212 [268]	220 [48]	0	0.74	0.98 (0.69, 1.40)	0.91
Congestive heart failure	7	980 [313]	209 [88]	0	0.73	1.78 (1.27, 2.50)	0.0008
Microbiologic data							
vancomycin MIC ≥1.5 mg/L (Etest method)	8	1,912 [559]	906 [268]	58	0.02	1.25 (0.83, 1.90)	0.28
h-VISA	6	1,145 [182]	182 [57]	63	0.02	1.74 (0.79, 3.85)	0.17
Agr dysfunction	4	863 [233]	449 [113]	36	0.2	1.11 (0.69, 1.79)	0.66
Positive *PVL* gene	4	930 [303]	47 [11]	0	0.44	0.68 (0.34, 1.36)	0.28
Site of acquisition							
Nosocomial acquisition	5	1,018 [253]	724 [211]	58	0.05	2.80 (1.41, 5.55)	0.003
Community acquisition	4	736 [181]	56 [13]	0	0.44	0.74 (0.38, 1.45)	0.38
Health-care acquisition	3	694 [171]	147 [22]	72	0.03	0.35 (0.12, 1.04)	0.06
Clinical severity							
Any metastatic infection at the time of diagnosis	5	1,305 [430]	217 [87]	57	0.05	1.42 (0.82, 2.46)	0.21
ICU admission	4	711 [163]	182 [66]	66	0.03	3.08 (1.49, 6.36)	0.002
Development of severe sepsis or septic shock	9	1,239 [367]	335 [168]	4	0.4	4.56 (3.37, 6.18)	<0.00001
Treatment variables							
Inappropriate empirical antimicrobial treatment	6	1,737 [499]	601 [219]	83	<0.0001	2.25 (1.16, 4.36)	0.02
Remove the eradicable foci	8	1,746 [538]	816 [192]	25	0.23	0.51 (0.40, 0.63)	<0.00001

MRSA, methicillin-resistant *Staphylococcus aureus*; BSI, bloodstream infection; COPD, chronic obstructive pulmonary disease; MIC, minimum inhibitory concentration; h-VISA, heterogeneous vancomycin-intermediate *S. aureus*; Agr, accessory gene regulator; PVL, Panton-Valentine leucocidin; ICU, intensive care unit.

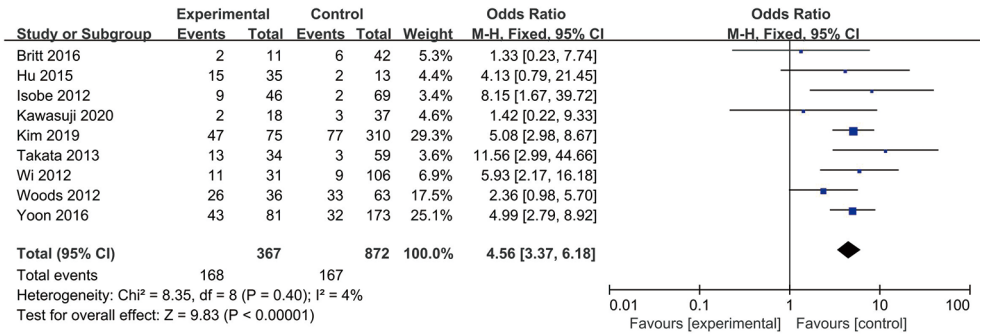

Figure 2 Meta-analysis on the forest plots of development of severe sepsis or septic shock.

Table 3 Continuous variables and risk for mortality in patients infected with MRSA bloodstream infection

Continuous variable	No. of studies	No. of patients in studies reporting specific data [non-survivors]	I² (%)	P value of heterogeneity	WMD (95% CI)	P value
Age (years)	14	2,288 [570]	55	0.007	5.77 (3.46, 8.08)	<0.00001
APACHE II score upon MRSA bloodstream infection diagnosis	6	1,014 [242]	80	0.0001	5.81 (3.03, 8.59)	<0.0001
Pitt BSI score	6	1,024 [243]	95	<0.00001	0.78 (–0.26, 1.83)	0.14
Charlson comorbidity index	6	935 [247]	84	<0.00001	1.02 (0.30, 1.74)	0.006
C-reactive protein level (mg/L)	3	352 [136]	80	0.007	15.05 (–27.60, 57.69)	0.49

APACHE II, Acute Physiology and Chronic Health Evaluation II score; MRSA, methicillin-resistant *Staphylococcus aureus*; BSI, bloodstream infection; WMD, weighted mean difference.

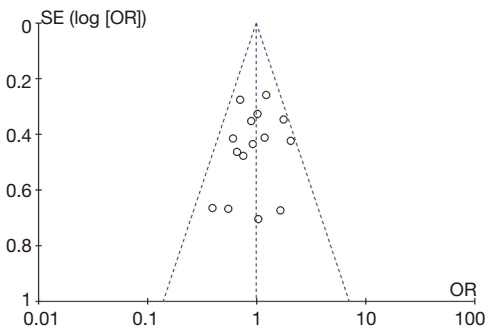

Figure 3 Funnel plot to assess publication bias for diabetes mellitus. OR, odds ratio.

and the corresponding 95% CIs for healthcare acquisition changed to 0.22 (95% CI: 0.09–0.51). The results and statistical significance changed for the metastatic infection factor and the health-care acquisition factor upon removal of these studies.

Publication bias evaluation

In this research, we assessed the publication bias for each related risk factor by funnel plot, and in each funnel plot, we failed to find any distinct asymmetry, which means that the bias was generally balanced. The results showed that the two sides were basically symmetrical, and individual studies were all within the 95% CI, suggesting that there was a small probability of publication bias in the included study. One representative funnel plot to assess publication bias for diabetes mellitus is shown in *Figure 3*.

Discussion

MRSA bloodstream infection is associated with a high mortality rate. It is critical to predict and improve the outcome of these patients. Here, we performed a meta-analysis of the existing literature to identify risk factors associated with mortality in patients with MRSA bacteremia,

thus providing possible suggestions for physicians on appropriate clinical decisions.

Comorbidities, including the presentation of congestive heart failure, infective endocarditis, liver cirrhosis, and malignancies, are associated with increased mortality, which may be expected. Patients with MRSA bloodstream infections with these comorbidities should be closely monitored, as they tend to have a poorer prognosis. In addition, the development of severe sepsis or septic shock increased the pooled mortality of patients with MRSA bloodstream infections more than four-fold, which is quite understandable considering that severe sepsis or septic shock always represents a rather severe condition of infection.

MRSA infection was once thought to be associated with hospitals and other healthcare settings. However, it has also now become one of the most common multidrug-resistant pathogens associated with community-acquired infections since community-acquired MRSA (CA-MRSA) infection was first reported in the 1980s (28,29). The number of patients with CA-MRSA bloodstream infection included in our study was much smaller than those with nosocomial infection, while the mortality rate was similarly lower (23.2% *vs.* 29.1%). Nevertheless, over the past decade, researchers have observed that MRSA strains can be transmitted between communities and hospitals (30); in some cases, highly virulent CA-MRSA strains can invade medical facilities, causing nosocomial infections (31).

Our research attempted to clarify the correlation between vancomycin MIC and outcomes in patients with MRSA bloodstream infections. Several methods can be used to determine the MIC of vancomycin for MRSA, and different antimicrobial susceptibility testing methods result in different results (32). We included the study detecting vancomycin MIC with the E-test method to avoid bias from different testing methods, and the results demonstrated that vancomycin MIC ≥1.5 mg/L is not a risk factor for mortality in adult patients (OR: 1.25, 95% CI: 0.83–1.90). This conclusion was partially in agreement with the results of the former study (33,34). We think that the increased vancomycin MIC maybe associated with changes in bacterial structure and protein transcription that impact bacterial fitness and virulence. In addition, the result of blood concentration test is not addressed in studies we included for analysis—judicious use of antimicrobials depending on their pharmacokinetics and pharmacodynamics is essential in MRSA bloodstream infections. However, given that the levels of evidence were low, further prospective cohort studies or randomized control trials are needed.

Heterogeneous vancomycin-intermediate *S. aureus* (h-VISA) is characterized by the presence of a resistant subpopulation, typically at a rate of 1 in 10^5 organisms, which constitutes the intermediate stage between fully vancomycin-susceptible *S. aureus* (VSSA) and vancomycin-intermediate *Staphylococcus aureus* (VISA) isolates. At present, it is usually assumed that h-VISA is the precursor of VISA and is associated with vancomycin treatment failure (35). In the studies we included, daptomycin, teicoplanin and other drugs were used to treat infection caused by the h-VISA strain, which may explain why the prognosis of the infection does not show a significant deterioration.

The quorum sensing system mediated by accessory gene regulator (Agr) is one of the most important kinds of two component regulatory systems in the pathogenic process of *Staphylococcus aureus* infection (36,37). In recent years, a high prevalence of clinical isolates of *Staphylococcus aureus* with Agr dysfunction has gained global visibility. The Agr system regulates the expression of virulence factors in *Staphylococcus aureus* infection. In a previous animal experiment, Agr-knockout strains showed reduced virulence and pathogenicity (38). However, clinical studies on MRSA bloodstream infection have shown that strains with Agr dysfunction are more prone to a chronic disease course. Adverse outcomes are thought to be associated with increased expression of staphylococcal protein A (SPA) and fibronectin binding protein (FnBP) due to the inhibition of the Agr system (39,40). We failed to determine the correlation between Agr dysfunction and the prognosis of MRSA bacteremia in our research, which may be explained by the difference in sample size, and the specific mechanism remains to be further explored.

The Panton-valentine leucocidin (*PVL*) gene was thought to be associated with the severity of MRSA infection. MRSA stains carrying the *PVL* gene can produce *PVL* toxin, which could cause host cell lysis, thus leading to clinical symptoms, even life-threatening symptoms (41). Early research suggests that the *PVL* gene exists only in CA-MRSA strains (42), but recent studies have found that nosocomial MRSA strains can also carry the gene (43). Our study suggests that carrying the *PVL* gene does not affect the prognosis of patients with MRSA bloodstream infections, and a study with a larger sample size is needed to verify this conclusion.

Our results clearly demonstrate that appropriate antimicrobial therapy can increase the survival rate of patients with MRSA bacteremia. Inappropriate empirical antimicrobial treatment increased the pooled mortality of

1,737 patients with MRSA bloodstream infection, which underlines the importance of bacterial resistance monitoring in healthcare facilities and the qualified use of antimicrobials by physicians. In the absence of bacterial identification or drug sensitivity results in clinical settings with a high prevalence of MRSA infection, a more aggressive initial regimen involving anti-MRSA antimicrobials, such as vancomycin, linezolid, and daptomycin, should be launched as soon as possible under the supervision of infectious disease specialists (44,45).

Notably, our study strengthened the opinion that removing eradicable foci in time served as a protective factor for patients with MRSA bloodstream infections. The common invasive routes of staphylococcal bloodstream infections are skin and soft tissues, lungs, wounds and venous catheters or other implants. It is highly clinically significant to identify the primary infection of MRSA bloodstream infection. For example, in catheter-related bloodstream infection, removal of the catheter is equivalent to complete clearance of infection foci (46). Similarly, early surgical intervention, especially the early removal of prosthetic joints that caused a MRSA bloodstream infection, is strongly associated with a better prognosis (47). According to a Spanish multicenter prospective observational study, source control significantly improved the clinical outcome of patients with severe sepsis and septic shock in the ICU (48). Disseminated infection often occurs in patients with MRSA bloodstream infections, such as pneumonia, purulent meninges and liver abscess, and drainage and surgery to remove metastatic foci can improve the final outcome. It is noteworthy that the role of the primary source and disseminated foci themselves can always be transformed; for instance, infective endocarditis often occurs secondary to bloodstream infection, while detachment of the infectious embolus can cause organ abscess.

Our analysis showed that among the continuous variables, older age and a higher APACHE II score were the main predictors of MRSA bloodstream infection mortality. The impact of age on outcome is quite understandable, since older patients may have more underlying diseases. In addition, the APACHE II score proved to be an important and useful tool for the evaluation of disease severity and the prediction of outcomes in patients with MRSA bacteremia, which has also been shown in the analysis of other pathogens, such as *Acinetobacter baumannii* (49).

Our research revealed that older age, comorbidities such as liver cirrhosis, congestive heart failure and malignancy are independent risk factors for mortality of MRSA bacteremia. Nosocomial acquisition of MRSA is also associated with poor prognosis. As a matter of fact, the receivers of palliative care are always the elderly patients with irreversible end-stage diseases who require long and frequent hospital stays-that means they are particularly vulnerable to MRSA bloodstream infection. Therefore, more active management could be taken in advance for patients with a potentially worse outcome, thus improving their chance of survival.

Limitations

There are several limitations of this study. First, most of the studies included in this analysis were retrospective observational studies, which may be susceptible to selection bias and thus should be considered lower-evidence studies. Further prospectively designed studies are required. Second, only studies written in English were included, which may introduce an additional level of bias. Last, it is not easy to reach a definitive conclusion according to the current evidence as a consequence of small sample sizes and poor control of confounding factors in the included studies.

Conclusions

Age, patient condition, timing and appropriate antimicrobial treatment, surgical intervention and disease severity evaluated by the APACHE II score are the most important predictors of mortality in patients with MRSA bloodstream infections. These findings may help physicians predict outcomes in patients especially who received palliative care with MRSA bloodstream infections and help to improve the management of these patients.

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Footnote

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Supplementary

Table S1 Search strategy

Database	Step	Search algorithm	Items found
Embase	#1	Staphylococcus aureus	207371
	#2	methicillin	74681
	#3	meticillin	21783
	#4	Resistance OR resistant	1605792
	#5	MRSA	55401
	#6	(#1 AND (#2 OR #3) AND #4)OR #5	65929
	#7	bloodstream	36515
	#8	bacteremia	62330
	#9	bacteraemia	54836
	#10	#7 OR #8 OR #9	95590
	#11	#6 AND #10	7567
	#12	mortality	1570485
	#13	fatality	139290
	#14	lethality	45576
	#15	prognosis	1005432
	#16	predictor	315055
	#17	survival	1824097
	#18	(((((mortality) OR fatality) OR lethality) OR prognosis) OR predictor) OR survival	3907424
	#19	#11 AND #18	2821
PubMed	#1	Staphylococcus aureus	126292
	#2	methicillin OR meticillin	38854
	#3	Resistance OR resistant	1183164
	#4	MRSA	36188
	#5	(#1 AND #2 AND #3) OR #4	38817
	#6	((bloodstream) OR bacteremia) OR bacteraemia	394310
	#7	(((((mortality) OR fatality) OR lethality) OR prognosis) OR predictor) OR survival	3925498
	#8	#5 AND #6 AND #7	1609
Cochrane	#1	Staphylococcus aureus	3700
	#2	methicillin OR meticillin	1572
	#3	Resistance OR resistant	76603
	#4	MRSA	1079
	#5	(#1 AND #2 AND #3) OR #4	1592
	#6	((bloodstream) OR bacteremia) OR bacteraemia	4153
	#7	(((((mortality) OR fatality) OR lethality) OR prognosis) OR predictor) OR survival	202440
	#8	#5 AND #6 AND #7	130

MRSA, Methicillin-resistant *Staphylococcus aureus.*

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