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Research article

Clinical characteristics of and risk factors for secondary bloodstream infection after pneumonia among patients infected with methicillin-resistant *Staphylococcus aureus*

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HIGHLIGHTS

- Secondary MRSA bloodstream infection is not uncommon in MRSA pneumonia.
- Some factors (e.g., high SOFA score) are predictors of bloodstream infection.
- Linezolid as a targeted antibiotic is a protective factor.
- Secondary bloodstream infection will worsen clinical outcomes of pneumonia.

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ABSTRACT

Purpose: To investigate the clinical features and risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia (MP) with secondary MRSA bloodstream infections (MRSA-BSI) (termed MP-BSI) compared with MP alone and to study the incidence of MP-BSI among patients with MP.

Methods: This was a retrospective, single-center study with clinical data derived from previous medical records. The cases were divided into groups: MP alone and MP-BSI. The determination of independent risk factors for MP-BSI relied on logistic regression analysis. Additionally, the crude outcomes were compared.

Results: A total of 435 patients with MP were recruited, with 18.9% (82/435) having MP-BSI. The median age was 62 (interquartile range, 51,72) years, and 74.5% of the patients were male. Multivariate analysis revealed that immunosuppression, community-acquired MP (CA-MP), time from initial to targeted antibiotic use, high Sequential Organ Failure Assessment (SOFA) score, increased respiratory rate, and elevated γ-GT level (all $p < 0.05$) were independent risk factors for MP-BSI, while targeted treatment with linezolid was a protective factor. Patients with MP-BSI had a longer duration of hospitalization (median days, 27.5 vs. 19, $p = 0.001$), a higher 28-day mortality rate (24.4% vs. 11.0%, $p = 0.001$), and a higher in-hospital mortality rate (26.8% vs. 14.7%, $p = 0.009$) than those with MP alone.

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Conclusion: Secondary MRSA-BSI among patients with MP is not rare. Immunosuppression, CA-MP, time from initial to targeted antibiotic use, high SOFA score, increased respiratory rate and elevated γ-GT level are all independent risk factors for MP-BSI; however, linezolid, as a targeted antibiotic, is a protective factor. Moreover, patients with MP may have worse clinical outcomes when they develop MRSA-BSI.

1. Introduction

Since it was first reported in 1961, methicillin-resistant *Staphylococcus aureus* (*S. aureus*) (MRSA) has become rapidly prevalent worldwide. Although there has been a decline in MRSA infections in the US and several European countries since 2005, owing primarily to a decrease in skin and soft tissue infections, MRSA-associated pneumonia and sepsis are still at a high level [1, 2]. In the past 3 decades, there appeared to be a modest and progressive decrease in mortality from *S. aureus* bacteremia; however, MRSA bacteremia was consistently associated with higher mortality [3]. In addition, the epidemiology of community-acquired MRSA has developed rapidly since the 1990s, and community-acquired MRSA can cause necrotizing pneumonia and sepsis with high mortality [4]. MRSA continues to be a leading cause of pneumonia and bloodstream infections (BSIs), with high morbidity and severe clinical consequences [5, 6, 7]. Furthermore, once patients with pneumonia develop secondary BSIs, the outcomes, including length of stay (LOS) and mortality, worsen [7, 8, 9, 10]. Thus, MRSA pneumonia (MP) or MRSA-BSI alone or MRSA pneumonia that develops secondary MRSA-BSI (termed MP with secondary MRSA-BSI, MP-BSI) has a high morbidity and adverse outcomes and causes substantial medical and economic burdens worldwide.

Previous studies have described these clinical features of bacteremic pneumonia [7, 9, 10, 11]; however, some limitations are listed below: (1) These studies focused primarily on the impact of combined bacteremia on the prognosis of pneumonia, with less emphasis on the risk factors for the progression of pneumonia alone to pneumonia with bacteremia [7, 9, 10, 11]. (2) Risk factors for bacteremic pneumonia caused by different pathogens were inconsistent [9, 10, 11], even when both were caused by *S. aureus* [10, 11]. Additionally, no similar study has been conducted to investigate the predictors of the development of secondary MRSA-BSI among individuals with MP. (3) Inconsistency was also evident in the clinical outcomes of these studies, such as mortality [7, 9, 10]. (4) The sample sizes in the two previous studies that included risk factors for *S. aureus*-associated bacteremic pneumonia were relatively small ($n < 100$), which would have weakened the statistical power. (5) In terms of data sources, the data came from the US and Spain, and it is unknown whether they were available in other regions, including China.

Given the worse outcomes of MP-BSI and the limited availability of such studies, it is urgent and crucial to identify some preventable factors to inhibit the development of secondary MRSA-BSI among patients with MP alone. In this study, we investigated the clinical features, risk factors, and crude prognosis of MP-BSI compared with MP alone in China.

2. Materials and methods

2.1. Population and study design

This retrospective observational study was conducted at the Second Affiliated Hospital, Zhejiang University School of Medicine, a 3200-bed tertiary care hospital, from January 2013 to December 2020. The Ethics Committee approved the project (No.2021–0300) and waived the requirement for informed consent.

Patients who met the diagnostic criteria for pneumonia and whose respiratory secretion cultures were positive for MRSA were recruited. The exclusion criteria included a) age <18 years or >85 years; b) MRSA that could not be identified as a responsible organism in pneumonia with mixed polymicrobial infections; c) MRSA colonization or contamination; d) multiple organ dysfunction on admission; e) incomplete or missing case data; f) secondary MP from MRSA-BSI; g) MP and MRSA-BSI simultaneously on admission and difficulty differentiating primary or secondary MRSA-BSI; and h) pregnant women.

2.2. Definitions

The diagnosis of pneumonia, hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and community-acquired pneumonia (CAP) was based on the CDC definitions [12, 13, 14]. Pneumonia was defined as the following: pulmonary radiological examination showing new or progressive infiltration, accompanied by at least one of the following: (1) fever and body temperature>38 °C, (2) peripheral blood white blood cell count>12 × 109/L or<4 × 109/L, (3) for adults ≥70 years of age, altered mental status without other recognized cause, and accompanied by at least two of the following: (1) new onset of purulent sputum or change in character of sputum, increased respiratory secretions, or increased suctioning requirements; (2) new onset or worsening cough or tachypnea; (3) rales or bronchial breath sounds; or (4) worsening gas exchange [12]. Nosocomial pneumonia was defined as HAP and VAP. MP-BSI was diagnosed based on the isolation of MRSA from blood culture specimens of MP patients, which were collected during the pneumonia secondary BSI attribution period, as well as the exclusion of other sources of infection and specimen contamination, as stated in Bloodstream Infection Events [15]. Immunosuppression was considered chronic steroid use at a dose of more than 10 mg/d of prednisone or equivalent for at least three months before the onset of pneumonia, chemotherapy during the last three months, or the existence of hematological malignancies. The initial antibiotic therapy was defined as antibiotics administered within the first 48 h after pneumonia onset, regardless of the pathogen [6]. Targeted antibiotic therapy was defined as antibiotics administered after microbiological sensitivity tests and to which MRSA was sensitive in vitro [6]. MRSA could not be identified as the responsible bacteria in patients with pneumonia whose respiratory secretion cultures were positive for multiple microorganisms if symptoms improved after receiving two or more antibiotics against different microorganisms simultaneously (one of which covered MRSA). If the antibiotics administered by clinicians did not cover MRSA, but the patient's pneumonia was still cured, we considered this MRSA as colonization or contamination; if the cure of pneumonia must rely on anti-MRSA therapy, it was considered that MRSA as the pathogenic bacteria. Secondary MRSA pneumonia from MRSA-BSI was defined as MRSA-BSI occurs before MP, while MRSA-BSI was from other infected site like catheter related infection or surgical site infection.

2.3. Data collection

Data were obtained by accessing electronic medical records, which included demographic data, antibiotic exposure in the 90 days before pneumonia, surgical exposure before BSI, pneumonia type, first vital signs and biological parameters obtained within 24 h of pneumonia onset, and severity of illness, including Glasgow Coma Scale score, oxygenation index, Acute Physiology and Chronic Health Evaluation (APACHE) II score in the first 24 h after pneumonia onset, and Sequential Organ Failure Assessment (SOFA) score. Anti-infection strategies and outcomes were also recorded.

2.4. Species identification and antibiotic sensitivity testing

Respiratory specimens were inoculated on chocolate or blood plates and incubated in a carbon dioxide incubator (Thermo Fisher Scientific,

USA). Blood specimens were cultured in a BacT/ALERT 3D system (bioMerieux, USA). Species identification relied on Bruker Daltonics data analysis (Bruker Daltonik GmbH, Germany). As specified by the Clinical and Laboratory Standards Institute (M100, 31st Edition) [16], vancomycin susceptibility testing was performed using the broth microdilution method to determine the minimal inhibitory concentration, and the equipment used was the Vitek 2 Compact system.

2.5. Statistics

Statistical analysis was performed using SPSS 24.0 (IBM Corp, Armonk, NY, USA). A two-tailed test was used for all tests, with $p < 0.05$ considered statistically significant. Normality of continuous variables was tested using the Kolmogorov–Smirnov test. If the continuous variables were normally distributed, they were represented as the means ± standard deviations; otherwise, they were represented as the medians and interquartile ranges (IQRs). The analysis of continuous variables was conducted using either the Mann–Whitney U test or Student's t test, while the Pearson $\chi 2$ or Fisher's exact test was used for analyzing categorical variables. Stepwise forward logistic regression was selected to confirm independent risk factors for secondary MRSA-BSI, and variables with $p < 0.05$ in univariate analysis were used to build the final multivariate model.

3. Results

Demographic data

During the eight-year study period, 435 patients with MP were ultimately recruited from an initial 1137 potential MP patients, and 82 (18.9%) of them developed secondary MRSA-BSI (MP-BSI) (Figure 1). Table 1 shows the demographic data. The median age was 62 (IQR, 51, 72) years, and 74.5% (324/435) of patients were male. The most common comorbidity was a cerebrovascular accident or traumatic brain injury (39.1%), followed by diabetes (15.4%) and chronic heart failure (8.5%). In the cohort, 58.6% (255/435) of patients had prior antibiotic exposure, and 51.7% (225/435) received surgery prior to MRSA-BSI. Nosocomial MP and CA-MP accounted for 81.4% and 18.6%, respectively. The number of secondary BSIs among CAP patients was significantly higher than that among HAP patients (35.8% vs. 15%, $p < 0.001$).

Compared to patients with MP only, patients with MP-BSI showed a high proportion of immunosuppression (13.4% vs. 1.7%, $p < 0.001$) and CA-MP (35.4% vs. 14.7%, $p < 0.001$), higher SOFA scores (median, 5 vs. 4, $p = 0.018$), faster heart rates (median, 102 vs. 87, $p < 0.001$), increased respiratory rates (RRs) (median, 20 vs. 18, $p < 0.001$), higher mean arterial pressure (median, 89.7 vs. 84.9, $p = 0.015$), and a lower oxygenation index (median, 248.4 vs. 280.0, $p = 0.007$), but there were no differences in other parameters (all $p > 0.05$) (Table 1).

Biological parameters

Table 2 depicts a comparison of biological parameters between the MP alone and MP-BSI groups. Alanine aminotransferase (ALT) (median, 38 vs. 31, $p = 0.011$), gamma-glutamyl transpeptidase (γ-GT) (median, 54.5 vs. 41.0, $p = 0.018$), lactic dehydrogenase (LDH) (median, 311.5 vs. 278.0, $p = 0.023$), direct bilirubin (DBil) (median, 5.4 vs. 4.2, $p = 0.017$) and blood lactate (median, 1.6 vs. 1.3, $p = 0.001$) levels were significantly higher, while albumin (mean, 30.01 vs. 32.00, $p = 0.006$) levels were significantly lower among patients with MP-BSI than among patients with MP alone.

Anti-infection strategy

Table 3 summarizes the anti-infection strategy. All participants received initial antibiotic therapy and were treated with targeted antibiotics prior to the onset of BSI. The most frequently administered

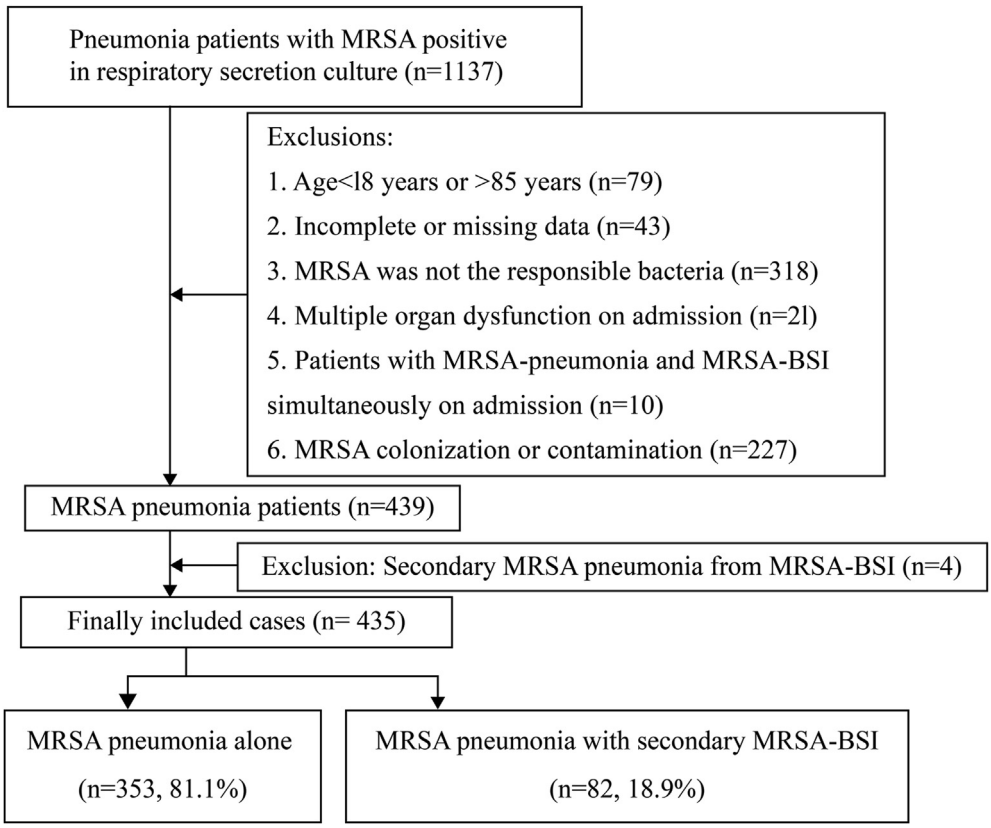

Figure 1. Flowchart of study participant enrollment **Abbreviation:** *MRSA* Methicillin-resistant *Staphylococcus aureus*, *BSI* Bloodstream infection.

Table 1. Demographic data of patients with MP alone or MP-BSI.

	Total (n = 435)	MP (n = 353)	MP- BSI (n = 82)	*P*-value
Age, median years (IQR)	62 (51,72)	64 (51,72)	58 (49,68)	0.032
Male, n (%)	324 (74.5%)	261 (73.9%)	63 (76.8%)	0.588
Severity of illness				
APACHE II score, median (IQR)	12 (9,16)	12 (9,16)	12 (9,17)	0.337
SOFA score, median (IQR)	4 (3,6)	4 (2.5,5)	5 (3,6)	0.018
PaO2/FiO2, median (IQR)	277.5 (221.3,335.0)	280.0 (230.5,337.1)	248.4 (175.3,318.1)	0.007
Glasgow coma score, median (IQR)	13 (8,15)	13 (8,15)	14 (7,15)	0.897
Co-morbidities, n (%)				
Diabetes mellitus	67 (15.4)	55 (15.6%)	12 (14.6%)	0.831
Chronic heart failure	37 (8.5%)	32 (9.1%)	5 (6.1%)	0.386
Chronic kidney disease	14 (3.2%)	12 (3.4%)	2 (2.4%)	0.923
Chronic liver disease	10 (2.3%)	7 (2.0%)	3 (3.7%)	0.615
Chronic pulmonary insufficiency	34 (7.8%)	30 (8.5%)	4 (4.9%)	0.271
Solid malignant tumor	33 (7.6%)	25 (7.1%)	8 (9.8%)	0.410
Cerebrovascular accident or traumatic brain injury	170 (39.1%)	143 (40.5%)	27 (32.9%)	0.205
Immunosuppression	17 (3.9%)	6 (1.7%)	11 (13.4%)	0.000
Antibiotic exposure before onset, n (%)	255 (58.6%)	209 (59.2%)	46 (56.1%)	0.607
Surgical exposure before BSI, n (%)	225 (51.7%)	186 (52.7%)	39 (47.6%)	0.402
Pneumonia type, n (%)				0.000
HAP or VAP	354 (81.4%)	301 (85.3%)	53 (64.6%)	
CAP	81 (18.6%)	52 (14.7%)	29 (35.4%)	
Vital signs				
Temperature (°C) (IQR)	38.2 (38.0,38.8)	38.2 (38.0,38.8)	38.3 (38.0,39.0)	0.122
Heart rate (cpm) (IQR)	90.0 (80.0,103.0)	87.0 (78.0,101.0)	102.0 (90.5,109.3)	0.000
Respiratory rate (cpm) (IQR)	18 (16,20)	18 (16,20)	20 (18,22)	0.000
Mean arterial pressure (mmHg)	86.0 (70.7,103.0)	84.9 (68.2,102.6)	89.7 (80.3,104.4)	0.015
(IQR)				

Abbreviations: *MP* Methicillin-resistant *Staphylococcus aureus* pneumonia, *MP-BSI* MP with secondary methicillin-resistant *Staphylococcus aureus* bloodstream infections, *IQR* Interquartile range, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment, *HAP* Hospital-acquired pneumonia, *VAP* Ventilator-associated pneumonia, *CAP* Community-acquired pneumonia, *cpm* Counts per minute.

targeted antibiotics for MP-BSI were glycopeptides (69.5%), followed by linezolid (22.0%) and other anti-MRSA antibiotics (8.5%), whereas in the MP group, they were linezolid (47.0%), glycopeptides (45.0%), and others (7.9%) ($p < 0.001$). Compared to the MP group, the MP-BSI group used a significantly lower proportion of linezolid than glycopeptides among targeted antibiotics ($p < 0.001$). Additionally, patients with MP-BSI initiated targeted antibiotics later than those with MP only (median days, 4 vs. 3, $p < 0.001$).

Independent risk factors for secondary MRSA-BSI

Immunosuppression (adjusted odds ratio [aOR], 13.599; 95% confidence interval [CI], 4.063–45.521; $p < 0.001$), CA-MP (aOR, 2.827; 95% CI, 1.496–5.343; $p = 0.001$), time from initial to targeted antibiotic use (aOR, 1.304; 95% CI, 1.136–1.497; $p < 0.001$), high SOFA score (aOR, 1.192; 95% CI, 1.065–1.333; $p = 0.002$), increased RR (aOR, 1.135; 95% CI, 1.066–1.209; $p < 0.001$), and elevated γ-GT level (aOR, 1.004; 95% CI, 1.001–1.008; $p = 0.016$) were independent risk factors for secondary MRSA-BSI, while linezolid as a targeted antibiotic was a protective factor (aOR, 0.224; 95% CI, 0.115–0.438; $p < 0.001$) (Table 4).

Outcomes

Patients with MP-BSI required a longer hospital stay after the onset of pneumonia than MP patients (median days, 27.5 vs. 19, $p = 0.001$), but there were no significant differences in LOS in the ICU (median days, 9.5 vs. 12, $p = 0.893$) or days of mechanical ventilation (median, 8 vs. 7, $p = 0.252$) (Table 5). The entire cohort had an all-cause hospital mortality rate of 17% (74/435), which was significantly higher among patients with MP-BSI than among those with MP alone (26.8% vs. 14.7%, $p = 0.009$). Similarly, the 28-day all-cause mortality rate was significantly higher among patients with MP-BSI than among patients with MP alone (24.4% vs. 11.0%, $p = 0.001$), which was consistent with the results shown by the survival curve (Figure 2).

4. Discussion

This study provided us with some useful information. First, secondary MRSA-BSI is not rare among patients with MP, and the incidence is higher among CA-MP patients than among nosocomial MP patients. Second, some risk factors associated with secondary MRSA-BSI were identified (Tables 1, 2, and 3). Importantly, multivariate analysis revealed that immunosuppression, CA-MP, time from initial to targeted antibiotic use, high SOFA score, increased RR, and elevated γ-GT level were all independent risk factors for secondary MRSA-BSI; notably, targeted treatment with linezolid was a protective factor (Table 4). Finally, patients with MP-BSI had worse crude outcomes (Table 5).

In fact, epidemiological information about the occurrence of MP-BSI among patients with MP is limited in previous studies. Regardless of the pathogen, Magret and colleagues noted that approximately 15% of patients with nosocomial pneumonia presented with bacteremia [9]. In our current study, the proportion was 18.9%, which was higher than that in a previous retrospective study (12.2%) [7]. The relatively low occurrence of comorbid bacteremia in Shorr's study [7] might be partially due to the difference in the inclusion criteria in which patients with concurrent episodes of pneumonia and bacteremia (only blood cultures drawn within 48 h of the onset of pneumonia were reviewed) were recruited, resulting in a lack of such cases with secondary MRSA-BSI in the middle to late stages of the disease. Consistent with our result, 20.3% (12/59) of patients with *S. aureus* pneumonia requiring mechanical ventilation had

Table 2. Comparison of biological indicators between patients with MP alone or MP-BSI.

Biological indicators	Total (n = 435)	MP (n = 353)	MP-BSI (n = 82)	*P*-value
Blood routine test				
WBC ($\times 10^9$/L) (IQR)	11.4 (8.6,15.0)	11.4 (8.6,14.5)	11.8 (7.6,15.8)	0.660
ANC (IQR)	9.7 (6.7,12.8)	9.6 (6.7,12.5)	10.0 (6.6,13.8)	0.707
Hemoglobin (g/L) (IQR)	98.0 (82.0,116.0)	98.0 (82.0,116.0)	98.0 (84.8,113.3)	0.747
Hematocrit (%) (IQR)	29.8 (25.3,35.1)	29.8 (24.9,35.3)	29.7 (25.9,35.0)	0.805
Platelet ($\times 10^9$/L) (IQR)	175.0 (124.0,232.0)	178.0 (128.5,232.5)	166.0 (107.5,229.0)	0.170
Liver and kidney function				
ALT (U/L) (IQR)	32.0 (19.0,58.0)	31.0 (18.5,54.0)	38.0 (25.5,70.8)	0.011
AST (U/L) (IQR)	35.0 (23.0,56.0)	34.0 (23.0,53.5)	38.0 (25.0,66.3)	0.138
ALP (U/L) (IQR)	85.0 (67.0,116.0)	84.4 (66.0,114.5)	89.5 (70.8,129.5)	0.110
γ-GT (U/L) (IQR)	43.0 (23.0,87.0)	41.0 (22.0,78.5)	54.5 (31.3,107.5)	0.018
LDH (U/L) (IQR)	284.0 (218.0,375.0)	278.0 (216.0,359.0)	311.5 (234.8,423.5)	0.023
Albumin (g/L) (mean ± S.D.)	31.63 ± 5.15	32.00 ± 4.88	30.01 ± 5.95	0.006
DBil (μmol/L) (IQR)	4.4 (2.6,7.9)	4.2 (2.6,7.6)	5.4 (2.8,10.2)	0.017
IBil (μmol/L) (IQR)	8.7 (5.5,13.5)	8.8 (5.5,13.4)	8.5 (5.1,14.5)	0.855
SCr (μmol/L) (IQR)	59.0 (46.0,81.0)	59.0 (46.0,79.0)	62.0 (44.0,88.5)	0.937
BUN (mmol/L) (IQR)	6.8 (4.7,9.7)	6.8 (4.7,9.6)	6.8 (4.7,9.8)	0.938
PCT (ng/ml) (IQR)	0.43 (0.18,0.98)	0.42 (0.20,0.91)	0.51 (0.17,1.20)	0.550
CRP (mg/L) (IQR)	76.6 (46.2,144.4)	74.2 (44.1,144.3)	84.3 (51.6,146.8)	0.227
Blood lactate (mmol/L) (IQR)	1.4 (1.1,1.9)	1.3 (1.0,1.9)	1.6 (1.2,2.2)	0.001

Abbreviations: *MP* Methicillin-resistant *Staphylococcus aureus* pneumonia, *MP-BSI* MP with secondary methicillin-resistant *Staphylococcus aureus* bloodstream infections, *IQR* Interquartile range, *WBC* White blood count, *ANC* Absolute neutrophil count, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *ALP* Alkaline phosphatase, *γ-GT* Gamma glutamyl transpeptidase, *LDH* Lactic dehydrogenase, *S.D.* Standard deviation, *DBil* Direct bilirubin, *IBil* Indirect bilirubin, *SCr* Serum creatinine, *BUN* Blood urea nitrogen, *PCT* Procalcitonin, *CRP* C-reactive protein.

Table 3. Anti-infection strategy of MP-BSI compared with MP alone.

	Total (n = 435)	MP (n = 353)	MP- BSI (n = 82)	*P*-value
Targeted antibiotic therapy, n (%)				0.000*
Glycopeptides[a]	216 (49.7%)	159 (45.0%)	57 (69.5%)	
Linezolid	184 (42.3%)	166 (47.0%)	18 (22.0%)	
Others[b]	35 (8.0%)	28 (7.9%)	7 (8.5%)	
Time from initial to targeted antibiotic use, median days (IQR)	3.0 (2.0,4.0)	3.0 (1.5,4.0)	4.0 (2.0,5.0)	0.000

Abbreviations: *MP* Methicillin-resistant *Staphylococcus aureus* pneumonia, *MP-BSI* MP with secondary methicillin-resistant *Staphylococcus aureus* bloodstream infections

[a] Vancomycin, teicoplanin

[b] Tigecycline, moxifloxacin, levofloxacin, clindamycin, ciprofloxacin.

* Further analysis with partition of chi-square: glycopeptides vs linezolid ($p < 0.001$), glycopeptides vs others ($p > 0.0167$), linezolid vs others ($p > 0.0167$).

combined bacteremia in Schreiber's study [10]. Combined with our and other previous studies, these results indicate that the occurrence of secondary BSI or comorbid BSI among patients with corresponding pneumonia, including MP, is relatively common, approximately 20%.

Several risk factors for MP-BSI were identified in this study. Immunosuppression is considered a predictor of infections caused by various pathogens, such as *S. aureus* or MRSA [17, 18], and it is associated with worse outcomes [19]. In our study, immunosuppression increased the risk of secondary MRSA-BSI among patients with MP by approximately 12-fold (aOR, 13.599; 95% CI, 4.063–45.521; $p < 0.001$). The SOFA score has been reported as a predictor of undesirable prognosis in pneumonia and BSI [19, 20]. Increased RR is usually an early indicator of pneumonia [21], and it is also a key predictor of pneumonia and sepsis prognoses [22, 23]. Previous literature on the role of γ-GT in pneumonia and BSI is very rare, but the predictive value of γ-GT for severe disease course and adverse outcomes among COVID-19 patients has made substantial progress in recent years [24, 25, 26, 27, 28]. Abnormal serum γ-GT levels are more common in patients with severe COVID-19 [24,26-28], and they may also be an indicator of intestinal dysfunction in COVID-19 patients [25], which might be attributed to the proinflammatory and pro-oxidant effects of γ-GT [29]. Consistent with these previous studies, our results also indicated that immunosuppression, high SOFA score, increased RR, and elevated γ-GT level were all independent risk factors for secondary MRSA-BSI among patients with MP.

Additionally, we discovered that CA-MP and time from initial to targeted antibiotic use were independent risk factors for secondary MRSA-BSI, whereas linezolid as a targeted treatment was a protective factor. Although MRSA is a relatively rare cause of CAP, the incidence of bacteremia among patients with CA-MP is high and often occurs early in the course of pneumonia [30]. This might be attributed to the fact that community-acquired MRSA usually carries the Panton-Valentine leucocidin gene, the smaller staphylococcal cassette chromosome mec [5], and secretes some toxins and exoenzymes against various immune defenses [31], making it more likely to disrupt the air–blood barrier. Our results are consistent with a previous report that indicated that patients with pneumonia would benefit from early initiation of anti-MRSA therapy after MRSA was identified as the pathogen [32]. Pneumonia-related guidelines [13, 14, 33] also recommended that empirical antibiotic regimens for patients at risk for MRSA infection should cover MRSA and obtain culture results as early as possible. Compared to glycopeptides, we discovered that linezolid, as a targeted antibiotic, was beneficial in reducing the incidence of secondary MRSA-BSI (aOR, 0.224; 95% CI, 0.115–0.438; $p < 0.001$). Our findings further confirmed the idea that linezolid might be superior to vancomycin in the treatment of MP [34, 35, 36]. This advantage could be associated with the high concentration of linezolid in the lung epithelial lining fluid and endotracheal tube biofilms [35, 36], which reinforces the air–blood barrier and prevents MRSA from invading the bloodstream. Taken together, these results suggest that early detection of causal pathogens such as community-acquired MRSA, rapid initiation of anti-MRSA treatment, and targeted antibiotic treatment with linezolid are essential in improving

Table 4. Multivariable logistic regression of factors associated with MRSA pneumonia with secondary MRSA-BSI.

Variable	Unadjusted OR (95%CI)	*p*-value	Adjusted OR (95%CI)	*P*-value
Age (years)	0.988 (0.973,1.003)	0.119		
SOFA score	1.116 (1.018,1.224)	0.019	1.192 (1.065,1.333)	0.002
PaO2/FiO2	0.996 (0.993,0.999)	0.004		
Immunosuppression	8.960 (3.209,25.022)	0.000	13.599 (4.063,45.521)	0.000
Pneumonia type (CA-MP)	3.167 (1.846,5.435)	0.000	2.827 (1.496,5.343)	0.001
Targeted antibiotic therapy				0.000
Glycopeptides[a]	1 (reference)		1 (reference)	
Linezolid	0.302 (0.171,0.536)	0.000	0.224 (0.115,0.438)	0.000
Others[b]	0.697 (0.289,1.684)	0.432	0.620 (0.222,1.734)	0.362
Time from initial to targeted Antibiotic use	1.272 (1.133,1.428)	0.000	1.304 (1.136,1.497)	0.000
Clinical and biological indicators				
Heart rate (cpm)	1.028 (1.015,1.042)	0.000		
Respiratory rate (cpm)	1.132 (1.073,1.195)	0.000	1.135 (1.066,1.209)	0.000
Mean arterial pressure (mmHg)	1.002 (0.995,1.009)	0.601		
ALT (U/L)	1.002 (0.999,1.005)	0.208		
γ-GT (U/L)	1.004 (1.001,1.007)	0.012	1.004 (1.001,1.008)	0.016
LDH (U/L)	1.001 (1.000,1.003)	0.069		
Albumin (g/L)	0.925 (0.880,0.971)	0.002		
DBil (μmol/L)	1.023 (1.003,1.042)	0.022		
Blood lactate (mmol/L)	1.231 (1.040,1.457)	0.016		

Abbreviations: *MRSA* Methicillin-resistant *Staphylococcus aureus*, *BSI* Bloodstream infection, *OR* odds ratio, *CI* confidence interval, *SOFA* Sequential Organ Failure Assessment, *CA-MP* Community-acquired MRSA pneumonia, *cpm* Counts per minute, *ALT* Alanine aminotransferase, *γ-GT* Gamma glutamyl transpeptidase, *LDH* Lactic dehydrogenase, *DBil* Direct bilirubin.

[a] Vancomycin, teicoplanin.

[b] Tigecycline, moxifloxacin, levofloxacin, clindamycin, ciprofloxacin.

the prognoses of patients with MP and inhibiting the development of MRSA-BSI from MP alone.

The crude prognosis of patients with MP-BSI was relatively worse than that of those with MP alone, as evidenced by longer hospital stays after the onset of pneumonia, higher 28-day mortality rates, and higher in-hospital mortality rates (Table 5). When bacteria invade the bloodstream, the organism itself can cause a more intense inflammatory response, damaging the endothelial cells throughout the body and causing organ dysfunction. Additionally, the fibrinogen-binding receptor of *S. aureus* interacts with plasma fibrinogen to make it more adhesive than other microorganisms [9], and this adhesive property may exacerbate endothelial cell damage and further amplify the inflammatory effect. Of course, this poor prognosis could also be associated with the initial inflammatory response, as our study showed that patients with MP-BSI had higher SOFA scores in the pneumonia stage.

There are several limitations in our study. First, this was a retrospective study, and all data were collected by accessing electronic medical records. Selection bias and information bias were inevitable. To minimize both biases, we recruited all patients who met the inclusion and exclusion criteria during the study period, and data for each patient were extracted independently using a predesigned data extraction form. Second, this was a single-center dataset with insufficient generalizability and may be difficult to replicate, and future multicenter studies are needed to verify the accuracy of the conclusions. Third, we may have overlooked other potential risk factors, such as the use of various invasive devices, the receipt of mechanical ventilation and admission to inpatient wards, which needs to be remedied by additional studies. Fourth, we found that the prognosis of patients with MP-BSI was worse than that of patients with MP alone. However, it was only a crude conclusion since there was no correction for treatment factors. Whether the prognosis of patients with MP-BSI is worse than that of patients with MP alone will need to be confirmed by further multicenter prospective randomized controlled trials. Finally, the current study discovered several independent factors, some of which are preventable or intervenable, such as time from initial to targeted antibiotic use and linezolid as a targeted treatment. Whether targeting these factors will be beneficial for improving the prognoses of MP patients requires further prospective multicenter investigation.

Table 5. Comparison of outcomes between groups of MP and MP-BSI.

Prognostic indicators	Total (n = 435)	MP (n = 353)	MP-BSI BSI (n = 82)	*P*-value
LOS after the onset of pneumonia, median days (IQR)	20 (11,32)	19.0 (11.0,30.5)	27.5 (14.8,49.0)	0.001
Total LOS in ICU, median days (IQR)	11 (2,24)	12 (3,23)	9.5 (0.0,31.3)	0.893
Days of mechanical ventilation, median days (IQR)	7 (0,17)	7 (0,16)	8.0 (1.0,22.3)	0.252
28 day all-cause mortality, n (%)	59 (13.6%)	39 (11.0%)	20 (24.4%)	0.001
In-hospital all-cause mortality, n (%)	74 (17.0%)	52 (14.7%)	22 (26.8%)	0.009

Abbreviations: *MP* Methicillin-resistant *Staphylococcus aureus* pneumonia, *MP-BSI* MP with secondary methicillin-resistant *Staphylococcus aureus* bloodstream infections, *LOS* Length of stay, *IQR* Interquartile range, *ICU* Intensive care unit.

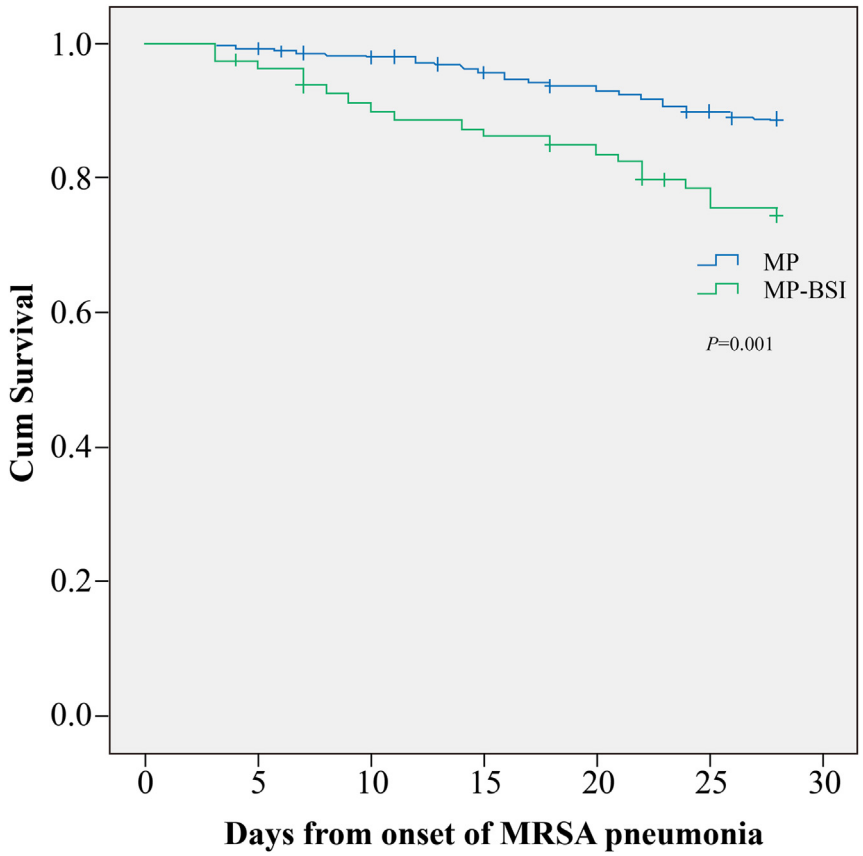

Figure 2. Kaplan-Meier estimates of survival in patients with MP and MP-BSI **Abbreviation:** *MRSA* Methicillin-resistant *Staphylococcus aureus*, *MP* MRSA pneumonia, *MP-BSI* MP with secondary MRSA bloodstream infection.

5. Conclusion

The occurrence of secondary MRSA-BSI was relatively high among patients with MP, accounting for approximately one-fifth of all cases. Several factors, including immunosuppression, CA-MP, time from initial to targeted antibiotic use, high SOFA score, increased RR, and elevated γ-GT level, were all independently associated with secondary MRSA-BSI among MP patients, while linezolid as a targeted antibiotic was a protective factor. Once patients with MP develop secondary MRSA-BSI, their clinical outcomes deteriorate; thus, it is crucial to prevent the development of MRSA-BSI from MP alone in the future.

Declarations

Author contribution statement

Gensheng Zhang, Shufang Zhang, Wei Cui: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Fangfang Huang, Ting Shen, Xin Hai: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Huiqing Xiu, Kai Zhang, Tiancha Huang, Juan Chen, Zhihui Guan, Hongwei Zhou, Jiachang Cai, and Zhijian Cai: Performed the experiments; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

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