Clinical Characteristics, Risk Factors and Outcomes of MRSA Pneumonia with Secondary MRSA Bloodstream Infection

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Research

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Abstract

Background

Methicillin-resistant Staphylococcus aureus (MRSA) pneumonia (MP) and MRSA bloodstream infections (MRSA-BSI) are relatively often described, but MP with secondary MRSA-BSI (termed as MP-BSI) is few reported. Herein, we attempted to investigate the clinical features, risk factors and outcomes of MP-BSI in comparison with MP alone.

Methods

Clinical data from patients with MP was retrospectively collected. The cases were divided into groups of MP alone and MP-BSI. Determination of independent risk factors for MP-BSI relied on binomial logistic regression analysis. In addition, the outcomes were also compared.

Results

A total of 435 patients with MP were recruited, 18.9% (82/435) of whom was MP-BSI. The median age was 62 (interquartile range,51,72) years, and 74.5% were male. Multivariate analysis revealed that high SOFA score, immunosuppression, community-acquired MRSA pneumonia (CA-MP), time from initial to targeted antibiotics, accelerated respiratory rate, elevated γ-GT (all $p<0.05$) were independent risk factors for MP-BSI, while targeted treatment with linezolid was a protective factor. The median length of hospitalization, 28-day mortality, and in-hospital mortality among total patients were 26 days, 13.6%, and 17.0%, respectively. Patients with MP-BSI had longer length of hospitalization, higher 28-day mortality and in-hospital mortality (all $p<0.05$).

Conclusions

Secondary MRSA-BSI among MRSA pneumonia is not uncommon. High SOFA score, immunosuppression, CA-MP, time from initial to targeted antibiotics, accelerated respiratory rate and elevated γ-GT are independent risk factors for MP with secondary MRSA-BSI; importantly, linezolid as targeted antibiotic is a protective factor. In addition, patients with MP have worse clinical outcomes when they are developed with MRSA-BSI.

1. Background

Methicillin-resistant Staphylococcus aureus (MRSA) has been rapidly prevalent worldwide since its first report in 1961. Although there has been a decline in MRSA infection in the US and several European countries since 2005, which is largely due to a decrease in skin and soft tissue infections, MRSA-associated pneumonia and sepsis still maintain at a high level[1, 2]. MRSA remains a main cause of pneumonia and bloodstream infections (BSI) and is associated with high morbidity and critical clinical consequences[3-5]. Moreover, once patients with pneumonia develop secondary BSI, the outcomes including length of stay (LOS) or mortality are worse[5-9]. Thus, either MRSA-pneumonia (MP) or MRSA-

BSI alone, or MRSA-pneumonia develop secondary MRSA-BSI (termed MRSA-pneumonia with secondary MRSA-BSI, MP-BSI) has a high rate of morbidity and mortality, and put a significant threat to medical and economic burden in the world.

Previous studies have described these clinical features of bacteremic pneumonia[5, 6, 8, 9], but some limitations are shown below: (1) These studies primarily concentrated on the impact of combined bacteremia on the prognosis of pneumonia, but less on the risk factors for the development from pneumonia alone to pneumonia with bacteremia[5, 6, 8, 9]. (2) Risk factors for bacteremic pneumonia due to different pathogens were inconsistent[6, 8, 9], even when both were caused by Staphylococcus aureus[6, 9]. Additionally, there is no such study to investigate predictors of the development of secondary MRSA-BSI among MP. (3) Inconsistency was also evident in the clinical outcomes of these studies, such as the mortality[5, 8, 9]. (4) In the two previous studies including risk factors for Staphylococcus aureus bacteremia pneumonia, the sample sizes were relatively small (n<100), which would weaken the statistic power. (5) These data are from the US and Spain, and it is not known whether they are available in other regions including China.

Give the worse outcomes of MP-BSI and few report of such studies, it will be urgent and significant to identify some preventable factors to block the development of secondary MRSA-BSI among MP alone. Herein, we investigated the clinical features, risk factors and prognosis of MP-BSI in comparison with MP alone in China.

2. Material And Methods

2.1 Population And Study Design

From January 2013 to December 2020, this retrospective observational study was carried out in the Second Affiliated Hospital, Zhejiang University School of Medicine, a 3200-bed tertiary care hospital. The Ethics Committee approved the project (NO.2021-0300) and waived informed consent.

Patients who met the diagnostic criteria of MP were recruited. Exclusion criteria include: a) Age<18 years old or>85 years old; b) MRSA couldn't be identified as responsible organism in pneumonia with mixed polymicrobial infections; c) MRSA colonization or contamination; d) Multiple organ dysfunction on admission; e) Cases data were incomplete or missed; f) Secondary MRSA-pneumonia from MRSA-BSI; g) Patients with MRSA-pneumonia and MRSA-BSI simultaneously on admission were difficult to differentiate primary or secondary MRSA-BSI; h) Pregnant woman.

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 definition[10, 11]. Nosocomial pneumonia was defined as HAP and VAP. MP-BSI was defined that MP patients combined with secondary MRSA-BSI, which was from primary MP with no other infectious source for MRSA-BSI[12].

Immunosuppression was considered as chronic steroid use at a dosage of more than 10 mg/d of prednisone or equivalent for at least 3 months before the onset of pneumonia, chemotherapy during the last 3 months or existence of hematological malignancies. The initial antibiotic therapy was defined as antibiotics administered within the first 48h after pneumonia onset, regardless of the pathogens[4]. If the antibiotics contained either vancomycin or linezolid, it was considered to have given empirical anti-MRSA therapy[10]. Targeted antibiotic therapy was defined as the antibiotics administered after microbiological sensitivity tests, and to which MRSA was sensitive in vitro[4].

2.3 Data Collection

Data was obtained by accessing electronic medical records, which included demographic data, antibiotic exposure in the 90 days before pneumonia, surgical exposure before BSI, pneumonia type, vital signs and biological parameters at onset, and severity of illness including Glasgow Coma Scale (GCS), oxygenation index, Acute Physiology and Chronic Health Evaluation (APACHE) II score in the first 24h following the onset of pneumonia, sequential organ failure assessment (SOFA) score. Anti-infection strategies and out comes were also recorded.

2.4 Species Identification And Antibiotic Sensitivity Testing

Respiratory samples were cultured with a carbon dioxide incubator (Thermo Fisher Scientific, USA) and blood samples were cultured in a BacT/ALERT 3D system (Becton-Dickinson, Sparks, MD, USA). Species identification relied on Bruker Daltonics Data Analysis. Using the Kirby-Bauer Disk Diffusion method (Oxoid, UK) as described by the Clinical and Laboratory Standards Institute (CLSI) to perform antibiotic susceptibility testing.

2.5 Statistics

Statistical analysis was performed using SPSS 24.0 (IBM Corp, Armonk, NY, USA). Two tailed test was used in all trials with $p<0.05$ considered statistically significant. If the continuous variables accorded with normally distributed, they were represented as mean ± standard deviation, otherwise by median and interquartile ranges (IQRs). The analysis of continuous variables was conducted with either Mann-Whitney U test or Student t test, and Pearson $\chi 2$ or Fisher exact test was used for the analysis of classified variables. Stepwise logistic regression was selected to confirm independent risk factors for secondary MRSA-BSI.

3. Results

3.1 Demographic data

During the eight-year study period, 435 patients with MP were finally recruited from the initial 1137 possible MP patients, and 82 (18.9%) of them developed secondary MRSA-BSI (MP-BSI) (Fig.1). The demographic data were listed in Table1. The median age was 62 (IQR,51,72) years, and 74.5% (324/435) of them were male. The most common comorbidity was cerebrovascular accident or traumatic brain

injury (39.1%), followed by diabetes (15.4%) and chronic heart failure (8.5%). 58.6% (255/435) of patients were exposed to antibiotics before the onset of pneumonia, and 51.7% (225/435) of them received surgery before MRSA-BSI. Nosocomial MP and community-acquired MP (CA-MP) accounted for 81.4% and 18.6%, respectively.

Compared with MP, 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), a higher SOFA score (median, 5 vs. 4, p=0.018), faster heart rate (HR) (median, 102 vs. 87, p<0.001), accelerated respiratory rate (RR) (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) (Table1).

3.2 Biological Parameters

A comparison of biological parameters between groups of MP and MP-BSI was illustrated in Table 2. Patients with MP-BSI were positively correlated with 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), but negatively correlated with albumin (mean, 30.01 vs. 32.00, p=0.006). Blood lactic acid was higher in MP-BSI than MP alone (median, 1.6 vs. 1.3, p=0.001).

3.3 Anti-infection Strategy

The anti-infection strategy was summarized in Table 3. All participants received initial antibiotic therapy and only a small proportion (10.3%) of them received empirical anti-MRSA therapy. The most administered targeted antibiotics in MP-BSI were glycopeptides (69.5%), followed by linezolid (22.0%) and other anti-MRSA antibiotics (8.5%), whereas they were linezolid (47.0%), glycopeptides (45.0%) and others (7.9%) in MP group (p<0.001). Compared with MP group, the MP-BSI group used a significantly lower proportion of linezolid than glycopeptides on targeted antibiotics (p<0.001). Additionally, patients with MP-BSI were delay in initiation of targeted antibiotics (median days, 4 vs. 3, p<0.001).

3.4 Independent Risk Factors For Secondary MRSA-BSI

High SOFA score (adjusted odds ratio[aOR], 1.192; 95% confidence interval [CI], 1.065–1.333; p=0.002), immunosuppression (aOR, 13.599; 95% 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 antibiotics (aOR, 1.304; 95% CI, 1.136–1.497; p<0.001), accelerated RR (aOR, 1.135; 95% CI, 1.066–1.209; p<0.001), elevated γ-GT (aOR, 1.004; 95% CI, 1.001–1.008; p=0.016) were independent risk factors for secondary MRSA-BSI, while linezolid as targeted antibiotic was a protective factor (aOR, 0.224; 95% CI, 0.115–0.438; p<0.001) (Table 4).

3.5 Outcomes

Compared with MP, patients with MP-BSI required a longer hospital LOS (median days, 35.5 vs. 25, p=0.015), but there were no significant differences in LOS of intensive care unit (ICU) (median days, 9.5 vs. 12, p=0.893) and days of mechanical ventilation (median, 8 vs. 7, p=0.252) (Table 5). The all-cause hospital mortality in the entire cohort was 17% (74/435), which was substantially higher in patients with MP-BSI than those with MP alone (26.8% vs. 14.7%, p=0.009). Similarly, the 28-day all-cause mortality was also substantially higher in MP-BSI than in MP alone (24.4% vs. 11.0%, p=0.001), which was consistent with the results shown by survival curve (Fig.2).

4. Discussion

In this study, we have gained some useful information. First, secondary MRSA-BSI is not uncommon among patients with MP, and the incidence is higher in patients with CA-MP than with nosocomial MP. Second, some risk factors associated with secondary MRSA-BSI were identified (Tables 1 to 3). Importantly, multivariate analysis revealed that high SOFA score, immunosuppression, CA-MP, time from initial to targeted antibiotics, accelerated RR and elevated γ-GT were independent risk factors for secondary MRSA-BSI; of note, targeted treatment with linezolid was a protective factor (Table 4). Finally, patients with MP-BSI have worse outcomes (Table 5).

In fact, the epidemiological information about the occurrence of MP-BSI among MP is limited in previous studies. Regardless of the pathogen, Magret and colleagues noted that about 15% of patients with nosocomial pneumonia presented with bacteremia[8]. In our current study, the proportion was 18.9%, which is higher than that in a previous retrospective study with 12.2% [5]. The relatively low occurrence of comorbid bacteremia in Shorr's study[5] might be partially related to the difference in the including criteria, in which the patients with concurrent episodes of pneumonia and bacteremia (only blood cultures drawn within 48h of the onset of pneumonia were reviewed) were recruited, leading to a missing 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 Staphylococcus aureus pneumonia requiring mechanical ventilation had combined bacteremia in Schreiber's study[9]. Combined with our and other previous studies, these results suggest that the occurrence of secondary BSI or comorbid BSI among patients with corresponding pneumonia including MP is relatively common, fluctuating at the percentage of 20%.

A number of risk factors for MP-BSI were identified in the present study. The SOFA score has been reported as a predictor of undesirable prognosis in pneumonia and BSI[13, 14]. Immunosuppression is considered as a predictor of infections caused by various pathogens like Staphylococcus aureus or MRSA[15, 16], and is associated with worse outcomes[13]. In our study, immunosuppression increased the risk of secondary MRSA-BSI in patients with MP by approximately 12-fold (aOR, 13.599; 95% CI, 4.063–45.521; p<0.001). Accelerated RR is usually an early clue to pneumonia[17], and also an important sign to predict the prognosis of pneumonia and sepsis[18, 19]. Although the literature about the role of γ-GT in pneumonia and BSI is extremely rare, which is only described in a few papers related to COVID-19[20, 21]. Abnormal levels of serum γ-GT are more common in patients with severe COVID-19[20] and may also be an indicator of intestinal dysfunction in COVID-19 patients[21], which might be attributed to

the pro-inflammatory and pro-oxidant effects of γ-GT[22]. Consistent with these previous studies, our results also showed that high SOFA score, immunosuppression, accelerated RR and elevated γ-GT were independent risk factors for secondary MRSA-BSI among patients with MP.

We also found that CA-MP and time from initial to targeted antibiotics were independent risk factors for secondary MRSA-BSI, whereas linezolid as targeted treatment was a protective factor. Although MRSA is a relatively rare cause of CAP, the incidence of bacteremia in patients with CA-MP is high and often occurs early in the course of pneumonia[23]. In the current study, the incidence of secondary MRSA-BSI in CA-MP patients is significantly higher than that of nosocomial MP patients (35.4% vs 14.7%, $p<0.001$). Our results are consistent with previous reports, indicating that empirical anti-MRSA therapy may not improve the prognosis of pneumonia[24, 25], but patients will benefit from early initiation of anti-MRSA treatment after MRSA is identified as the pathogen[26]. Pneumonia-related guidelines[10, 11, 27] also recommend that empirical coverage only for patients at risk for MRSA infection and that pathogen testing results should be obtained early. Of note, we found that linezolid as targeted antibiotic was beneficial in reducing the incidence of secondary MRSA-BSI in comparison with glycopeptides (aOR, 0.224; 95% CI, 0.115–0.438; $p<0.001$). Our result further confirmed the idea that linezolid might be superior to vancomycin in the treatment of MP[28-30]. Taken together, these results suggest that early detection of causal pathogens like community-acquired MRSA, rapid initiation of anti-MRSA treatment and targeted antibiotic treatment with linezolid would be critical to improve the progress of patients with MP and block the development of MRSA-BSI from MP alone.

The prognosis of patients with MP-BSI was relatively worse compared with MP alone, evidenced by longer hospital stays, higher 28-day mortality, and higher in-hospital mortality (Table 5). As we all know that when bacteria invade the bloodstream, the organism itself can cause a more intense inflammatory response, and this dysregulated inflammatory response will damage endothelial cells throughout the body and cause organ dysfunction; in addition, the fibrinogen-binding receptor of Staphylococcus aureus interacts with plasma fibrinogen to make it more adhesive than other microorganisms[8], and this adhesive property may exacerbate endothelial cell damage and further amplify inflammatory effect.

There are also several inadequacies in our study. First, this is a retrospective study and data were obtained by accessing the electronic medical record. Selection bias and some missing data are inevitable. But we recruited all patients who met the inclusion and exclusion criteria over the study period and data for each patient were extracted independently according to a pre-designed data extraction form to minimize selection bias; furthermore, as the variables in this study were all conventional parameters, the data were fully recorded for almost all patients, and for the very few missing values we interpolated. Second, this is a single-center data. However, our sample size was relatively large compared to several previous studies on bacteremic pneumonia that were also single-center studies[5-7, 9]. Finally, many independent factors are found in the current study, among of which are preventable or interventable like diagnosis of CA-MP, time from initial to targeted antibiotics and linezolid as targeted treatment. Whether it will be beneficial for improvement of progress in patients with MP via targeting these factors need further prospective multicenter investigation.

5. Conclusion

The occurrence of secondary MRSA-BSI is relatively high among patients with MP with an approximate proportion of one fifth. Many factors including high SOFA score, immunosuppression, CA-MP, time from initial to targeted antibiotics, accelerated RR and elevated γ-GT were independently related to secondary MRSA-BSI in patients with MP, while linezolid as targeted antibiotic is a protective factor. Once patients with MP develop secondary MRSA-BSI, their clinical outcomes become worse, which will be significant that how to inhibit or block the development of MRSA-BSI from MP alone in the future.

Abbreviations

MRSA: Methicillin-resistant Staphylococcus aureus; MP: Methicillin-resistant Staphylococcus aureus pneumonia; MRSA-BSI: Methicillin-resistant Staphylococcus aureus bloodstream infections; MP-BSI: Methicillin-resistant Staphylococcus aureus pneumonia with secondary Methicillin-resistant Staphylococcus aureus bloodstream infections; CA-MP: Community-acquired Methicillin-resistant Staphylococcus aureus pneumonia; BSI: Bloodstream infections; LOS: Length of stay; HAP: Hospital-acquired pneumonia; VAP: Ventilator-associated pneumonia; CAP: Community-acquired pneumonia; GCS: Glasgow Coma Scale; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment; CLSI: Clinical and Laboratory Standards Institute; IQRs: Interquartile ranges; HR: Heart rate; RR: Respiratory rate; ALT: Alanine aminotransferase; γ-GT: Gamma glutamyl transpeptidase; LDH: Lactic dehydrogenase; DBil: Direct bilirubin; aOR: Adjusted odds ratio; CI: Confidence interval; ICU: Intensive care unit.

Declarations

Ethics approval and consent to participate

This study was approved by the Human Ethics Board of the Ethics Committee of the Second Affiliated Hospital of Zhejiang University Medical College (NO.2021-0300). We ensured the confidentiality of patient data and complied with the Declaration of Helsinki. Given the retrospective nature of the study, the Ethics Committee decided to waive informed consent.

Consent for publication

Not applicable.

Availability of data and materials

We declare that the database is available from the first author (FF Huang, 616844390@qq.com) or corresponding author (GS Zhang, genshengzhang@zju.edu.cn) upon reasonable requirement.

Competing interests

The authors read the final manuscript and declared no conflicts of interest in the study.

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Authors' Contributions

GZ, SZ and WC designed the study, revised the manuscript and gave final approval of the work to be published. FH, TS and HX wrote the draft of the manuscript. FH, TS, HX, HQX, KZ, TH, JC, ZG, HZ, JC and ZC collected and analyzed the data.

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Tables

Table 1 Demographic data of patients with MP 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)	9(12,16)	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 scale, median (IQR)	13(8,15)	8(13,15)	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) (IQR)	86.0(70.7,103.0)	84.9(68.2,102.6)	89.7(80.3,104.4)	0.015

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.

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

Biological indicators	Total (n=435)	MP (n=353)	MP-BSI (n=82)	*P*-value
Blood routine test				
WBC (× 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 (×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 lactic acid (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.

Table3 Anti-infection strategy of MP-BSI compared with MP

	Total (n=435)	MP (n=353)	MP- BSI (n=82)	*P*-value
Empirical anti-MRSA therapy, n (%)	45(10.3%)	39(11.0%)	6(7.3%)	0.318
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 antibiotics, 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 ($p>0.0167$).

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 antibiotics	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 lactic acid (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.

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
Total hospital LOS, median days (IQR)	26(17,41)	25(17,38)	35.5(15.0,56.0)	0.015
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.

Figures

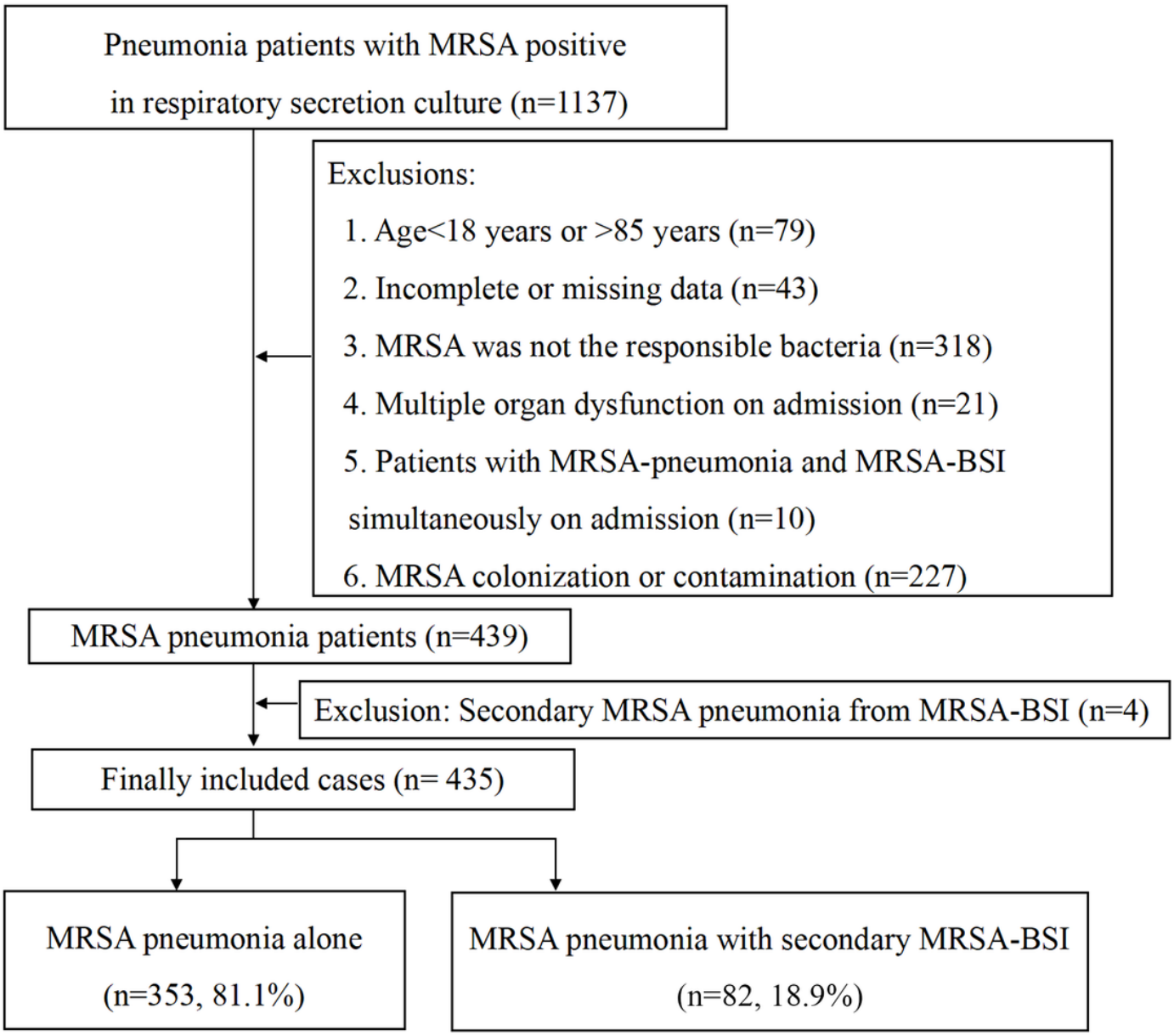

Figure 1

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

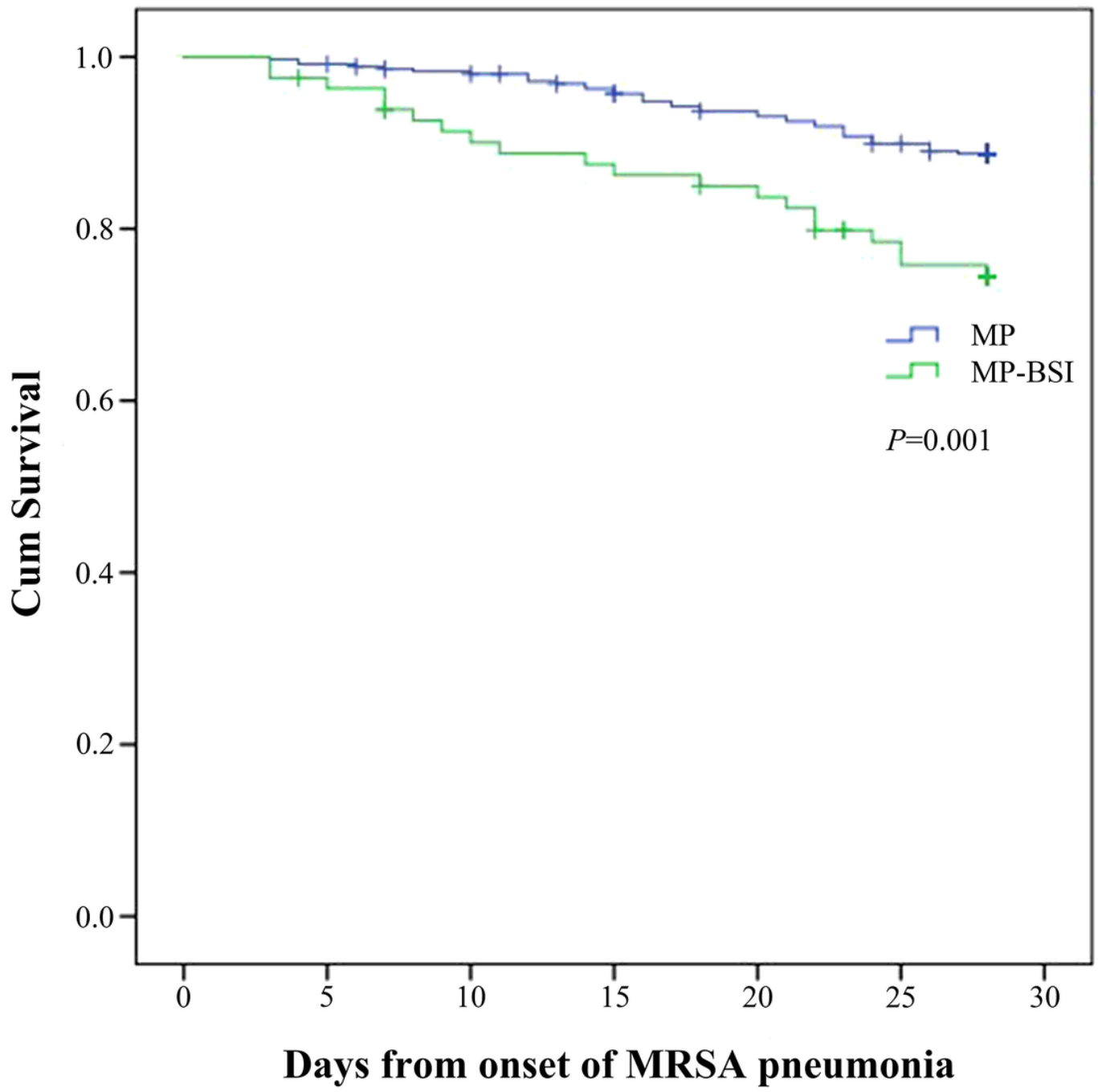

Figure 2

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