Submitted: 09 September, 2021 Accepted: 14 October, 2021 Published: 08 September, 2022 DOI:10.22514/sv.2022.003

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ORIGINAL RESEARCH

Risk factors of methicillin-resistant *Staphylococcus aureus* bacteremic pneumonia in the emergency department

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Abstract

The infection rate of methicillin-resistant *Staphylococcus aureus* (MRSA) has increased worldwide and MRSA bacteremic pneumonia is associated with a high mortality rate. This is a retrospective study conducted at a university hospital in Korea involving adult patients diagnosed as bacteremic pneumonia caused by *S. aureus* in the ED between January 2009 and December 2019. We compared MRSA bacteremic pneumonia patients (n = 56) to methicillin-susceptible *S. aureus* bacteremic pneumonia patients (n = 49). Our study showed that that underlying hypertension (OR = 5.68; 95% CI = 2.00–16.11; p = 0.001) and cerebrovascular disease (OR = 3.54; 95% CI = 1.06–11.75; p = 0.038), recent intravenous therapy within 1 month (OR = 8.38; 95% CI = 2.88–24.38; p = 0.0001), and pleural effusion on chest radiography (OR = 5.77; 95% CI = 1.79–18.57; p = 0.003) were independent risk factors for MRSA bacteremic pneumonia presenting to the ED. Although MRSA infection has been more frequently derived from the community than before, inappropriate empiric antibiotic treatment was overwhelmingly observed in the majority of patients in our study. Considering the resistance of MRSA to the typical empiric regimen prescribed for community-acquired pneumonia, emergency physicians should pay attention to the predictors for MRSA bacteremic pneumonia including pleural effusion on chest radiography when deciding on the appropriate empiric antimicrobial therapy for pneumonia patients in the ED.

Keywords

Methicillin-resistant *Staphylococcus aureus*; Bacteremia; Pneumonia; Risk factor; Emergency department

1. Introduction

Staphylococcus aureus is a common human pathogen that can trigger various infectious diseases, such as skin and soft tissue infections, osteomyelitis, endocarditis, bacteremia, and lethal pneumonia [1]. In recent decades, due to the bacterial evolution and the abuse of antibiotics, the drug resistance of *S. aureus* has gradually increased, leading to the increased infection rate of methicillin-resistant *S. aureus* (MRSA) worldwide [2]. MRSA has been historically thought to be confined to nosocomial processes [3]. However, the incidence of invasive community-acquired MRSA infections has been increasingly reported [4].

S. aureus bacteremic pneumonia is associated with a high mortality rate (30-day mortality, 46.9%) [5]. Rello *et al.* [6] reported that MRSA in pneumonia confers a higher risk of mortality and bacteremia compared to methicillin-susceptible *S. aureus* (MSSA). Similarly, a meta-analysis of 31 studies demonstrated that MRSA bacteremia was associated with a higher mortality than MSSA [7]. Paul *et al.* [8] also revealed that mortality was significantly higher among patients receiving inappropriate antibiotic treatment than among those receiving appropriate empirical antibiotic treatment.

Given the resistance of MRSA to the typical empiric regimen prescribed for community-acquired pneumonia (ceftriaxone plus a macrolide or a respiratory quinolone) in the emergency department (ED), identifying clinical risk factors that are associated with MRSA bacteremia would help emergency physicians in determining the appropriate empiric antimicrobial therapy. Our study aimed to evaluate the clinical risk factors for MRSA bacteremic pneumonia by retrospectively reviewing the characteristics of patients presenting to the ED with *S. aureus* bacteremic pneumonia over ten years.

2. Material and methods

2.1 Study design and population

This was a single-center retrospective study to compare the characteristics of adult patients diagnosed with bacteremic pneumonia caused by MSSA and MRSA in the ED. This study was conducted in a university hospital in an 895-bed

university hospital in Korea that caters to 60,000 patients annually, according to the annual census of ED visits.

We retrospectively reviewed the records of all patients aged $\geq$ 18 years who had positive blood cultures for *S. aureus* in the ED from January 2009 to December 2019. *S. aureus* bacteremic pneumonia was considered when the patient had clinical symptoms suggestive of lower respiratory tract infection and new pulmonary infiltrates on a chest X-ray in the ED, coinciding with the isolation of *S. aureus* in at least one positive blood culture with clinical significance without any other source of bacteremia. A specialist in infectious diseases analyzed the charts and excluded other sources of *S. aureus* infection, such as catheter-related bloodstream infection, arteriovenous fistula infection, skin and soft tissue infection, bone and joint infection, urinary tract infection, or infective endocarditis. On the other hand, an emergency physician double-checked with the enrolled cases. Polymicrobial bacteremia and clinically insignificant bacteremia (e.g., cases where MRSA grew in a single blood culture and were not treated) and cases without any evidence of pneumonia in the ED were excluded.

This study was approved by the institutional review board of the hospital (Inha University Hospital, IRB no. 2020-06-028-000), and the need for informed consent was waived.

2.2 Data collection and definitions

The following variables were collected from the medical charts of *S. aureus* bacteremic pneumonia patients: age, gender, origin of pneumonia, presence of medical device, comorbidities (including immunosuppression), previous hospitalization within 90 days, and prior antibiotics within 30 days. Vital signs, laboratory test results (including antimicrobial susceptibility of *S. aureus* isolates), nasal swab and sputum culture, and radiologic characteristics of enrolled patients were recorded upon arrival at the ED. To estimate the severity of illness, we also calculated the qSOFA (quick sepsis-related organ failure assessment), simplified Pitt bacteremia score; CURB-65, and pneumonia severity index (PSI).

We documented all antibiotic treatment administered from ED until the appropriate antibiotics were initiated. The appropriateness of empiric antimicrobial treatment in patients was established when the isolated pathogens were susceptible in vitro to one or more of the antimicrobial administered in the ED. Enrolled patients were followed up until discharge, and clinical outcome variables such as ICU admission, hospital days, transfer, or death were also documented.

The origin of pneumonia was considered to be hospital-acquired if (1) the patients were transferred from another hospital after >48 h of hospitalization; (2) the patients were discharged from a hospital within three days; (3) the patients underwent surgery within 30 days. Immunosuppression was categorized as acquired immune deficiency syndrome, use of long-term corticosteroids (>10 mg/d), or other immunosuppressive drugs (e.g., biologics for rheumatologic disorder).

2.3 Statistical analyses

Patients were divided into the MSSA and MRSA groups, and the characteristics of each group were compared. Data with a normal distribution were expressed as mean $\pm$ standard deviation and were analyzed using the independent samples *t* test. Data with a skewed distribution were expressed as medians and interquartile ratios and were analyzed using the Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher's exact test, depending on the sample size. Univariate analysis followed by multivariable logistic regression analysis was performed to identify the independent risk factors of MRSA bacteremic pneumonia in the ED. Variables with a *p* value of <0.10 in the univariate analysis were candidates for multivariate analysis using a backward elimination method. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using Medcalc for Windows (version 19.4, MedCalc Software, Ostend, Belgium).

3. Results

3.1 Study population

From January 2009 to December 2019, a total of 4821 patients with positive blood cultures were identified, and *S. aureus* growth was observed in 344 patients. Of the 344 patients, 239 were excluded due to having other sources of *S. aureus* bacteremia other than pneumonia, polymicrobial bacteremia, no evidence of pneumonia or clinically insignificant bacteremia. As such, the study population comprised a total of 105 patients diagnosed with *S. aureus* pneumonia in the ED. Among the cases of *S. aureus* bacteremic pneumonia, 56 (53%) were caused by MSSA, while 49 (46%) were caused by MRSA (Fig. 1). Specifically, 27 (55%) of the 49 patients with MRSA bacteremic pneumonia were community-acquired.

3.2 Comparison between MRSA and MSSA bacteremic pneumonia

The clinical characteristics of the study population are summarized in Table 1. Compared to the MSSA group, MRSA bacteremic pneumonia group was older and more likely to have a gastric tube or urinary catheter in place. The MRSA group also showed a statistically significant predominance for hospital-acquired infection, episodes of recent hospitalization within three months, and prior antibiotics use or intravenous therapy within one month. Regarding comorbid conditions, hypertension, chronic renal failure, and cerebrovascular disease were more prevalent in the MRSA group. No difference was found in the vital signs upon arrival at the ED.

The additional characteristics of patients with MSSA and MRSA bacteremic pneumonia are shown in Table 2. As for the laboratory results in the ED, only the serum creatinine levels were higher in the MRSA group than in the MSSA group. Notably, the chest X-ray finding of pleural effusion was more likely in patients with MRSA bacteremia. The calculated PSI was higher among patients with MRSA bacteremic pneumonia, but the other severity assessment models (qSOFA, simplified Pitt bacteremia score, and CURB-65) showed no differences between the groups. The nasal swab or sputum culture results were only available for a limited number of patients in both groups. Bacteriologic concordance with the nasal swab or sputum culture was observed in less than 50% of the cases.

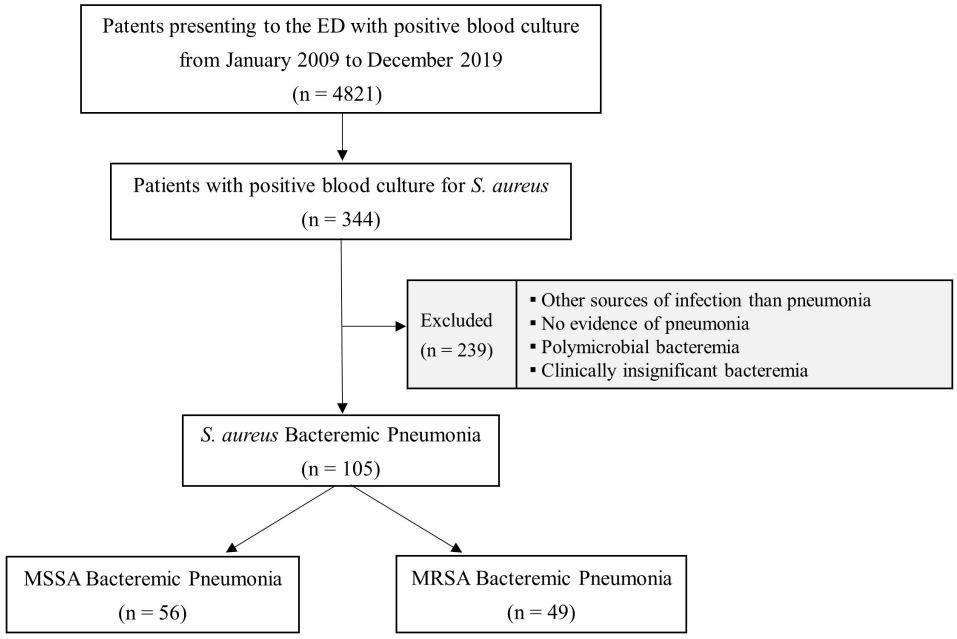

FIGURE 1. Algorithm of enrollment. ED, Emergency Department; MSSA, Methicillin-susceptible *Staphylococcus aureus*; MRSA, Methicillin-resistant *Staphylococcus aureus*.

3.3 Appropriateness of empiric antimicrobial treatment

The choice in empirical antibiotics was made by the emergency physician in charge of the patient. The appropriate antibiotics were prescribed in the ED in all patients with bacteremic pneumonia caused by MSSA, while only 6% (3 out of 49) of patients with MRSA bacteremia pneumonia received the appropriate antimicrobial therapy in the ED. During post-admission follow-up, appropriate antibiotics were initiated in the MRSA group 90.5 h (73–143) after their arrival to the ED.

3.4 Clinical outcomes

The clinical outcomes of patients with MSSA and MRSA bacteremic pneumonia are also shown in Table 2. Inotropics were initiated in the ED in 43% of the MSSA group and 41% of the MRSA group. In the MRSA group, the mortality rate was 35% on the second day and 55% on the 28th day compared to 30% and 62% in the MSSA group, respectively.

3.5 Risk factors for MRSA Bacteremic pneumonia

The results of the multivariate logistic regression analysis are presented in Table 3. Regression analysis showed that underlying hypertension (OR = 5.68; 95% CI = 2.00–16.11; $p = 0.001$) and cerebrovascular disease (OR = 3.54; 95% CI = 1.06–11.75; $p = 0.038$), recent intravenous therapy within one month (OR = 8.38; 95% CI = 2.88–24.38; $p = 0.0001$), and pleural effusion on chest X-ray (OR = 5.77; 95% CI = 1.79–18.57; $p = 0.003$) were the independent risk factors for MRSA bacteremic pneumonia presenting to ED.

4. Discussion

Reports on *S. aureus* bacteremic pneumonia are rare. There were published reports by Watanakunakorn *et al*. [9] in the 80s and Gonzalez *et al*. [10]] in the 90s. DeRyke *et al*. [11] described 60 nosocomial cases from 1999 to 2004, with an overall mortality rate of 55%. Most recently, Calle *et al*. [5] reviewed 98 patients in Spain from 2000 to 2014 and demonstrated that it is still a severe infection with a high mortality rate (47%). Furthermore, 28% of the MRSA bacteremic pneumonia cases were community-acquired, and previous antibiotics therapy within a month with beta-lactams or fluoroquinolones and cardiovascular disease were independent predictors of MRSA infection.

In comparison, our results showed considerable mortality of 32% on the second day and 60% on the 28th day of admission. Almost half (48.5%) of the MRSA bacteremic pneumonia cases were community-acquired, which has increased since the study by Calle *et al*. [5]. Notably, only 6% of the MRSA group in our study received appropriate empirical treatment in the ED compared to 38% in Spain. Considering the report that appropriate empirical antibiotic treatment provides a significant survival benefit in MRSA bacteremia [8], identifying the risk factors for MRSA infection is of paramount importance in the setting of ED, where empiric therapy is initiated. It is notable that it took 90.5 h after their arrival to the ED before patients with MRSA bacteremic pneumonia received the appropriate antibiotics.

Our study showed that underlying hypertension, underlying cerebrovascular disease, recent intravenous therapy within 1 month, and pleural effusion on chest X-ray were the independent risk factors for MRSA bacteremic pneumonia presenting to ED. The results were in line with a multicenter study in America that suggested a risk score for MRSA pneumonia [12]. Interestingly, concordance rates with nasal swabs or

TABLE 1. Clinical characteristics of patients presenting to the emergency department with bacteremic pneumonia caused by methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) from January 2009 to December 2019.

Characteristics	MSSA (n = 56)	MRSA (n = 49)	*p* value
Age, years	73 ± 12.2	82 (75–87)	0.004**
Male, no. (%)	31 (55)	35 (71)	0.107
Bed-ridden, no. (%)	21 (37)	23 (46)	0.330
Mental change, no. (%)	34 (60)	28 (57)	0.711
Medical device, no. (%)			
Nasogastric tube/Gastrostomy	3 (5)	13 (26)	0.005**
Tracheostomy	1 (1)	5 (10)	0.095
Urinary catheter/Cystostomy	5 (8)	15 (30)	0.005**
Intravenous line (central, peripheral)	3 (5)	8 (16)	0.108
Infection type, no. (%)			
Community-acquired	47 (83)	27 (55)	0.001**
Hospital-acquired	9 (16)	22 (44)	
Ventilator-associated	0	0	
Comorbid conditions, no. (%)			
Diabetes mellitus	18 (32)	24 (48)	0.080
Hypertension	22 (39)	34 (69)	0.002**
Cardiovascular disease	10 (17)	11 (22)	0.559
Respiratory disease	3 (5)	3 (6)	1.0
Chronic renal failure	7 (12)	18 (36)	0.003**
Liver disease	3(5)	5 (10)	0.468
Rheumatologic disease	3 (5)	2 (4)	1.0
Cerebrovascular disease	19 (33)	30 (61)	0.005**
Solid malignancy	23 (41)	16 (32)	0.375
Hematologic malignancy	2 (3)	2 (4)	1.0
Immunosuppressed	3 (5)	3 (6)	1.0
Past history, no. (%)			
Hospitalization within 3 months	20 (35)	33 (67)	0.001**
Antibiotics use within 1 month	9 (16)	21 (42)	0.002**
Chemotherapy within a month	5 (8)	1 (2)	0.211
Intravenous therapy within 1 month	17 (30)	32 (65)	0.0004***
Invasive procedure/surgery within 1 months	2 (3)	7 (14)	0.078
Vital signs on presentation			
SBP, mm Hg	107.7 ± 25.6	118 ± 35.0	0.487
DBP, mm Hg	66 ± 18.5	63.4 ± 19.3	0.489
PR, beats/min	109.5 ± 22.6	103.2 ± 21.4	0.145
RR, breaths/min	24 (18–30)	20 (18–26.5)	0.437
Body temperature, °C	36.6 (36.0–37.4)	36.6 (36.0–37.0)	0.697
Saturation, %	92 (85–97)	94.5 (90.0–97.0)	0.263

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$: *significant change from baseline values.*
SBP, Systolic blood pressure; DBP, Diastolic blood pressure; PR, Pulse rate; RR, Respiratory rate.

sputum cultures were less than 50% in both groups in our study.

Being one of the largest studies regarding MRSA bacteremic pneumonia, our results may help us understand the current situation of this serious infection. We also identified factors associated with MRSA bacteremic pneumonia that have not previously been linked in a study in Sprain that did not evaluate

TABLE 2. Comparison of the laboratory and radiologic findings and clinical outcomes of patients presenting to the emergency department with bacteremic pneumonia caused by methicillin-susceptible *S. aureus* (MRSA) and methicillin-resistant *S. aureus* (MSSA) from January 2009 to December 2019.

Characteristics	MSSA (n = 56)	MRSA (n = 49)	*p* value
Complete blood cell counts			
Leukocyte count, $\times 10^9$ cells/mL	13,835 (7505–17,000)	10,630 (7375–18,620)	0.709
Hemoglobin, g/dL	10.7 ± 3.0	10.3 (8.75–11.52)	0.467
Platelet, $\times 10^3/\mu$L	207 (98–347)	149 (91–301)	0.489
Other laboratory findings			
CRP, mg/dL	21.5 (8.7–30.7)	20.56 ± 12.29	0.898
Glucose, mg/dL	139.5 (111–190)	130 (91–225)	0.664
Creatinine, mg/dL	1.58 (0.98–2.38)	2.02 (1.13–4.05)	0.038*
Albumin, g/dL	2.78 ± 0.72	2.59 ± 0.67	0.166
Sodium, mEg/L	137 (130–141.5)	138.1 ± 10.1	0.401
Arterial blood gas analysis			
pH	7.43 (7.30–7.47)	7.40 (7.72–7.45)	0.303
Pco_2, mm Hg	31.2 ± 8.9	32.2 (26.5–37.0)	0.641
PO_2, mm Hg	64.3 (51.4–79.1)	71.9 ± 24.2	0.252
HCO_3^-, mmol/L	18.8 ± 7.1	18.3 ± 7.2	0.725
SaO_2, mm Hg	92.1 (85.8–95.9)	92.6 (87.9–96.0)	0.693
Lactic acid, mmol/L	2.95 (2.15–4.77)	3.86 (1.90–7.10)	0.579
Chest X-ray finding, no (%)			
Bilateral infiltration	34 (61)	34 (69)	0.355
Pleural effusion	8 (14)	19 (39)	0.004**
Concordance with nasal swab, no (%)	5 out of 14 (36%)	4 out of 9 (44%)	
with sputum culture	17 out of 34 (50%)	10 out of 29 (34%)	
Assessment models			
qSOFA	2 (1–3)	2 (1–3)	0.354
qPitt	2 (1–3)	2 (1–3)	0.344
CURB-65	3 (2–4)	3 (3–4)	0.691
PSI	157.9 ± 44.1	176.3 ± 45.8	0.038*
Appropriateness of empirical therapy, no (%)	56 (100)	3 (6)	<0.001***
Use of inotropics in the ED	24 (43)	20 (41)	
2-day mortality, no (%)	17 (30)	17 (35)	
28-day mortality, no (%)	35 (62)	27 (55)	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$: significant change from baseline values.*
CRP, C-reactive protein; qSOFA, quick sepsis-related organ failure assessment; qPitt, simplified Pitt bacteremia score; CURB-65, confusion, blood urea >19 mg/dL, respiratory rate ≥ 30/min, systolic blood pressure <90 mmHg or diastolic blood pressure ≤ 60 mmHg, age ≥ 65; PSI, pneumonia severity index.

cerebrovascular disease and recent intravenous therapy. Moreover, considering that positive cultures of the respiratory tract can represent colonization and not true infection, our research was distinct since we only included MRSA as a true pathogen in contrast to the multicenter study mentioned above.

There were several limitations to the present investigation. First, the sample size was small. In addition, the data were derived from a single center, limiting generalizability of our findings. Second, its retrospective nature exposed it to various forms of bias. Finally, it was possible that we did not identify all cases of *S. aureus* bacteremic pneumonia given the constraints of our definition and the possibility of the blood culture's false-negative results.

TABLE 3. Risk factors associated with bacteremic pneumonia cause by methicillin-resistant *Staphylococcus aureus* (MRSA) in the emergency department.

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.04 (1.01–1.08)	0.005**		
Infection type				
Community-acquired	4.25 (1.71–10.55)	0.001**		
Medical device				
Nasogastric tube/Gastrostomy	6.37 (1.69–23.99)	0.002**		
Urinary catheter/Cystostomy	4.50 (1.49–13.53)	0.004**		
Comorbid conditions				
Hypertension			5.68 (2.00–16.11)	0.001**
Chronic renal failure	4.06 (1.52–10.85)	0.003**		
Cerebrovascular disease			3.54 (1.06–11.75)	0.038*
Past history				
Hospitalization within 3 months	3.71 (1.65–8.34)	0.001**		
Antibiotics use within 1 month, no	3.91 (1.57–9.73)	0.002**		
Intravenous therapy within 1 month			8.38 (2.88–24.38)	0.0001***
Serum creatinine	1.31 (1.03–1.66)	0.012*		
Pleural effusion on chest X-ray			5.77 (1.79–18.57)	0.003**
Pneumonia severity index (PSI)	1.00 (1.00–1.01)	0.03*		

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$: *significant change from baseline values.*
CI, confidence interval; OR, odds ratio.

5. Conclusions

In conclusion, our study showed *S. aureus* bacteremic pneumonia is still a rare but severe infection. There were more cases of community-acquired MRSA infection than in the past, and inappropriate empiric antibiotic treatment was overwhelmingly observed in most patients in the ED. The risk factors for MRSA bacteremic pneumonia identified in our study (underlying hypertension, underlying cerebrovascular disease, recent intravenous therapy within 1 month, and pleural effusion on chest X-ray) should be considered by emergency physicians when deciding the appropriate empiric antimicrobial therapy for pneumonia patients in the ED.

AUTHOR CONTRIBUTIONS

HJ—critical writing. JHK, YS, and SBH—analysis and interpretation of data. AD—conception and design, critical writing, and final approval.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the institutional review board of the hospital (Inha University Hospital, IRB no. 2020-06-028-000), and the need for informed consent was waived.

ACKNOWLEDGMENT

Thanks to frontline medical staff in the COVID-19 era.

FUNDING

This work was supported by Inha University Research Grant (63738-01).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Haesuk Jung, Youngho Seo, Seung Baik Han, Ji Hye Kim, Areum Durey. Risk factors of methicillin-resistant Staphylococcus aureus bacteremic pneumonia in the emergency department. Signa Vitae. 2022; 18(5): 103-109. doi:10.22514/sv.2022.003.