**Title**

# Molecular epidemiology and clinical characteristics of *Staphylococcus aureus* bacteremia in Japanese adults

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**Authorship statement**

Kei Kasahara and Keiichi Mikasa designed the study, the main conceptual ideas, and the proof outline. Kohsuke Tsubaki and Tomoko Asada collected the data. Ryuichi Nakano and Akiyo Nakano aided in classifying SCC*mec*, multilocus sequence typing, and polymerase chain reaction-based open reading frame typing. Kohsuke Tsubaki analyzed the data, supervised by Kei Kasahara and Masahiko Kawaguchi. Hisakazu Yano supervised the project. Kohsuke Tsubaki wrote the manuscript with support from Kei Kasahara and Hisakazu Yano. All authors discussed the results and commented on the manuscript. All authors meet the ICMJE authorship criteria.

**Abstract**[1]

**Introduction:** *Staphylococcus aureus* bacteremia (SAB), especially when caused by methicillin-resistant *S. aureus* (MRSA), is of considerable clinical importance. In recent years, the proportion of MRSA among *S. aureus* has decreased, and a relative increase in the proportion of methicillin-susceptible *S. aureus* (MSSA) has been observed. It is therefore necessary to consider both MRSA and MSSA when assessing the microbiological and clinical significance of SAB.

**Materials and Methods:** We included SAB cases from the Nara Medical University Hospital between January 2015 and February 2017. We performed drug susceptibility testing, toxicity gene analysis, multilocus sequence typing (MLST), and polymerase chain reaction-based open reading frame typing (POT) of stored strains to integrate clinical and bacteriological characteristics.

**Results:** There were 90 cases during the experimental period (42 MRSA and 48 MSSA), with 30-day mortality rates of 19% for MRSA and 10.4% for MSSA. Deaths were more frequently complicated by septic shock and disseminated intravascular coagulation. MLST studies showed that ST8, ST764, ST1, and ST15 were prevalent in the MRSA group, whereas ST5, ST188, and ST12 were prevalent in MSSA. Infective endocarditis cases had a long time from onset to the initiation of effective antimicrobials and were all MSSA. MLST and POT results correlated well, and POT appeared to have better discriminatory power.

**Conclusions:** The severity and mortality of SAB, along with the microbiological characteristics of causative isolates, vary by location and time. Continued studies integrating clinical and microbiological investigations are thus needed.

**Keywords:** methicillin-resistant *Staphylococcus aureus*, methicillin-susceptible *Staphylococcus aureus*, *Staphylococcus aureus* bacteremia, sequence type, molecular epidemiology

## Introduction

*Staphylococcus aureus* is a major cause of bloodstream infections, contributing to substantial morbidity and mortality [1]. The precise incidence of *S. aureus* bacteremia (SAB) is difficult to ascertain and varies considerably depending on healthcare systems, infection control

[1] Abbreviations: CCI, Charlson comorbidity index; DIC, disseminated intravascular coagulation; IE, infective endocarditis; MLST, multilocus sequence typing; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; POT, polymerase chain reaction-based open reading frame typing; SAB, *Staphylococcus aureus* bacteremia; SOFA, sequential organ failure assessment; ST, sequence type.

measures, and geographical locations. However, it is estimated to range from 10 to 30 cases per 10,000 person-years [2]. SAB-associated mortality has decreased over time owing to the introduction of antimicrobials and other treatments. However, it has remained relatively stable in recent years, at approximately 20% [3,4].

Serious complications in patients with *S. aureus* infection include sepsis, septic shock, infective endocarditis (IE), disseminated intravascular coagulation (DIC), and death. A patient's age has been identified as a predictor of prognosis [4]. Similarly, methicillin-resistant *S. aureus* (MRSA) has been identified as a predictor of a worse prognosis. In a previous study, the 30-day mortality rates were 26% for MRSA and 13% for methicillin-susceptible *S. aureus* (MSSA) [5]. The ratio of MRSA to MSSA and its trends have fluctuated over time across different countries [2].

The molecular epidemiological classification of *S. aureus* strains employs several techniques, including pulse-field gel electrophoresis, multilocus sequence typing (MLST), *Staphylococcus* protein A typing, and polymerase chain reaction-based open reading frame typing (POT) [6]. However, there is a paucity of studies investigating the relationship between molecular epidemiology and patient characteristics, and this relationship remains unclear. Herein, we investigated the molecular epidemiology and clinical characteristics of SAB in Japanese adults.

## Materials and Methods

*Study settings and patients*

Nara Prefecture is located in the Kinki region, which is situated approximately in the center of Japan. The blood culture results were monitored between January 2015 and February 2017 at the Nara Medical University Hospital (927 beds). All patients aged 18 years with one or more *S. aureus* strains detected in blood cultures were included in the study.

*Clinical data collection*

Patient information was obtained from electronic medical records. Age, sex, time of onset, medical history, clinical and laboratory information on the current hospitalization, medical treatment provided, diagnosis of IE according to the modified Duke diagnostic criteria, highest Sequential Organ Failure Assessment（SOFA) score in the 24 h before and after treatment initiation, Pitt bacteremia score, and 30-day mortality were examined [7,8]. Patients younger than 18 years were excluded. Among the antimicrobial agent used in patients as treatment for SAB, the one used for the longest period of time was defined as the primary antimicrobial agent. Sepsis-3 diagnostic criteria were used to diagnose sepsis and septic shock caused by SAB from the time of onset to the end of antimicrobial therapy [8]. The development of DIC was evaluated from the onset of SAB until the completion of antimicrobial therapy using the Japanese Association for Acute Medicine-DIC diagnostic criteria[9]. Comorbidities were quantified using the Charlson Comorbidity Index (CCI) [10]. Community-acquired infections were defined as those occurring within 72 h of admission and nosocomial infections were defined as those occurring later. Recurrence was defined as bacteremia caused by the same organism after the completion of antimicrobial therapy.

*Biochemical and molecular assessment*

*S. aureus* isolated from blood cultures were identified using a VITEK-MS system (bioMérieux, Marcy-l'Étoile, France) and confirmed using PCR for the presence of 16S ribosomal RNA (*Staphylococcus* genus-specific) and *nuc* (*S. aureus* species-specific) genes, as previously described [11]. The presence of *luk-PV* (Panton-Valentine leucocidin, a toxin associated with increased virulence), *tst* (toxic shock syndrome toxin, linked to toxic shock syndrome), and *arcA* (a part of arginine catabolic mobile element, related to enhanced bacterial fitness) as virulence factors and *mecA* (conferring methicillin resistance) and *blaZ* (beta-lactamase gene, providing resistance to penicillin) as drug resistance factors was investigated. MRSA was confirmed by the presence of *mecA*.

The minimal inhibitory concentration of the collected isolates was evaluated using the broth dilution method according to Clinical and Laboratory Standards Institute guidelines [12].

Type classification was performed using POT and MLST. POT analysis was performed for all *S. aureus* isolates using a Cica Geneus® Staph POT KIT (Kanto Chemical Co. Tokyo, Japan) according to the manufacturer's instructions and previous studies [13]. MLST was performed using seven housekeeping genes (*arcC*, *aroE*, *glpF*, *gmk*, *pta*, *tpi*, and *yqiL*) [14]. DNA sequence variation was analyzed using the MLST database for *S. aureus* (https://pubmlst.org/organisms/staphylococcus-aureus) to determine the sequence type (ST) of the isolates. SCC*mec* typing was performed based on the primers and PCR methods reported by Zhang et al [15].

*Statistical analysis*

All numerical results are expressed as the mean ± SD. Unpaired t-tests and Fisher's exact probability tests were used to compare the MSSA and MRSA groups with the surviving and 30-day mortality groups, respectively.

*Ethical approval*

This study was approved by the Nara Medical University Ethics Committee (No. 3812).

## Results

Between January 2015 and February 2017, 90 unique cases of SAB were reported at the Nara Medical University Hospital. There were no significant differences between the MRSA (42 cases, 46.7%) and MSSA groups (48 cases, 53.3%) in mean age, sex, community onset, or CCI score (Table 1). The 30-day mortality rates were 19% and 10.4% in the MRSA and MSSA groups, respectively, with higher rates in the MRSA group; however, the difference was not significant. Overall, sepsis was present in 25.6%, septic shock in 10%, and DIC in 18.9% of patients, with no significant difference between the MRSA and MSSA groups. The time to initiation of effective antimicrobials tended to be longer in the MSSA group than in the MRSA group. IE was significantly more common in the MSSA group than in the MRSA group, with all IE cases occurring exclusively in patients with MSSA. Notably, six out of the seven patients with IE had community-acquired infections, and the average time between SAB onset and the initiation of effective antimicrobial therapy was 3.1 days.

The 30-day mortality group had a predominantly higher CCI score than the survival group (Table 2). The Pitt bacteremia score, SOFA score, and incidences of septic shock and septic shock with DIC were also higher in the mortality group than in the survival group. There were no significant differences in strain characteristics between the death and survival groups.

The MLST and POT results, various virulence factors, and the frequencies of 30-day mortality and sepsis for strains isolated in the MRSA and MSSA groups are shown in Table 3. Forty-two strains in the MRSA group were classified into seven different STs, with ST8, ST764, and ST1 being the most frequently observed. In the MSSA group, 48 isolates were classified into 20 STs, with ST15, ST5, ST188, and ST12 being frequently observed. There was no particular ST bias in the cases of death within 30 days, sepsis, or DIC complications; however, patients with four out of the five ST188 isolates exhibited sepsis. In addition, three of the five ST5 strains of MSSA and two of four ST188 strains elicited complications with IE.

## Discussion

According to the inpatient/clinical laboratory division of the Japan Nosocomial Infections Surveillance, the national infection surveillance institution in Japan, the proportion of MRSA among all *S. aureus* cases decreased from 60.0% in 2008 to 45.6% in 2022 [16]. In our study, MRSA accounted for 42 (46.7%) of all SAB cases (n=90), similar to the results of the national surveillance.

The 30-day mortality is often used as an indicator of the burden or severity of infection. The UK Health Security Agency's annual report showed that in the year 2021–2022, the 30-day mortality rate for MRSA bacteremia was 26.3% and that for MSSA bacteremia was 22.1% [16,17]. In a study on bacteremia utilizing the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), Tsuzuki et al. reported a 30-day mortality rate of 36.7% for MRSA and 15% for MSSA [18]. Our data (19.0% MRSA bacteremia and 10.4% MSSA bacteremia) were somewhat lower than these results. Recently, improved outcomes of SAB have been reported with the involvement of infectious disease physicians in the management of SAB. At our institution, infectious disease physicians are often involved with SAB cases, which may lead to improved prognoses [18,19]. Studies have shown that the risk of IE associated with SAB is higher in community onset or MSSA and that a longer time between onset and diagnosis or effective treatment is considered a risk factor [19,20], which was also the case in our study. Although not statistically significant, there were cases of community-acquired infections in the MSSA group. This may contribute to delays in initiating effective intravenous antimicrobial therapy, stemming from both patient delay (patients may choose to wait at home rather than promptly seeking medical attention) and physician delay (doctors may not promptly obtain blood cultures, leading to delayed diagnosis of bacteremia). Consequently, such delays may ultimately lead to the development of metastatic foci infections, such as IE or vertebral osteomyelitis [21]. CCI and Pitt bacteremia scores have been reported as risk factors associated with mortality in SAB [4,22]. In our study, the CCI and Pitt bacteremia scores were significantly higher in the death group than in the survival group.

Bacteremia is one of the most severe infectious diseases. Hence, it is necessary to diagnose shock and DIC, particularly at an early stage, and to implement multidisciplinary treatment led by an intensive care team [8,23,24]. There are few reports on the incidence of shock and septic shock in SAB, and, in particular, we could not find any studies on the incidence of DIC complicating SAB using firm diagnostic criteria in the literature review. These should be assessed not only at the time of onset, but also over time; however, most studies assessed the incident of sepsis only when SAB was diagnosed or did not specify the time of sepsis diagnosis. In an observational study of SAB in Norway, Paulsen et al. found that 29.8% of patients with SAB developed severe sepsis and 12.9% developed septic shock, with 30-day mortality rates of 39.9% and 57.3%, respectively [25]. The assessment of sepsis-induced DIC over time and appropriate intervention may improve prognosis [26-28]. In our study, the 30-day mortality rate was higher in patients with septic shock and septic shock complicated by DIC than in patients without septic shock, suggesting the importance of assessing the presence or absence of sepsis and DIC complications in patients with SAB. We could not examine the presence or absence of treatment for sepsis or DIC and its efficacy in the present study. Thus, future studies should investigate these aspects as well as the risk factors for septic shock and DIC complications.

Regarding MRSA typing, in their review of 2,413 MRSA strains collected from inpatients at four acute-care hospitals in Kyoto and Shiga, Japan between 2014 and 2019, Matsumura et al. reported that ST8 and ST1 were common as community-acquired MRSA (CA-MRSA), in addition to ST764 and ST12 as healthcare-associated MRSA (HA-MRSA) [29]. Although the specimens examined in their study were not limited to blood cultures, a similar frequency of isolation of MRSA ST types was noted; however, ST12 was not isolated in our study. Yamaguchi et al. also examined 1,770 MRSA strains from skin and pus, reporting an increase in Panton-Valentine leucocidin- and toxic shock syndrome toxin-1-producing ST22 [30]. However, ST22 was not detected in our study. Although the limited number of strains examined herein precludes definitive conclusions, it is plausible that the probability of causing bacteremia may vary depending on the MRSA ST type.

To the best of our knowledge, there are no studies on MSSA bacteremia that integrated both microbiological and clinical aspects, as well as genomic investigations of MSSA in Japan. Obata et al. performed a molecular epidemiological study of *S. aureus* isolated from Japanese patients with atopic dermatitis and noted that ST188 and ST12 may correlate with the severity of atopic dermatitis [31]. Hirose et al. also conducted a molecular epidemiological study of *S. aureus* on hospital staff and dental patients, reporting that ST15, ST8, ST12, ST97, and ST188 were commonly isolated from oral cavity and hands [32]. Moreover, Jian et al. reported an increase in the frequency of ST5 with various virulence factors, including a higher ability to adhere epithelial cells [33]. In MRSA, ST764 is known as a single-locus variant of ST5, but is genetically distant from ST5 in MSSA. Given that the proportion of MRSA is decreasing proportionally while that of MSSA is increasing, continuous molecular epidemiological studies on MSSA isolated from blood cultures in Japan are necessary [16].

POT is a molecular epidemiological method for classifying MRSA that was developed mainly in Japan. It has been widely used in Japan owing to its simplicity of operation, leading to the accumulation of considerable data [34]. In our study, the majority of strains exhibited identical MLST results when the POT was identical, indicating a high correlation between the two typing methods. Furthermore, even when the MLST was identical, the POT was often different, suggesting that POT has a higher discriminatory ability in classifying *S. aureus* than MLST. However, there are few studies using the POT for MSSA detection, which represents a limitation of the current study that should be addressed in future research [35].

In patients who died within 30 days, the most prevalent STs were ST1, ST8, and ST764 in the MRSA group, whereas those in the MSSA group included ST45, ST97, ST15, and ST121. Given the limited number of deaths observed in our study, no significant association was identified between mortality and specific ST. Four of the five cases of MSSA bacteremia developed sepsis and DIC due to ST188. Obata et al. reported that ST188 is correlated with the severity of atopic dermatitis, but it has not been reported that ST188 causes more severe conditions of SAB [31]. Wang et al. reported an increase in ST188 in MSSA among *S. aureus* isolates collected in Shanghai, China, from 2012 to 2014; it had strong epithelial adhesion and biofilm-forming capacity in both animals and humans [36]. ST188 and ST5 have also been isolated from patients with IE in our study. Therefore, it is important to conduct further comprehensive studies focusing on both clinical and microbiological features.

The current study had several limitations. This was a single-center, retrospective study, and the number of patients and strains was limited. Moreover, the possibility of contamination cannot be ruled out as a problem during sample collection. Additionally, if a patient with SAB spontaneously recovers or dies without a blood culture, SAB cannot be diagnosed, and the isolate cannot be obtained.

## Conclusions

In conclusion, a clinical and microbiological investigation of SAB was conducted at our institution to determine clinical parameters, including severity and mortality, as well as the genetic characteristics of the isolates. MRSA was classified in a relatively limited number of STs, while MSSA was classified in more STs. Despite the limited number of cases, there may be a relationship between certain STs and the clinical presentation of SAB. We also revealed associations between MLST and POT. The epidemiology of SAB exhibits considerable variability across different geographical locations and time periods. It is therefore recommended that such studies also be performed in the future.

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**Declarations of Interest:**

None

**Table 1**

Univariate analysis of clinical characteristics associated with MRSA and MSSA in patients with bacteremia

| | Total | MRSA | MSSA | *P*-value |
|---|---|---|---|---|
| Number of cases | 90 | 42 (46.7%) | 48 (53.3%) | |
| Age, mean, y | 65.8±17.7 | 67.7±14.9 | 64.2±19.8 | 0.36 |
| Sex: male | 58 (64.4%) | 30 (71.4%) | 28 (58.3%) | 0.27 |
| BMI | 22.0±4.9 | 21.7±4.3 | 22.3±5.4 | 0.60 |
| Community-acquired | 35 (38.9%) | 14 (33.3%) | 21 (43.8%) | 0.39 |
| CCI score | 6.5±3.3 | 6.6±2.9 | 6.4±3.6 | 0.75 |
| Comorbid conditions | | | | |
| Malignancy | 22 (24.4%) | 10 (23.8%) | 12 (25.0%) | 1 |
| CKD stages 3–5 | 37 (41.1%) | 18 (42.9%) | 19 (39.6%) | 0.83 |
| Renal replacement therapy | 21 (23.3%) | 10 (23.8%) | 11 (22.9%) | 1 |
| Hemodialysis | 18 (20%) | 10 (23.8%) | 8 (16.7%) | 0.44 |
| Cardiovascular disease | 51 (56.7%) | 27 (64.3%) | 24 (50.0%) | 0.20 |
| Peripheral vascular disease | 9 (10.0%) | 4 (9.5%) | 5 (10.4%) | 1 |
| Cerebral vascular disease | 21 (23.3%) | 11 (26.2%) | 10 (20.1%) | 0.62 |
| Paraplegia or hemiplegia | 3 (3.3%) | 1 (2.4%) | 3 (3.3%) | 1 |
| Dementia | 18 (20.0%) | 11 (26.2%) | 7 (14.6%) | 0.20 |
| Liver cirrhosis | 4 (4.4%) | 1 (2.4%) | 3 (6.3%) | 0.62 |
| Connective tissue disease | 11 (12.2%) | 7 (16.7%) | 4 (8.3%) | 0.34 |
| Diabetes mellitus | 25 (27.8%) | 10 (23.8%) | 15 (31.3%) | 0.49 |
| Insulin-dependent diabetes mellitus | 6 (6.7%) | 4 (9.5%) | 2 (4.2%) | 0.41 |
| Chronic pulmonary disease | 7 (7.8%) | 5 (11.9%) | 2 (4.2%) | 0.24 |
| Leukemia | 2 (2.2%) | 0 (0%) | 2 (4.2%) | 0.50 |
| Lymphoma | 5 (5.6%) | 4 (9.5%) | 1 (2.1%) | 0.18 |

| | | | | |
|---|---|---|---|---|
| Peptic ulcer | 1 (1.1%) | 1 (2.4%) | 0 (0%) | 0.47 |
| Corticosteroid use | 14 (15.6%) | 5 (11.9%) | 9 (18.8%) | 0.40 |
| Immunosuppressants | 3 (3.3%) | 1 (2.4%) | 2 (4.2%) | 1 |
| Chemotherapy within 90 days | 8 (8.9%) | 5 (11.9%) | 2 (4.2%) | 0.47 |
| Febrile neutropenia | 2 (2.2%) | 1 (2.4%) | 1 (2.1%) | 1 |
| Solid organ transplantation | 3 (3.3.%) | 2 (4.8%) | 1 (2.1%) | 0.60 |
| General anesthesia within 30 days | 6 (6.7%) | 3 (7.1%) | 3 (6.3%) | 1 |
| Foreign body | | | | |
| Prosthetic joint | 4 (4.4%) | 2 (4.8%) | 2 (4.2%) | 1 |
| Prosthetic valve | 2 (2.2%) | 0 (0%) | 2 (4.2%) | 0.50 |
| Prosthetic vascular graft | 2 (2.2%) | 1 (2.4%) | 1 (2.1%) | 1 |
| Artificial cardiac pacemaker | 2 (2.2%) | 0 (0%) | 2 (4.2%) | 0.50 |
| Central venous catheter present | 27 (30.0%) | 15 (35.7%) | 12 (25.0%) | 0.36 |
| Central venous catheter removed | 23 (85.2%) | 14 (93.3%) | 9 (75.0%) | 0.29 |
| Primary site of infection | | | | |
| Unknown | 28 (31.1%) | 12 (28.6%) | 16 (33.3% | 0.66 |
| Catheter-associated | 15 (16.7%) | 9 (21.4%) | 6 (12.5%) | 0.27 |
| Pneumonia | 9 (10.0%) | 5 (11.9%) | 4 (8.3%) | 0.73 |
| Skin and soft tissue | 30 (30.3%) | 12 (28.6%) | 12 (25.0%) | 0.81 |
| Bone and joint | 1 (1.1%) | 0 (0%) | 1 (2.1%) | 1 |
| Urinary tract | 7 (7.8%) | 3 (7.1%) | 4 (8.3%) | 1 |
| Intra-abdominal | 3 (3.3%) | 1 (2.4%) | 2 (4.2%) | 1 |
| Procedure performed for source control | | | | |
| Incision and drainage | 8 (8.9%) | 4 (9.5%) | 4 (8.3%) | 1 |
| Intensive care unit admission before infection | 3 (3.3%) | 1 (2.4%) | 2 (4.2%) | 1 |
| Transit to intensive care unit after infection | 10 (11.1%) | 4 (9.5%) | 6 (12.5%) | 0.75 |
| Pitt bacteremia score | 2.0±2.2 | 2.3±2.2 | 1.8±2.2 | 0.30 |
| Complicated SAB | 30 (30.3%) | 15 (35.7%) | 15 (31.3%) | 0.66 |
| Infective endocarditis | 7 (7.8%) | 0 (0%) | 7 (14.6%) | <0.05 |
| Metastatic infection | 11 (12.2%) | 4 (9.5%) | 7 (14.6%) | 0.53 |
| SOFA score | 5.02±3.07 | 5.14±3.08 | 4.92±3.05 | 0.80 |
| Sepsis | 23 (25.6%) | 11 (26.2%) | 12 (25.0%) | 1 |
| Septic shock | 9 (10.0%) | 6 (14.3%) | 3 (6.3%) | 0.29 |
| DIC | 17 (18.9%) | 8 (19.0%) | 9 (18.8%) | 1 |
| Sepsis with DIC | 17 (18.9%) | 8 (19.0%) | 9 (18.8%) | 1 |
| Septic shock with DIC | 6 (6.7%) | 4 (9.5%) | 2 (4.2%) | 0.41 |
| 30-day mortality | 13 (14.4%) | 8 (19.0%) | 5 (10.4%) | 0.37 |
| Recurrence | 4 (4.4%) | 2 (4.8%) | 2 (4.2%) | 1 |
| Time to start effective antimicrobial therapy | | | | |
| Prior to SAB onset | 3 (3.3%) | 3 (7.1%) | 0 (0%) | 0.10 |
| On the day of SAB onset | 43 (47.8%) | 24 (57.1%) | 19 (39.6%) | 0.14 |
| 1-day delay from onset of SAB | 18 (20.0%) | 8 (19.0%) | 10 (20.8%) | 1 |
| 2-day delay from onset of SAB | 5 (5.6%) | 1 (2.4%) | 4 (8.3%) | 0.37 |
| 3 or more days of delay from the onset of SAB | 20 (22.2%) | 6 (14.3%) | 14 (29.2%) | 0.13 |
| Mainly used antimicrobials | | | | |
| Vancomycin | 28 (31.1%) | 23 (54.8%) | 5 (10.4%) | |
| Linezolid | 6 (6.7%) | 6 (14.3%) | 0 (0%) | |
| Daptomycin | 8 (8.9%) | 6 (14.3%) | 2 (4.2%) | |
| Teicoplanin | 3 (3.3%) | 3 (7.1%) | 0 (0%) | |
| Cefazolin | 22 (24.4%) | 0 (0%) | 22 (24.4%) | |
| Ceftriaxone | 8 (8.9%) | 2 (4.8%) | 6 (12.5%) | |
| Sulbactam / ampicillin | 4 (4.4%) | 0 (0%) | 4 (8.3%) | |
| Tazobactam / piperacillin | 4 (4.4%) | 1 (2.4%) | 3 (6.3%) | |
| Meropenem | 2 (2.2%) | 0 (0%) | 2 (4.2%) | |
| Levofloxacin | 1 (1%) | 0 (0%) | 1 (2.1%) | |
| Other | 4 (4.4%) | 1 (2.4%) | 3 (6.3%) | |

| | | | | |
|---|---|---|---|---|
| concomitant use with rifampicin | 3 (3.3%) | 1 (2.4%) | 2 (4.2%) | 1 |
| concomitant use with minocycline | 2 (2.2%) | 1 (2.4%) | 1 (2.1%) | 1 |
| concomitant use with clindamycin | 3 (3.3%) | 1 (2.4%) | 2 (4.2%) | 1 |
| Virulence genes | | | | |
| *luk-PV* | 2 (2.2%) | 2 (4.8%) | 0 (0%) | 0.22 |
| *tst* | 10 (11.1%) | 7 (16.7%) | 3 (6.3%) | 0.18 |
| *arcA* | 3 (3.3%) | 3 (7.1%) | 0 (0%) | 0.10 |

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; BMI, body mass index; CCI, Charlson comorbidity index; CKD, chronic kidney disease; SAB, *Staphylococcus aureus* bacteremia; SOFA, sequential organ failure assessment; DIC, disseminated intravascular coagulation.

**Table 2**

Univariate analysis of risk factors for 30-day mortality after onset of SAB.

| | Survived | Died | *P*-value |
|---|---|---|---|
| Number of cases | 77 (85.6%) | 13 (14.4%) | |
| Age, mean, y | 69.7±16.7 | 65.2±17.8 | 0.40 |
| Sex: male | 50 (64.9%) | 8 (61.5%) | 1 |
| BMI | 21.9±4.89 | 22.6±5.13 | 0.65 |
| Community-acquired | 33 (42.9%) | 2 (15.3%) | 0.065 |
| CCI score | 6.22±3.29 | 8.46±2.79 | <0.05 |
| Comorbid conditions | | | |
| Malignancy | 19 (24.7%) | 3 (23.1%) | 1 |
| CKD stage3-5 | 30 (39.0%) | 7 (53.8%) | 0.37 |
| Renal replacement therapy | 18 (23.4%) | 3 (23.1%) | 1 |
| Hemodialysis | 15 (19.5%) | 3 (23.1%) | 0.72 |
| Cardiovascular disease | 44 (57.1%) | 7 (53.8%) | 1 |
| Peripheral vascular disease | 9 (11.7%) | 0 (0%) | 0.35 |
| Cerebral vascular disease | 18 (23.4%) | 3 (23.1%) | 1 |
| Paraplegia or hemiplegia | 2 (2.6%) | 1 (7.7%) | 0.38 |
| Dementia | 15 (19.5%) | 3 (23.1%) | 0.72 |
| Liver cirrhosis | 2 (2.6%) | 2 (15.4%) | 0.10 |
| Connective tissue disease | 10 (13.0%) | 1 (7.7%) | 1 |
| Diabetes mellitus | 22 (28.6%) | 3 (23.1%) | 1 |
| Insulin-dependent diabetes mellitus | 6 (7.8%) | 0 (0%) | 0.59 |
| Chronic pulmonary disease | 6 (7.8%) | 1 (7.7%) | 1 |
| Leukemia | 2 (2.6%) | 0 (0%) | 1 |
| Lymphoma | 2 (2.6%) | 3 (23.1%) | <0.05 |
| Peptic ulcer | 0 (0%) | 1 (7.7%) | 0.14 |
| Corticosteroid use | 11 (14.3%) | 3 (23.1%) | 0.42 |
| Immunosuppressants | 3 (3.9%) | 0 (0%) | 1 |
| Chemotherapy within 90 days | 4 (5.2%) | 4 (30.8%) | <0.05 |
| Febrile neutropenia | 1 (1.3%) | 1 (7.7%) | 0.27 |
| Solid organ transplantation | 3 (3.9%) | 0 (0%) | 1 |
| General anesthesia within 30 days | 5 (6.5%) | 1 (7.7%) | 1 |
| Foreign body | | | |
| Prosthetic joint | 4 (5.2%) | 0 (0%) | 1 |
| Prosthetic valve | 2 (2.6%) | 0 (0%) | 1 |
| Prosthetic vascular graft | 2 (2.6%) | 0 (0%) | 1 |
| Artificial cardiac pacemaker | 3 (3.9%) | 0 (0%) | 1 |
| Central venous catheter present | 23 (29.9%) | 4 (30.8%) | 1 |
| Central venous catheter removed | 20 (87.0%) | 3 (75.0%) | 0.50 |
| Primary site of infection | | | |
| Unknown | 22 (28.6%) | 6 (46.2%) | 0.21 |
| Catheter-associated | 14 (18.2%) | 1 (7.7%) | 0.69 |
| Pneumonia | 5 (6.5%) | 3 (23.1%) | 0.09 |
| Skin and soft tissue | 22 (28.6%) | 2 (15.4%) | 0.50 |
| Bone and joint | 1 (1.3%) | 0 (0%) | 1 |
| Urinary tract | 7 (9.1%) | 0 (0%) | 0.59 |
| Intra-abdominal | 3 (3.9%) | 0 (0%) | 1 |
| Procedure performed for source control | | | |
| Incision and drainage | 8 (10.4%) | 0 (0%) | 0.60 |
| Intensive care unit admission before infection | 3 (3.9%) | 0 (0%) | 1 |
| Transit to intensive care unit after infection | 8 (10.4%) | 2 (15.4%) | 0.63 |
| Pitt bacteremia score | 1.79±1.95 | 3.38±3.10 | <0.05 |
| Complicated SAB | 27 (35.1%) | 3 (23.1%) | 0.53 |
| Infective endocarditis | 7 (9.1%) | 0 (0%) | 0.59 |

| | | | |
|---|---|---|---|
| Metastatic infection | 11 (14.3%) | 0 (0%) | 0.35 |
| SOFA score | 4.52±2.78 | 8.00±2.79 | <0.01 |
| Sepsis | 17 (22.1%) | 6 (46.2%) | 0.09 |
| Septic shock | 4 (5.2%) | 5 (38.5%) | <0.01 |
| DIC | 14 (18.2%) | 3 (23.1%) | 0.71 |
| Sepsis with DIC | 14 (18.2%) | 3 (23.1%) | 0.71 |
| Septic shock with DIC | 3 (3.9%) | 3 (23.1%) | <0.05 |
| Recurrence | 4 (5.2%) | 0 (0%) | 1 |
| Time to start effective antimicrobial therapy | | | |
| Prior to SAB onset | 2 (2.6%) | 1 (7.7%) | 0.38 |
| On the day of SAB onset | 37 (48.1%) | 6 (46.2%) | 1 |
| 1-day delay from onset of SAB | 15 (19.5%) | 3 (23.1%) | 0.72 |
| 2-day delay from onset of SAB | 6 (7.8%) | 0 (0%) | 1 |
| 3 or more days of delay from the onset of SAB | 18 (23.4%) | 3 (23.1%) | 1 |
| Appropriate empiric therapy | 14 (18.2%) | 3 (23.1%) | 0.71 |
| mainly used antimicrobials | | | |
| Vancomycin | 20 (26.0%) | 8 (61.5%) | 0.02 |
| Linezolid | 6 (7.8%) | 0 (0%) | 0.59 |
| Daptomycin | 8 (10.4%) | 0 (0%) | 0.60 |
| Teicoplanin | 2 (2.6%) | 1 (7.7%) | 0.38 |
| Cefazolin | 20 (26.0%) | 2 (15.4%) | 0.51 |
| Ceftriaxone | 8 (10.4%) | 0 (0%) | 0.60 |
| Sulbactam/ampicillin | 4 (5.2%) | 0 (0%) | 1 |
| Tazobactam/piperacillin | 4 (5.2%) | 1 (7.7%) | 0.55 |
| Meropenem | 2 (2.6%) | 0 (0%) | 1 |
| Levofloxacin | 1 (1.3%) | 0 (0%) | 1 |
| Other | 3 (3.9%) | 1 (7.7%) | 0.47 |
| concomitant use with rifampicin | 3 (3.9%) | 0 (0%) | 1 |
| concomitant use with minocycline | 2 (2.6%) | 0 (0%) | 1 |
| concomitant use with clindamycin | 3 (3.9%) | 0 (0%) | 1 |
| Virulence genes | | | |
| *luk-PV*[a] | 2 (2.6%) | 0 (0%) | 1 |
| *tst*[b] | 7 (9.1%) | 3 (23.1%) | 0.15 |
| *arcA*[c] | 2 (2.6%) | 1 (7.7%) | 0.38 |
| Antimicrobial resistance genes | | | |
| *blaZ* | 55 (61.1%) | 10 (84.6%) | 1 |
| MRSA | 34 (44.2%) | 8 (61.5%) | 0.37 |
| SCC*mec* I | 0 (0%) | 0 (0%) | |
| SCC*mec* II | 14 (18.2%) | 4 (30.8%) | 0.28 |
| SCC*mec* III | 1 (1.3%) | 0 (0%) | 1 |
| SCC*mec* IV | 18 (23.4%) | 4 (30.8%) | 0.73 |
| SCC*mec* V | 1 (1.3%) | 0 (0%) | 1 |
| ST764 | 9 (11.7%) | 3 (23.1%) | 0.37 |
| ST45 | 1 (1.3%) | 2 (15.4%) | 0.05 |
| ST8 | 8 (10.4%) | 2 (15.4%) | 0.63 |
| ST1 | 7 (9.1%) | 2 (15.4%) | 0.61 |
| ST5 | 8 (10.4%) | 1 (7.7%) | 1 |
| ST15 | 6 (7.8%) | 1 (7.7%) | 1 |
| ST97 | 0 (0%) | 1 (7.7%) | 0.14 |
| ST121 | 2 (2.6%) | 1 (7.7%) | 0.38 |
| Others | 36 (46.8%) | 0 (0%) | <0.01 |

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; CKD, chronic kidney disease; SAB, *Staphylococcus aureus* bacteremia; SOFA, sequential organ failure assessment; DIC, disseminated intravascular coagulation, MRSA, methicillin-resistant *Staphylococcus aureus.*

**Table 3**

Drug resistance genes, virulence genes, and clinical characteristics categorized by methicillin susceptibility, MLST, and POT

| | MLST | n | POT | n | SCC*mec* | *blaZ* | Virulence genes | | | 30-day mortality | sepsis | septic shock | DIC | IE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *luk-PV* | *arcA* | *tst* | | | | | |
| MRSA | 8 | 15 | 106-137-80 | 6 | IV | 6 | - | - | - | 1 | 2 | 1 | 2 | |
| | | | 106-9-80 | 2 | IV | 2 | - | - | 2 | | 1 | | | |
| | | | 93-80-9 | 1 | II | 1 | - | - | - | | | | | |
| | | | 106-41-62 | 1 | IV | 1 | - | - | 1 | | 1 | | 1 | |
| | | | 106-121-98 | 1 | IV | 1 | - | - | 1 | 1 | 1 | 1 | | |
| | | | 106-125-113 | 1 | IV | 1 | 1 | - | - | | | | | |
| | | | 106-137-2 | 1 | IV | 1 | - | - | - | | | | | |
| | | | 106-155-120 | 1 | IV | 1 | - | - | - | | | | | |
| | | | 122-137-2 | 1 | IV | 1 | - | - | - | | | | | |
| | 764 | 12 | 93-191-103 | 3 | II | 3 | - | 1 | - | | | | | |
| | | | 93-181-45 | 2 | II | 1 | - | - | - | | 1 | | 1 | |
| | | | 93-153-127 | 2 | II | 2 | - | 1 | - | 1 | | | | |
| | | | 93-153-125 | 1 | II | - | - | - | - | | | | | |
| | | | 93-183-101 | 1 | II | 1 | - | - | - | | | | | |
| | | | 93-187-56 | 1 | II | 1 | - | - | - | 1 | | | | |
| | | | 93-189-125 | 1 | II | 1 | - | - | - | 1 | 1 | 1 | 1 | |
| | | | 93-190-98 | 1 | II | 1 | - | - | - | | | | | |
| | 1 | 8 | 106-183-45 | 5 | IV | 5 | - | - | - | 1 | 1 | 1 | | |
| | | | 106-183-40 | 2 | IV | 2 | - | - | - | 1 | | | | |
| | | | 106-183-61 | 1 | IV | 1 | - | - | - | | | | | |
| | 5 | 4 | 93-137-16 | 1 | II | 1 | - | - | 1 | | | | | |
| | | | 93-153-56 | 1 | II | - | - | - | 1 | 1 | 1 | 1 | 1 | |
| | | | 93-153-61 | 1 | II | 1 | - | - | 1 | | 1 | | 1 | |
| | | | 93-182-107 | 1 | II | 1 | - | - | - | | | | | |
| | 30 | 1 | 110-16-49 | 1 | II | 1 | 1 | - | - | | 1 | 1 | 1 | |
| | 188 | 1 | 68-59-32 | 1 | III | 1 | - | - | - | | | | | |
| | 672 | 1 | 64-27-112 | 1 | V | - | - | - | - | | | | | |
| MSSA | 15 | 7 | 2-1-0 | 2 | - | 2 | - | - | - | | | | | |
| | | | 2-17-93 | 1 | - | 1 | - | - | - | | | | | |
| | | | 2-49-64 | 1 | - | 1 | - | - | - | 1 | | | | |
| | | | 2-51-13 | 1 | - | 1 | - | - | - | | | | | |
| | | | 2-89-33 | 1 | - | 1 | - | - | - | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 16-0-1 | 1 | - | - | - | - | - | | | | | |
| 5 | 5 | 4-8-2 | 1 | - | - | - | - | - | | | | | 1 |
| | | 4-8-80 | 1 | - | - | - | - | - | | 1 | | 1 | 1 |
| | | 4-9-16 | 1 | - | - | - | - | - | | | | | 1 |
| | | 4-19-113 | 1 | - | - | - | - | - | | | | | |
| | | 32-111-58 | 1 | - | 1 | - | - | - | | | | | |
| 188 | 4 | 4-1-0 | 1 | - | - | - | - | - | | 1 | | 1 | 1 |
| | | 4-90-64 | 1 | - | - | - | - | - | | 1 | | 1 | 1 |
| | | 4-122-73 | 1 | - | - | - | - | - | | 1 | | 1 | |
| | | 32-66-48 | 1 | - | - | - | - | - | | 1 | | 1 | |
| 12 | 4 | 0-8-80 | 2 | - | 1 | - | - | - | | | | | |
| | | 0-80-8 | 1 | - | - | - | - | - | | | | | |
| | | 0-24-84 | 1 | - | - | - | - | - | | | | | |
| 7 | 3 | 0-9-80 | 1 | - | - | - | - | - | | 1 | | 1 | |
| | | 0-80-9 | 1 | - | 1 | - | - | - | | | | | |
| | | 0-112-27 | 1 | - | 1 | - | - | - | | | | | |
| 121 | 3 | 6-18-1 | 2 | - | 2 | - | - | - | 1 | 1 | | 1 | 1 |
| | | 6-18-81 | 1 | - | 1 | - | - | - | | 1 | 1 | | |
| 20 | 3 | 0-1-1 | 1 | - | 1 | - | - | - | | | | | |
| | | 0-9-16 | 1 | - | 1 | - | - | - | | | | | |
| | | 0-73-81 | 1 | - | 1 | - | - | - | | | | | |
| 45 | 3 | 4-8-80 | 1 | - | 1 | - | - | - | 1 | | | | |
| | | 32-80-9 | 1 | - | - | - | - | 1 | 1 | 1 | | | |
| | | 32-112-27 | 1 | - | 1 | - | - | - | | | | | 1 |
| 6 | 2 | 0-17-67 | 1 | - | 1 | - | - | - | | | | | |
| | | 0-25-113 | 1 | - | 1 | - | - | - | | | | | |
| 8 | 2 | 2-9-80 | 1 | - | 1 | - | - | - | | | | | |
| | | 2-11-81 | 1 | - | 1 | - | - | 1 | | | | | |
| 508 | 2 | 4-16-48 | 1 | - | - | - | - | 1 | | 1 | 1 | 1 | |
| | | 6-26-81 | 1 | - | - | - | - | - | | | | | |
| 398 | 2 | 0-8-80 | 1 | - | - | - | - | - | | | | | |
| | | 0-80-8 | 1 | - | - | - | - | - | | | | | |
| 1 | 1 | 2-1-1 | 1 | - | 1 | - | - | - | | | | | |
| 97 | 1 | 0-83-65 | 1 | - | - | - | - | - | 1 | | | | |
| 291 | 1 | 0-16-17 | 1 | - | - | - | - | - | | | | | |
| 630 | 1 | 18-17-0 | 1 | - | 1 | - | - | - | | | | | |
| 845 | 1 | 2-1-1 | 1 | - | 1 | - | - | - | | | | | |
| 2867 | 1 | 0-17-1 | 1 | - | - | - | - | - | | | | | |
| 9368 | 1 | 32-0-24 | 1 | - | 1 | - | - | - | | 1 | | | |
| 9369 | 1 | 6-18-2 | 1 | - | 1 | - | - | - | | 1 | 1 | 1 | |

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MLST, multilocus sequence typing; POT, PCR-based open reading frame typing; DIC, disseminated intravascular coagulation; IE, infective endocarditis.

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