Open Forum Infectious Diseases

MAJOR ARTICLE

Clinical and Microbiological Characteristics of Hospital-Acquired Methicillin-Resistant *Staphylococcus aureus* Bacteremia Caused by a Community-Associated PVL-Negative Strain

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Background. ST72-SCC*mec*IV, a community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) strain in Korea, originated in the community and has been spreading in health care settings. Herein, we describe the clinical and microbiological characteristics of patients with hospital-acquired MRSA bacteremia (MRSAB) caused by community-associated strains.

Methods. We analyzed hospital-acquired MRSAB cases caused by ST72-SCC*mec*IV using a prospective cohort of patients with SAB in a tertiary hospital in Korea from July 2008 to December 2018. We compared the clinical and microbiological characteristics of ST72-SCC*mec*IV with ST5-SCC*mec*II, a representative hospital-associated genotype strain.

Results. Of the 1782 *S. aureus* bacteremia (SAB) cases, 628 (35.2%) were hospital-acquired MRSAB. Of the 628 isolates, 431 (68.6%) were ST5-SCC*mec*II and 152 (24.2%) were ST72-SCC*mec*IV. Patients with ST72-SCC*mec*IV were younger than those with ST5-SCC*mec*II and less likely to have a history of recent surgery, antibiotic treatment, nasal MRSA colonization, and central venous catheter placement. Compared with ST5-SCC*mec*II, ST72-SCC*mec*IV isolates were more likely to have vancomycin MICs ≤1.0 mg/L ($P < .001$). Osteoarticular infection as the site of infection (7.2% [11/152] vs 1.4% [6/431]) was more common in patients with ST72-SCC*mec*IV. There were no significant differences in the rate of recurrence (≤90 days), persistent bacteremia (≥7 days), or 30- and 90-day mortality rates between the 2 groups.

Conclusions. Osteoarticular infections were more prevalent in ST72-SCC*mec*IV MRSAB. Mortality rates between the ST72-SCC*mec*IV and ST5-SCC*mec*II groups were not significantly different.

Keywords. bacteremia; hospital-acquired infection; methicillin-resistant *Staphylococcus aureus*; outcome; Panton-Valentine Leukocidin-negative.

Methicillin-resistant *Staphylococcus aureus* (MRSA) exhibits enhanced virulence and causes a wide range of infections from mild to life-threatening conditions in both hospital and community settings. Historically, MRSA infections have primarily occurred among hospitalized patients. However, a growing number of community-associated MRSA (CA-MRSA) infections have recently emerged worldwide [1, 2], and new MRSA strains, often called CA-MRSA strains, have been isolated. As such, their virulence factors have not yet been completely established. CA-MRSA strains present different characteristics from those of the traditional hospital-associated MRSA (HA-MRSA) strains [3].

S. aureus can evade the host innate immunity [4] and may secrete toxins such as Panton-Valentine leukocidin (PVL), which is lytic to human neutrophils and has pro-inflammatory effects [5]. The distribution and prevalence of dominant CA-MRSA clones and PVL gene status vary among countries [3]. In the United States, CA-MRSA isolates are mostly attributed to the single-clone sequence type (ST) 8 (pulsotype USA 300) possessing PVL [6, 7]. In South Korea, ST72-SCC*mec*IV is the major CA-MRSA clone [8, 9] and is distinct from other clones in Asia and around the world [10]. Particularly, unlike the PVL-positive CA-MRSA isolates from Western countries, ST72-SCC*mec*IV isolates do not carry the PVL gene. This PVL-negative ST72-SCC*mec*IV CA-MRSA strain first emerged in the community and has been spreading in health care settings [11–13]. However, there have only been a few reports on hospital-acquired MRSA bacteremia (MRSAB) caused by ST72-SCC*mec*IV [14–16].

Received 7 April 2021; editorial decision 4 August 2021; accepted 13 August 2021.

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Open Forum Infectious Diseases®2021

https://doi.org/10.1093/ofid/ofab424

We thus evaluated the clinical and microbiological characteristics and outcomes of Korean patients with MRSAB caused by ST72-SCC*mec*IV and compared them with those caused by ST5-SCC*mec*II, a representative HA-MRSA genomic strain in Korea.

METHODS

Study Design and Patients

This prospective cohort study was conducted at the Asan Medical Center (Seoul, Republic of Korea) from July 2008 through December 2018. This 2700-bed institution is a university-affiliated teaching hospital that provides both primary and tertiary care. All adult patients with *S. aureus* bacteremia (SAB) were prospectively enrolled and observed for 90 days. SAB cases were reviewed by infectious disease (ID) experts within 2 or 3 days after the identification of *S. aureus* on blood culture tests. ID experts recommended the following routine as protocol. Follow-up blood cultures were performed every 2 to 3 days until the patient tested negative. Echocardiography and fundoscopic examination were recommended to detect cardiac vegetation and endophthalmitis, respectively. It was also recommended that vancomycin trough concentrations be monitored and maintained at 15–20 mg/L in patients with SAB. Patients were excluded from the analysis if they had polymicrobial bacteremia, had been discharged before obtaining positive blood culture results, or had SAB within the previous 3 months. Demographic characteristics, underlying diseases or conditions and their severity, severity of bacteremia, place of infection, initial source of SAB, presence of a central venous catheter (CVC) or other prosthetic devices, patient management, and clinical outcomes were recorded. The Charlson Comorbidity Index (CCI) was used to measure the composite score of severity of preexisting comorbidities [17]. A positive culture from a patient who had been hospitalized for ≥48 hours was defined as hospital-acquired bloodstream infection [18]. Within this SAB cohort, hospital-acquired MRSAB cases caused by ST72-SCC*mec*IV and ST5-SCC*mec*II strains were selected and analyzed.

Patient Consent

The protocol of this study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2013-0234), which waived the requirement for written or verbal consent from the patients based on the observational nature of the study.

Laboratory and Microbiological Data

All *S. aureus* isolates were identified using the standard methods. The first blood isolate obtained from the patient was used for microbiological and molecular assessments. The minimum inhibitory concentration (MIC) of vancomycin was determined using the broth microdilution method. All isolates underwent vancomycin susceptibility testing according to the Clinical and Laboratory Standards Institute (CLSI) guidelines with the inclusion of 1.5-mg/L dilution [19–21]. Antimicrobial susceptibilities were determined using the MicroScan system (Dade Behring, West Sacramento, CA, USA) and the standard criteria of the CSLI. Polymerase chain reaction of the *mec*A gene was performed to confirm methicillin resistance. δ-hemolysin activity was used to determine *agr* functionality as described previously [22]. PVL genes, the staphylococcal cassette chromosome *mec* (SCC*mec*) type, and the multilocus sequence type (MLST) were identified as previously described [23–27]. MLST allele names and STs were derived from the MLST database (http://www.mlst.net).

Data Collection and Information on Variables

Data on the following variables were obtained from all patients: age, sex, underlying diseases or conditions, recent surgery history, history of immunosuppressive therapy, presence or absence of medical devices, primary site of infection, metastatic infection, antibiogram results, patient management, and clinical outcome. The site of infection was determined based on clinical, radiological, and bacteriological investigations performed at the time of initial blood culture. Infective endocarditis was defined according to the modified Duke criteria [28]. We classified bacteremia without an identifiable site of infection as primary bacteremia. Metastatic infection was defined as the development of a new sterile site infection if it was neither clinically apparent at the time of initial blood culture nor detected in the initial diagnostic tests. Infection foci were evaluated for focus removal and categorized as eradicable and noneradicable foci. Eradicable foci were subdivided into eradicated and not eradicated; eradicable foci included surgically removable infections or drainable abscesses and indwelling foreign bodies such as intravenous catheters. Noneradicable foci included pneumonia, endocarditis, primary bacteremia, and osteomyelitis or arthritis. Prosthetic devices included orthopedic devices, cardiovascular electronic devices, prosthetic valves, and vascular grafts. Septic shock was defined as sepsis with persistent hypotension that requires vasopressors to maintain mean arterial pressure ≥65 mmHg and lactate level ≥2 mmol/L despite adequate fluid resuscitation [29]. Recurrent bacteremia was defined as SAB occurrence within 90 days of resolution of the first episode, whereas persistent bacteremia was defined as SAB lasting at least 7 days.

Statistical Analysis

Pearson's χ-square test or the Fisher exact test was used to analyze the categorical variables, whereas the Student *t* test and Mann-Whitney *U* test were used to analyze normally and non–normally distributed continuous variables, respectively. Univariable and multivariable analyses using logistic regression models were performed to identify the independent risk factors for crude mortality. Age, sex, MRSA genotype, and variables

with $P < .05$ in the univariable analysis were included in the multivariable logistic regression model. Odds ratios and their 95% CIs were calculated. All *P* values were 2-tailed, and *P* values <.05 were considered statistically significant. Data were analyzed using SPSS, version 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Study Population

We found 1782 SAB cases, comprising 924 (51.9%) MRSA and 628 (35.2%) hospital-acquired MRSA bacteremia. Of the 628 isolates, 431 (68.6%) were ST5-SCC*mec*IV and 152 (24.2%) were ST72-SCC*mec*II. Therefore, we analyzed 583 hospital-acquired MRSAB cases. Excluded 45 (7.2% of the total hospital-acquired MRSAB) isolates that belonged to the 14 MLST types other than ST72-SCC*mec*II or ST5-SCC*mec*IV (Supplementary Table 1).

Patient Characteristics

The clinical characteristics of 583 patients with hospital-acquired MRSAB caused by ST72-SCC*mec*IV and ST5-SCC*mec*II strains are summarized in Table 1. Patients with ST72-SCC*mec*IV were younger than those with ST5-SCC*mec*II (median age, 63 vs 65 years; $P = .013$) and had hematologic malignancy more frequently (13.8% [21/152] vs 4.6% [20/431]). There were no significant differences in the frequency of other underlying diseases and CCI between the 2 groups. Meanwhile, patients with ST72-SCC*mec*IV were less likely to have a history of recent surgery (27% [41/152] vs 39.9% [172/431]; $P = .004$), prior antibiotic treatment (within 1 month; 41.4% [63/152] vs 86.5% [373/431]; $P < .001$), nasal MRSA colonization (16.4% [25/152] vs 45.2% [195/431]; $P < .001$), and central venous catheter placement (17.7% [68/152] vs 73.5% [317/431]; $P = .001$). The ST72-SCC*mec*IV strain caused more frequent osteoarticular infections than ST5-SCC*mec*II (7.2% [11/152] vs 1.4% [6/431]; $P = .001$). Intravascular catheter–related infections were more common in the ST5-SCC*mec*II group (43.4% [66/152] vs 52.9% [228/431]; $P = .044$). There were no significant differences in the frequency of metastatic infections or vancomycin use as definitive antibiotic therapy between the 2 groups. In univariable and multivariable logistic regression analyses to identify clinical factors associated with infections with ST72-SCC*mec*IV, end-stage renal disease, prior antibiotic treatment, and *agr* dysfunction were significantly associated with ST72-SCC*mec*IV MRSAB (Supplementary Table 2). An association between the osteoarticular infection for primary infection foci and ST72-SCC*mec*IV MRSAB showed borderline significance ($P = .052$). Considering the rarity of hospital-onset bone and joint infections excluding postoperative infection, we further reviewed the cases of osteoarticular infections (Supplementary Table 3). Symptoms in all patients with osteoarticular infections, with exception of 3 patients for whom symptom onset could not be confirmed from the medical record, began before admission (median [range], 4 [1–20] days).

Microbiological Characteristics

The microbiological characteristics and antibiotic susceptibilities of MRSA strains are summarized in Table 2. Most of the ST5-SCC*mec*II isolates (96.1%) had *agr* dysfunction, whereas most of the ST72-SCC*mec*IV isolates (90.1%) possessed *agr* function. ST72-SCC*mec*IV isolates exhibited lower vancomycin MIC distribution and were less likely to be resistant to various classes of antibiotics, including clindamycin, ciprofloxacin, erythromycin, fusidic acid, gentamicin, and rifampicin, than ST5-SCC*mec*II isolates (Table 2).

Treatment Outcomes

Table 3 compares the treatment outcomes of patients with ST72-SCC*mec*IV vs ST5-SCC*mec*II isolates. Those with ST5-SCC*mec*II isolates were more likely to receive medical care in the intensive care unit (35.7% [154/431] vs 12.5% [19/152]; $P < .001$). However, there were no significant differences in terms of 30- and 90-day mortality or persistent (≥7 days) and recurrent bacteremia between the 2 groups. Univariable and multivariable logistic regression analyses were performed to identify independent risk factors for mortality (Table 4).

In univariable analyses, high CCI (>4), pneumonia as the site of infection, and noneradicated foci were significantly associated with 30-day mortality, whereas underlying hypertension was negatively correlated with 30-day mortality. Vancomycin MICs were not associated with 30-day mortality. In addition, the ST72-SCC*mec*IV strain had no significant effect on mortality.

In multivariable analyses, after controlling for several confounders and including other significant variables, there was no significant difference in 30-day mortality between the ST72-SCC*mec*IV and ST5-SCC*mec*II groups. CCI >4 (adjusted odds ratio [aOR], 2.80; 95% CI, 1.79–4.40), pneumonia as the site of infection (aOR, 3.64; 95% CI, 1.84–7.20), noneradicated foci (aOR, 2.43; 95% CI, 1.02–5.82), and underlying hypertension (aOR, 0.40; 95% CI, 0.24–0.66) were independently associated with 30-day mortality. After stratification by strain type, hypertension (aOR, 0.38; 95% CI, 0.21–0.37), CCI >4 (aOR, 2.11; 95% CI, 1.26–3.52), pneumonia (aOR, 3.46; 95% CI, 1.60–7.47), and noneradicated foci (aOR, 3.21; 95% CI, 1.06–9.69) were independently associated with 30-day mortality in the ST5-SCC*mec*II group. In the ST72-SCC*mec*IV group, CCI >4 (aOR, 6.95; 95% CI, 2.22–21.76) and pneumonia (aOR, 5.75; 95% CI, 1.18–28.01) showed significance (Supplementary Table 4). There were no significant differences in 30-day mortality in the ST72-SCC*mec*IV group compared with hospital-associated MRSA strains including ST5-SCC*mec*II and others (Supplementary Table 5). We performed a sensitivity analysis after excluding patients with osteoarticular infections, but mortality was not

Table 1. Clinical Characteristics of Adult Patients With Hospital-Acquired MRSAB (n = 583)

Characteristics	ST5 (n = 431)	ST72 (n = 152)	P
Age, median (IQR), y	65 (55–73)	63 (50–71)	.013
Male	285 (66.1)	87 (57.2)	.050
Underlying diseases			
Solid cancer	199 (46.2)	65 (42.8)	.468
Hematologic malignancy	20 (4.6)	21 (13.8)	<.001
Diabetes mellitus	131 (30.4)	47 (30.9)	.904
Liver cirrhosis	64 (14.8)	26 (17.1)	.508
End-stage renal disease	33 (7.7)	14 (9.2)	.545
Chronic pulmonary disease[a]	18 (4.2)	3 (1.3)	.096
Heart failure	22 (5.1)	8 (5.3)	.939
Hypertension	171 (39.7)	56 (36.8)	.538
Solid organ transplantation	40 (9.3)	10 (6.6)	.306
CCI, median (IQR)	3 (2–5)	2 (2–5)	.821
CCI >4	114 (26.5)	38 (25.0)	.726
Predisposing condition			
Recent surgery[b]	172 (39.9)	41 (27.0)	.004
Prior antibiotic treatment [b]	373 (86.5)	63 (41.4)	<.001
Nasal MRSA colonization[c]	195 (45.2)	25 (16.4)	<.001
Immunosuppressive treatment[b]	136 (31.6)	52 (34.2)	.547
Central venous catheter	317 (73.5)	68 (44.7)	<.001
Noncatheter prosthetic devices[d]	58 (13.5)	22 (14.5)	.754
Septic shock[e]	62 (14.4)	22 (14.5)	.979
Primary site of infection			
Intravascular catheter–related	228 (52.9)	66 (43.4)	.044
Pneumonia	47 (10.9)	13 (8.6)	.412
Surgical site infection	36 (8.4)	13 (8.6)	.939
Osteoarticular infection	6 (1.4)	11 (7.2)	<.001
Skin and soft tissue infection	12 (2.8)	5 (3.3)	.750
Infective endocarditis	4 (0.9)	4 (2.6)	.121
Other	45 (10.4)	12 (7.9)	.363
Unknown (primary bacteremia)	51 (11.8)	23 (15.1)	.294
Metastatic infection	55 (12.8)	21 (13.8)	.740
Source control			.003
Eradicated	255 (59.2)	72 (47.4)	
Not eradicated	16 (3.7)	15 (9.9)	
Noneradicable foci	160 (37.1)	65 (42.8)	
Definitive antibiotic treatment			
Vancomycin	352 (81.7)	122 (80.3)	.702
Teicoplanin	108 (25.1)	41 (27.0)	.642
Initial vancomycin trough level, median (IQR), mg/L	18.3 (10.0–23.3)	17.0 (10.2–22.4)	.100

Data are presented as No. (%), unless otherwise indicated.

Abbreviations: CCI, Charlson Comorbidity Index; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSAB, hospital-acquired methicillin-resistant *Staphylococcus aureus* bacteremia.

[a]Includes chronic pulmonary obstructive lung disease and bronchiectasis.

[b]Within a month before MRSA bacteremia.

[c]Positive result of the nasal swab test performed within 48 hours after confirmation of positive blood culture.

[d]Includes pacemaker/implantable cardioverter-defibrillator (8 patients), prosthetic heart valves (20 patients), orthopedic devices (21 patients), and vascular grafts (27 patients).

[e]Sepsis with persistent hypotension that requires vasopressors to maintain mean arterial pressure ≥65 mmHg and lactate level ≥2 mmol/L despite adequate fluid resuscitation.

associated with any specific sequence type (Supplementary Table 6).

DISCUSSION

In this study, we evaluated the clinical characteristics and outcomes of patients with hospital-acquired MRSAB caused by ST72-SCC*mec*IV, a representative PVL-negative CA-MRSA strain in Korea, by comparing with the clinical characteristics and outcomes of patients with ST5-SCC*mec*II, a representative HA-MRSA strain in Korea. Osteoarticular infections were more frequently observed in ST72-SCC*mec*IV MRSAB, and ST72-SCC*mec*IV isolates were more likely to have vancomycin MICs ≤1.0 mg/L than ST5-SCC*mec*II. Mortality and recurrence rates were not significantly different between the 2 groups.

Table 2. Microbiologic Characteristics of 583 MRSA Isolates Causing Bloodstream Infections

Characteristic	ST5 (n = 431)	ST72 (n = 152)	P
agr dysfunction	414 (96.1)	15 (9.9)	<.001
Vancomycin MIC by BMD			
≤1.0 mg/L	302 (70.1)	136 (89.5)	<.001
1.5 mg/L	117 (27.1)	15 (9.9)	<.001
≥2.0 mg/L	12 (2.8)	1 (0.7)	.127
Resistance to:			
Clindamycin	422 (97.9)	33 (21.7)	<.001
Ciprofloxacin	427 (99.1)	13 (8.6)	<.001
Erythromycin	426 (98.8)	39 (25.7)	<.001
Fusidic acid	372 (86.3)	2 (1.3)	<.001
Gentamicin	339 (78.7)	14 (9.2)	<.001
Rifampin	41 (9.5)	2 (1.3)	.001
Trimethoprim/sulfamethoxazole	9 (2.1)	1 (0.7)	.243

Abbreviations: BMD, broth microdilution method; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*.

Osteoarticular infections were more prevalent in ST72-SCC*mec*IV MRSAB in our study cohort. According to Lee et al., who analyzed CA-MRSA bacteremia cases and compared them with CA-MSSA, bone and joint infections were independent risk factors for CA-MRSA caused by ST72-SCC*mec*IV [30]. In another study on MRSAB, ST72-SCC*mec*IV isolates caused osteoarticular infection more frequently than ST5-SCC*mec*II [13]. Therefore, ST72-SCC*mec*IV is suggested to play a role in the predominance of osteoarticular infections in patients with CA-MRSA bacteremia. However, the association between osteoarticular infections and ST72-SCC*mec*IV observed in our study should be interpreted cautiously. Although the prevalence of osteoarticular infection was higher in the ST72-SCC*mec*IV MRSAB group than in the ST5-SCC*mec*II MRSAB group, the proportion was low (7%) relative to other infection sources. Given that most osteoarticluar infection cases in the ST72 group had symptoms before admission, they may have been misclassified as having hospital-acquired infection.

Furthermore, we found that ST72-SCC*mec*IV isolates were more likely to have vancomycin MICs ≤1.0 mg/L than ST5-SCC*mec*II isolates. MIC values of CA-MRSA clones are usually lower than those of HA-MRSA clones [31]. Because only hospital infections were analyzed, this study was consistent with previous studies. Several studies have shown that a high vancomycin MIC is associated with worse clinical outcomes [32–34]. In our study, however, increased vancomycin MICs were not associated with mortality.

Whether there are differences in mortality associated with infections caused by CA-MRSA and HA-MRSA strains remains controversial [2, 35–38]. Previous studies have found that the mortality rate associated with infections caused by ST72-SCC*mec*IV was similar to or lower than that of infections caused by ST5-SCC*mec*II or other comparative HA-MRSA strains [13, 16]. In this study, we controlled the potential confounding factors and included only hospital-acquired SAB for a more accurate comparison. As a result, mortality was not significantly different between the 2 groups. Although ST72-SCC*mec*IV may be more virulent in theory, the real-world outcome is complex. The exact reasons have not been elucidated; however, we attribute this to 3 factors. First, a previous study revealed that strain-specific virulence factors such as staphylococcal superantigen genes, including *sel*, *sec*, and *tst*, which are less commonly found in ST72-SCC*mec*IV isolates, might contribute to higher mortality in ST5-SCC*mec*II infections [13]. Second, because vancomycin MICs in the ST5-SCC*mec*II group were higher, its bactericidal activity is reduced. Lastly, the percentage of patients with recent surgery or CVC presence was higher in the ST5-SCC*mec*II group than in the ST72-SCC*mec*IV group, suggesting that ST72-SCC*mec*IV can invade the host bloodstream without those portals of entry. However,

Table 3. Clinical Outcomes of 583 Adult Patients With Hospital-Acquired MRSAB

Outcome	ST5 (n = 431)	ST72 (n = 152)	P
ICU	154 (35.7)	19 (12.5)	<.001
Mortality (within 30 d)	91 (21.1)	24 (15.8)	.156
Mortality (within 90 d)	147 (34.1)	41 (27.0)	.106
Persistent bacteremia ≥7 d	75/429 (17.5)	18/145 (12.4)	.152
Recurrent bacteremia within 90 d	20 (4.6)	4 (2.6)	.284

Abbreviations: ICU, intensive care unit; MRSAB, hospital-acquired methicillin-resistant *Staphylococcus aureus* bacteremia.

Table 4. Univariable and Multivariable Analysis of Risk Factors Associated With 30-Day Mortality in 583 Adult Patients With Hospital-Acquired MRSAB

	Univariable Analysis		Multivariable Analysis[a]	
Risk Factor	OR (95% CI)	P	OR (95% CI)	P
Age ≥65 y	1.04 (0.69–1.57)	.836	1.35 (0.86–2.13)	.197
Male	0.94 (0.62–1.43)	.765	0.86 (0.55–1.35)	.523
Underlying solid cancer	1.35 (0.90–2.03)	.148		
Hematologic malignancy	1.34 (0.64–2.83)	.438		
Diabetes mellitus	0.81 (0.51–1.27)	.353		
Liver cirrhosis	1.60 (0.96–2.70)	.074		
End-stage renal disease	0.69 (0.30–1.59)	.388		
Chronic pulmonary disease[b]	1.37 (0.49–3.86)	.548		
Heart failure	1.02 (0.41–2.55)	.969		
Hypertension	0.49 (0.31–0.77)	.002	0.40 (0.24–0.66)	<.001
Solid organ transplantation	0.64 (0.28–1.46)	.291		
CCI >4	2.63 (1.71–4.04)	<.001	2.80 (1.79–4.40)	<.001
Intravascular catheter–related	0.84 (0.56–1.27)	.406		
Pneumonia	3.44 (1.96–6.02)	<.001	3.64 (1.84–7.20)	<.001
Surgical site infection	0.44 (0.17–1.13)	.088		
Osteoarticular infection	0.25 (0.03–1.89)	.178		
Skin and soft tissue infection	0.25 (0.03–1.89)	.178		
Infective endocarditis	1.36 (0.27–6.84)	.707		
Unknown (primary bacteremia)	0.94 (0.51–1.75)	.852		
Metastatic infection	1.43 (0.81–2.51)	.217		
Source control				
Eradicated	1	NA	1	NA
Not eradicated	2.12 (0.92–4.85)	.077	2.43 (1.02–5.82)	.046
Noneradicable foci	1.59 (1.04–2.44)	.032	1.10 (0.66–1.86)	.692
MRSA genotype				
ST5-SCC*mec II*	1	NA	1	NA
ST72-SCC*mec IV*	0.70 (0.43–1.15)	.158	0.65 (0.39–1.10)	.116
agr dysfunction	1.56 (0.94–2.56)	.083		
Vancomycin MIC by BMD				
≤1.0 mg/L	1	NA		
1.5 mg/L	0.93 (0.57–1.52)	.771		
≥2.0 mg/L	0.72 (0.16–3.22)	.677		

Abbreviations: BMD, broth microdilution; CCI, Charlson Comorbidity Index; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSAB, hospital-acquired methicillin-resistant *Staphylococcus aureus* bacteremia; NA, not applicable; OR, odds ratio; SCC, staphylococcal cassette chromosome; ST, sequence type.

[a]Multivariable analysis included age, sex, MRSA genotype, and variables showing significant differences ($P < 0.05$) in the univariable analysis.

[b]Includes chronic pulmonary obstructive lung disease and bronchiectasis.

given the readily removable nature of vascular catheters such as central-line catheters, the higher rate of indwelling CVC may be conversely responsible for the lower mortality. Overall, the ST72-SCC*mec*IV strain might be more virulent itself, as it caused bacteremia in the absence of these prerequisites. Given this, mortality may be more related to the patient's comorbidities and site of acquisition rather than the strain itself.

Our study had some limitations. First, patients included those only from a single hospital; therefore, our findings may not be entirely representative of CA-MRSA strains in Korea. Second, because our comparative analysis only included hospital-acquired infections and excluded community-acquired infections, our findings cannot be generalized to all ST72-SCC*mec*IV strains. Third, we did not perform high-resolution methods such as whole-genome sequencing, which could provide information on resistance and virulence as well as genotype [39]. Therefore, further studies with whole-genome sequencing analysis are needed. Lastly, distinguishing infection foci and metastatic infection could be challenging, as we did not routinely perform tests that are highly sensitive to detect early infections such as positron emission tomography scans.

In conclusion, osteoarticular infection was more frequently observed in hospital-acquired MRSAB caused by ST72-SCC*mec*IV than in hospital-acquired MRSAB caused by ST5-SCC*mec*II. The ST72-SCC*mec*IV strain was not associated with worse clinical outcomes, including 30-day mortality, 90-day mortality, persistent bacteremia, and recurrence, when compared with ST5-SCC*mec*II.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader,

the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

We sincerely thank Bo Min Kwon and Jung-A Eum for their support with data collection.

Financial support. This work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) and was funded by the Ministry of Health & Welfare, Republic of Korea (HI15C2918).

Potential conflicts of interest. The authors declare that they have no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Vandenesch F, Naimi T, Enright MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: worldwide emergence. Emerg Infect Dis **2003**; 9:978–84.
2. DeLeo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated methicillin-resistant *Staphylococcus aureus*. Lancet **2010**; 375:1557–68.
3. David MZ, Daum RS. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. Clin Microbiol Rev **2010**; 23:616–87.
4. DeLeo FR, Diep BA, Otto M. Host defense and pathogenesis in *Staphylococcus aureus* infections. Infect Dis Clin North Am **2009**; 23:17–34.
5. Otto M. Community-associated MRSA: what makes them special? Int J Med Microbiol **2013**; 303:324–30.
6. Lakhundi S, Zhang K. Methicillin-resistant *Staphylococcus aureus*: molecular characterization, evolution, and epidemiology. Clin Microbiol Rev **2018**; 31: e00020–18.
7. Chua K, Laurent F, Coombs G, et al. Antimicrobial resistance: not community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA)! A clinician's guide to community MRSA - its evolving antimicrobial resistance and implications for therapy. Clin Infect Dis **2011**; 52:99–114.
8. Kim ES, Song JS, Lee HJ, et al. A survey of community-associated methicillin-resistant *Staphylococcus aureus* in Korea. J Antimicrob Chemother **2007**; 60:1108–14.
9. Park C, Lee DG, Kim SW, et al. Predominance of community-associated methicillin-resistant *Staphylococcus aureus* strains carrying staphylococcal chromosome cassette *mec* type IVA in South Korea. J Clin Microbiol **2007**; 45:4021–6.
10. Chuang YY, Huang YC. Molecular epidemiology of community-associated methicillin-resistant *Staphylococcus aureus* in Asia. Lancet Infect Dis **2013**; 13:698–708.
11. Park SH, Park C, Yoo JH, et al. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* strains as a cause of healthcare-associated bloodstream infections in Korea. Infect Control Hosp Epidemiol **2009**; 30:146–55.
12. Kim ES, Lee HJ, Chung GT, et al. Molecular characterization of methicillin-resistant *Staphylococcus aureus* isolates in Korea. J Clin Microbiol **2011**; 49:1979–82.
13. Park KH, Chong YP, Kim SH, et al. Community-associated MRSA strain ST72-SCC*mec*IV causing bloodstream infections: clinical outcomes and bacterial virulence factors. J Antimicrob Chemother **2015**; 70:1185–92.
14. Joo EJ, Chung DR, Ha YE, et al. Community-associated Panton-Valentine leukocidin-negative methicillin-resistant *Staphylococcus aureus* clone (ST72-MRSA-IV) causing healthcare-associated pneumonia and surgical site infection in Korea. J Hosp Infect **2012**; 81:149–55.
15. Joo EJ, Chung DR, Ha YE, et al. Clinical predictors of community-genotype ST72-methicillin-resistant *Staphylococcus aureus*-SCC*mec* type IV in patients with community-onset *S. aureus* infection. J Antimicrob Chemother **2012**; 67:1755–9.
16. Joo EJ, Chung DR, Kim SH, et al. Emergence of community-genotype methicillin-resistant *Staphylococcus aureus* in Korean hospitals: clinical characteristics of nosocomial infections by community-genotype strain. Infect Chemother **2017**; 49:109–16.
17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
18. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med **2002**; 137:791–7.
19. Kruzel MC, Lewis CT, Welsh KJ, et al. Determination of vancomycin and daptomycin MICs by different testing methods for methicillin-resistant *Staphylococcus aureus*. J Clin Microbiol **2011**; 49:2272–3.
20. van Hal SJ, Barbagiannakos T, Jones M, et al. Methicillin-resistant *Staphylococcus aureus* vancomycin susceptibility testing: methodology correlations, temporal trends and clonal patterns. J Antimicrob Chemother **2011**; 66:2284–7.
21. Edwards B, Milne K, Lawes T, Cook I, et al. Is vancomycin MIC "creep" method dependent? Analysis of methicillin-resistant *Staphylococcus aureus* susceptibility trends in blood isolates from North East Scotland from 2006 to 2010. J Clin Microbiol **2012**; 50:318–25.
22. Sakoulas G, Eliopoulos GM, Moellering RC Jr, et al. Accessory gene regulator (*agr*) locus in geographically diverse *Staphylococcus aureus* isolates with reduced susceptibility to vancomycin. Antimicrob Agents Chemother **2002**; 46:1492–502.
23. Gillet Y, Issartel B, Vanhems P, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet **2002**; 359:753–9.
24. Ito T, Katayama Y, Asada K, et al. Structural comparison of three types of staphylococcal cassette chromosome *mec* integrated in the chromosome in methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **2001**; 45:1323–36.
25. Enright MC, Day NP, Davies CE, et al. Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus*. J Clin Microbiol **2000**; 38:1008–15.
26. Oliveira DC, de Lencastre H. Multiplex PCR strategy for rapid identification of structural types and variants of the *mec* element in methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **2002**; 46:2155–61.
27. Jarraud S, Mougel C, Thioulouse J, et al. Relationships between *Staphylococcus aureus* genetic background, virulence factors, *agr* groups (alleles), and human disease. Infect Immun **2002**; 70:631–41.
28. Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis **2000**; 30:633–8.
29. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA **2016**; 315:801–10.
30. Lee JY, Chong YP, Kim T, et al. Bone and joint infection as a predictor of community-acquired methicillin-resistant *Staphylococcus aureus* bacteraemia: a comparative cohort study. J Antimicrob Chemother **2014**; 69:1966–71.
31. Nichol KA, Adam HJ, Hussain Z, et al. Comparison of community-associated and health care-associated methicillin-resistant *Staphylococcus aureus* in Canada: results of the CANWARD 2007–2009 study. Diagn Microbiol Infect Dis **2011**; 69:320–5.
32. Bae IG, Federspiel JJ, Miró JM, et al; International Collaboration on Endocarditis-Microbiology Investigator. Heterogeneous vancomycin-intermediate susceptibility phenotype in bloodstream methicillin-resistant *Staphylococcus aureus* isolates from an international cohort of patients with infective endocarditis: prevalence, genotype, and clinical significance. J Infect Dis **2009**; 200:1355–66.
33. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis **2011**; 52:975–81.
34. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. Antimicrob Agents Chemother **2008**; 52:3315–20.
35. Eells SJ, McKinnell JA, Wang AA, et al. A comparison of clinical outcomes between healthcare-associated infections due to community-associated methicillin-resistant *Staphylococcus aureus* strains and healthcare-associated methicillin-resistant *S. aureus* strains. Epidemiol Infect **2013**; 141:2140–8.
36. Wang JT, Wang JL, Fang CT, et al. Risk factors for mortality of nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infection: with investigation of the potential role of community-associated MRSA strains. J Infect **2010**; 61:449–57.
37. Wu HS, Kuo SC, Chen LY, et al. Comparison between patients under hemodialysis with community-onset bacteremia caused by community-associated and healthcare-associated methicillin-resistant *Staphylococcus aureus* strains. J Microbiol Immunol Infect **2013**; 46:96–103.
38. Robinson JO, Pearson JC, Christiansen KJ, et al. Community-associated versus healthcare-associated methicillin-resistant *Staphylococcus aureus* bacteraemia: a 10-year retrospective review. Eur J Clin Microbiol Infect Dis **2009**; 28:353–61.
39. Priest NK, Rudkin JK, Feil EJ, et al. From genotype to phenotype: can systems biology be used to predict *Staphylococcus aureus* virulence? Nat Rev Microbiol **2012**; 10:791–7.