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

Yun Woo Lee,1* Seongman Bae,1 Eunmi Yang,1 Hyemin Chung,1 Eunsil Kim,2 Jiwon Jung,1 Yong Pil Chong,1 Sung-Han Kim,1,2 Sang-Ho Choi,1 Min Jae Kim,1 Young-Ik Ko,1 and Yang Soo Kim1,2

1Division of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, and 2Center for Antimicrobial Resistance and Microbial Genetics, University of Ulsan College of Medicine, Seoul, Republic of Korea

**Background.** ST72-SCCmecIV, 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 (MRSA-B) caused by community-associated strains.

**Methods.** We analyzed hospital-acquired MRSA-B cases caused by ST72-SCCmecIV 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-SCCmecIV with ST5-SCCmecII, a representative hospital-associated genotype strain.

**Results.** Of the 1782 *S. aureus* bacteremia (SAB) cases, 628 (35.2%) were hospital-acquired MRSA-B. Of the 628 isolates, 431 (68.6%) were ST5-SCCmecII and 152 (24.2%) were ST72-SCCmecIV. Patients with ST72-SCCmecIV were younger than those with ST5-SCCmecII and less likely to have a history of recent surgery, antibiotic treatment, nasal MRSA colonization, and central venous catheter placement. Compared with ST5-SCCmecII, ST72-SCCmecIV 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-SCCmecIV. 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-SCCmecIV MRSA-B. Mortality rates between the ST72-SCCmecIV and ST5-SCCmecII 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-SCCmecIV 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-SCCmecIV isolates do not carry the PVL gene. This PVL-negative ST72-SCCmecIV 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 (MRSA-B) caused by ST72-SCCmecIV [14–16].
We thus evaluated the clinical and microbiological characteristics and outcomes of Korean patients with MRSAB caused by ST72-SCCmecIV and compared them with those caused by ST5-SCCmecII, 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-SCCmecIV and ST5-SCCmecII 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 CLSI. Polymerase chain reaction of the mecA 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 (SCCmec) 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-SCCmec IV and 152 (24.2%) were ST72-SCCmec II. Therefore, we analyzed 583 hospital-acquired MRSA cases. Excluded 45 (7.2% of the total hospital-acquired MRSAB) isolates that belonged to the 14 MLST types other than ST72-SCCmec IV or ST5-SCCmec IV (Supplementary Table 1).

**Patient Characteristics**
The clinical characteristics of 583 patients with hospital-acquired MRSAB caused by ST72-SCCmec IV and ST5-SCCmec II strains are summarized in Table 1. Patients with ST72-SCCmec IV were younger than those with ST5-SCCmec 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-SCCmec 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-SCCmec IV strain caused more frequent osteoarticular infections than ST5-SCCmec II (7.2% [11/152] vs 1.4% [6/431]; $P = .001$). Intravascular catheter-related infections were more common in the ST5-SCCmec 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-SCCmec IV, end-stage renal disease, prior antibiotic treatment, and agr dysfunction were significantly associated with ST72-SCCmec IV MRSAB (Supplementary Table 2). An association between the osteoarticular infection for primary infection foci and ST72-SCCmec 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-SCCmec II isolates (96.1%) had agr dysfunction, whereas most of the ST72-SCCmec IV isolates (90.1%) possessed agr function. ST72-SCCmec 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-SCCmec II isolates (Table 2).

**Treatment Outcomes**
Table 3 compares the treatment outcomes of patients with ST72-SCCmec IV vs ST5-SCCmec II isolates. Those with ST5-SCCmec 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-SCCmec 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-SCCmec IV and ST5-SCCmec 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, 0.21–0.71), 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. After stratification by strain type, hypertension (aOR, 0.38; 95% CI, 0.21–0.71), 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 ST72-SCCmec 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-SCCmec IV group compared with hospital-associated MRSA strains including ST5-SCCmec II and others (Supplementary Table 5). We performed a sensitivity analysis after excluding patients with osteoarticular infections, but mortality was not
DISCUSSION

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

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

|                      | ST5 (n = 431) | ST72 (n = 152) |
|----------------------|---------------|----------------|
| 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 diseasea | 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

|                            | ST5 (n = 431) | ST72 (n = 152) | P     |
|----------------------------|---------------|----------------|-------|
| Recent surgeryb            | 172 (39.9)    | 41 (27.0)      | .004  |
| Prior antibiotic treatmentb | 373 (86.5)    | 63 (41.4)      | <.001 |
| Nasal MRSA colonizationc   | 195 (45.2)    | 25 (16.4)      | <.001 |
| Immunosuppressive treatmenta | 136 (31.6)   | 52 (34.2)      | .547  |
| Central venous catheter    | 317 (73.5)    | 68 (44.7)      | <.001 |
| Noncatheter prosthetic devicesd | 58 (13.5)    | 22 (14.5)      | .754  |
| Septic shocke              | 62 (14.4)     | 22 (14.5)      | .979  |

Primary site of infection

|                                | ST5 (n = 431) | ST72 (n = 152) |
|--------------------------------|---------------|----------------|
| 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 (72)        | <.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 (79)        | .363  |
| Unknown (primary bacteremia)   | 51 (11.8)     | 23 (16.1)      | .294  |
| Metastatic infection           | 55 (12.8)     | 21 (13.8)      | .740  |

Source control

|                       | ST5 (n = 431) | ST72 (n = 152) |
|-----------------------|---------------|----------------|
| 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

|                     | ST5 (n = 431) | ST72 (n = 152) |
|---------------------|---------------|----------------|
| 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) | 170 (10.2–22.4) | .100  |

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

aIncludes chronic pulmonary obstructive lung disease and bronchiectasis.
bWithin a month before MRSA bacteremia.
cPositive result of the nasal swab test performed within 48 hours after confirmation of positive blood culture.
dIncludes pacemaker/implantable cardioverter-defibrillator (8 patients), prosthetic heart valves (20 patients), orthopedic devices (21 patients), and vascular grafts (27 patients).
eSepsis with persistent hypotension that requires vasopressors to maintain mean arterial pressure ≥65 mmHg and lactate level ≥2 mmol/L despite adequate fluid resuscitation.

Data are presented as No. (%), unless otherwise indicated.
Osteoarticular infections were more prevalent in ST72-SCCmecIV MRSA 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-SCCmecIV [30]. In another study on MRSAB, ST72-SCCmecIV isolates caused osteoarticular infection more frequently than ST5-SCCmecII [13]. Therefore, ST72-SCCmecIV 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-SCCmecIV observed in our study should be interpreted cautiously. Although the prevalence of osteoarticular infection was higher in the ST72-SCCmecIV MRSA group than in the ST5-SCCmecII MRSA group, the proportion was low (7%) relative to other infection sources. Given that most osteoarticular 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-SCCmecIV isolates were more likely to have vancomycin MICs ≤1.0 mg/L than ST5-SCCmecII 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-SCCmecIV was similar to or lower than that of infections caused by ST5-SCCmecII 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-SCCmecIV 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-SCCmecIV isolates, might contribute to higher mortality in ST5-SCCmecII infections [13]. Second, because vancomycin MICs in the ST5-SCCmecII group were higher, its bactericidal activity is reduced. Lastly, the percentage of patients with recent surgery or CVC presence was higher in the ST5-SCCmecII group than in the ST72-SCCmecIV group, suggesting that ST72-SCCmecIV can invade the host bloodstream without those portals of entry. However,

### 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 (28.7) | <.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*.

### 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.
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-SCCmeCIV strain might be more virulent itself, as it caused bacteremia in the absence of these pre-requisites. 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-SCCmeCIV 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 MRSA caused by ST72-SCCmeCIV than in hospital-acquired MRSA caused by ST5-SCCmeCII. The ST72-SCCmeCIV strain was not associated with worse clinical outcomes, including 30-day mortality, 90-day mortality, persistent bacteremia, and recurrence, when compared with ST5-SCCmeCII.

**Supplementary Data**

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

---

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

| Risk Factor                          | Univariable Analysis |  | Multivariable Analysis<sup>a</sup> |  |
|--------------------------------------|----------------------|---|-----------------------------------|---|
|                                      | 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<sup>b</sup>| 1.37 (0.49–3.86)     | .548 |                                  |   |
| Heart failure                        | 1.02 (0.41–2.55)     | .969 |                                  |   |
| Hypertension                         | 0.49 (0.31–0.77)     | .02  | 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 |
| MRSAs genotype                       |                      |    |                                  |   |
| ST5-SCCmeCII                         | 1 NA                 |    | 1 NA                             |   |
| ST72-SCCmeCIV                        | 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.

<sup>a</sup> Multivariable analysis included age, sex, MRSA genotype, and variables showing significant differences (P < 0.05) in the univariable analysis.

<sup>b</sup> Includes chronic pulmonary obstructive lung disease and bronchiectasis.
the posted materials are not copyrighted 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 (H11SC2918).

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. Meticillin-resistant Staphylococcus aureus: molecular characterization, evolution, and epidemiology. Clin Microbiol Rev 2018; 31: e00200–18.
7. Chua K, Laurent P, 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 chromosomal 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 HJ, 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-SCCmecIV causing bloodstream infections: clinical outcomes and bacterial virulence factors. J Antimicrob Chemother 2015; 70:1185–92.
14. Ioo EI, Chung DR, Ha YE, et al. Community-associated Panton-Valentine leukocidin-negative methicillin-resistant Staphylococcus aureus clone (ST72-MRSA-IV) causing bloodstream-associated pneumonia and surgical site infection in Korea. J Hosp Infect 2012; 81:149–55.
15. Ioo EI, Chung DR, Ha YE, et al. Clinical predictors of community-genotype ST72-methicillin-resistant Staphylococcus aureus-SCCmec type IV in patients with community-onset S. aureus infection. J Antimicrob Chemother 2012; 67:1755–9.
16. Ioo EI, 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. Chaelson ME, Pompeii 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, Barbariaanakos 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, Moeller 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, Isaretel B, Vanehrs M, 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 characterisation of methicillin-resistant and methicillin-susceptible clones of Staphylococcus aureus. J Clin Microbiol 2000; 38:1008–15.
26. Oliveira DC, de Lancastre H. Multiplex PCR strategy for rapid identification of structural types and variants of the mec element in methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother 2003; 47:1292–300.
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 YJ, Chong YP, Kim T, et al. Bone and joint infection as a predictor of community-onset methicillin-resistant Staphylococcus aureus bacteriaemia: 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 healthcare-associated meticillin-resistant Staphylococcus aureus in Canada: results of the CANWARD 2007–2009 study. Diagn Microbiol Infect Dis 2011; 69:320–5.
32. Bae IG, Federovich JJ, Miró J, 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 targeted strategies. 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. Comparison of clinical outcomes between healthcare-associated infections due to community-associated methicillin-resistant Staphylococcus aureus 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; 46:496–103.
38. Robinson JO, Pearson JC, Christiansen KJ, et al. Community-associated versus healthcare-associated meticillin-resistant Staphylococcus aureus bacteremia: a 10-year retrospective review. Eur J Clin Microbiol Infect Dis 2009; 28:353–61.
39. Priest NK, Rudkin JK, Eil EI, et al. From genotype to phenotype: can systems biology be used to predict Staphylococcus aureus virulence? Nat Rev Microbiol 2012; 10:791–7.