INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a prominent cause of bloodstream infections, and the disease has a particularly high incidence and high mortality rate. Despite the availability of appropriate therapies, the 30-day mortality rate of patients with MRSA bloodstream infections remains at 36% to 40%. Recent surveillance data on MRSA infections in the United States shows that 60% of in-hospital deaths occurred...
within 7 days of the initial MRSA infection [5]. One report estimates that 4.9% of patients die within 2 days after the onset of MRSA bacteremia (MRSAB) [6]. Nevertheless, most previous studies of patients with MRSAB focused on the prognostic factors associated with later mortality, such as 30-day mortality [7-13]. Only one recent study appears to have investigated the predictive factors for early mortality, defined as in-hospital death within 2 days of the onset of bacteremia, but that report did not fully investigate microbiological factors, using only an antimicrobial susceptibility test and molecular epidemiology [6]. Information on risk factors including microbiologic factors could be used to establish the prognosis for MRSAB, identify potential targets for therapeutic agents, and increase understanding of the pathogenesis of MRSA.

Using a prospective cohort of MRSAB patients, we performed a study to identify the clinical and microbiologic factors associated with early mortality. We also investigated the risk factors associated with severe sepsis or septic shock.

METHODS

Study population and study design
This prospective cohort study was conducted between August 2008 and June 2011 at the Asan Medical Center, a-2,700-bed hospital in Seoul that provides primary and tertiary care for patients from throughout Korea. By reviewing daily computerized reports on blood cultures, all patients aged ≥ 18 years with a MRSA-positive blood culture were identified and enrolled in the study. Patients were excluded if clinical isolates of MRSA were not available for microbiologic tests, or if they had polymicrobial bacteremia or clinically insignificant MRSAB. Insignificant bacteremia was defined as satisfying all of the following conditions: isolation from only one blood culture, no clinical finding consistent with bacteremia, and no anti-staphylococcal treatment. The study consisted of two sets of analyses: early mortality versus non-early mortality, and severe sepsis or septic shock versus non-severe sepsis or septic shock (Fig. 1). Early mortality was defined as death within 2 days of blood culture, since it takes about 48 hours to react to target concentrations of vancomycin as the drug of choice [12,14]. Late mortality was defined as death within 28 days of blood culture. The other patients were classified into the survival group. Severe sepsis or septic shock was defined according to International Sepsis Definitions Conference 2001 criteria [15]. The study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2008-0274).

Data collection and definitions
The following were recorded: demographic characteristics of the patients, days spent in the hospital before detection of MRSAB, underlying diseases or conditions, severity of illness, presence or absence of foreign material such as an intravenous catheter or prosthetic device, site of infection (catheter-related bloodstream infection, arteriovenous fistula infection, pneumonia, skin and soft tissue infection, bone and joint infection, urinary tract infection, and/or infective endocarditis), susceptibility to antibiotics, antibiotics used to treat MRSA (vancomycin, teicoplanin, tigecycline, and linezolid), and in-hospital mortality. If the site of infection could not be determined, it was considered to be unknown. Hospital-acquired bacteremia was defined as a positive blood culture obtained from a patient who had been hospitalized for 48 hours or longer. Community-acquired bacteremia and healthcare-associated bacteremia were defined as described by Friedman et al. [16]. To estimate the severity of the illness, the sepsis grade [17] and Pitt bacteremia score [18] were obtained. To estimate the severity of comorbidities, the Charlson comorbidity score (CCS) was calculated, as previously described [19]. When blood culture was performed, disease severity was classified according to the McCabe and Jackson classification system [20]. Eradicable foci included surgically removable infections, drainable abscesses, and indwelling foreign bodies such as peripheral and central intravenous catheters [21]. Early removal of eradicable foci was defined as removal within 2 days of blood culture. Patients with non-eradicable foci and whose eradicable foci were not removed early were categorized as having non-eradicated foci. If vancomycin, teicoplanin, tigecycline, or linezolid was prescribed, the department of infectious diseases was automatically consulted and the appropriateness of the treatment was reviewed. Vancomycin dose was adjusted according to the report published by the American Society of Health-System Pharmacists [22].
Microbiological methods
All isolates were confirmed as MRSA by polymerase chain reaction (PCR) for the mecA gene, and tested for antimicrobial susceptibility by standard techniques according to Clinical and Laboratory Standards Institute guidelines [23]. Staphylococcal cassette chromosome (SCC) mec type MRSA was identified [24]. The presence of bacterial virulence factors, including adhesins and toxins, was examined by multiplex PCR [25,26], and multi-locus sequence typing was also performed [27]. To examine agr dysfunction, the extent of ß-hemolysin production was measured by streaking each MRSA isolate next to a ß-hemolysin disk (Remel, Lenexa, KS, USA) [28]. The vancomycin minimum inhibitory concentrations (MICs) were determined using the vancomycin E-test (AB Biodisk, Piscataway, NJ, USA) on Mueller-Hinton agar. Heteroresistant vancomycin-intermediate S. aureus was identified by a modified population analysis profile-area under curve ratio method [29].

Statistical analysis
Statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were compared using the Mann-Whitney U test or Student t test. Categorical variables were compared using the Pearson chi-square test or Fisher exact test. Binary logistic regression was used to identify variables significantly associated with early mortality before detection of MRSAB by blood culture. Owing to the small size of the early-mortality group, the number of variables had to be minimized. Variables found to be statistically significant at the 5% level in the univariate analysis were included in the multivariate analysis. Underlying disease was introduced as a comorbidity variable only, and CCS and McCabe and Jackson classification were not included. Severe sepsis or septic shock was used to define severity of illness. Early removal of eradicable foci in early mortality did not receive anti-MRSA therapy within 24 hours. Anti-MRSA therapy was also excluded from the multivariate analysis because the frequency of non-treated patients was less than two in the late mortality and survival groups. Variables found to be statistically significant at the 10% level in the univariate analysis were included in the multivariate analysis of risk factors for severe sepsis or septic shock. If no patient fit the criteria for any group, that variable was excluded from the multivariable analysis. There was no multicollinearity among the variables included in the multivariate analysis. All significance tests were two-tailed, and a p < 0.05 was considered significant.

RESULTS

Study population
During the study period, 577 patients with MRSAB aged ≥ 18 years were identified. Of these patients, 192 were excluded for the following reasons: clinical isolates were not collected (117 patients), polymicrobial bacteremia was found (66 patients), or the MRSAB was clinically insignificant (nine patients). Of the 385 enrolled patients, 158 (41.0%) died; 25 patients (6.5%) died early and 50 patients (13%) died within 28 days. Severe sepsis or septic shock occurred in 124 patients (32.2%) with MRSAB bacteremia. Ultimately, of 385 enrolled patients, 25 (6.5%), 50 (13.0%), and 310 patients (80.5%) were assigned to the early mortality, late mortality, and survival groups (Fig. 1). Also, 124 (32.2%) and 261 patients (67.8%) were assigned to the severe sepsis or septic shock group and non-severe sepsis or septic shock group (Fig. 1).

Risk factors associated with early mortality of patients with MRSAB
The clinical and microbiological characteristics of patients in the early mortality, late mortality, and survival groups are shown in Table 1. According to the severity index, the patients with early mortality had more severe disease than did those in the late mortality or survival groups. Early removal of eradicable foci in early mortality patients was less frequent than in the late mortality or survival groups. Of the patients treated with antibiotics, 221 (92.1%), 14 (3.5%), three (0.8%), and one (0.3%) were treated with vancomycin, teicoplanin, linezolid, and tigecycline, respectively. Some of the patients with early mortality did not receive anti-MRSA therapy within 24 hours.

ST5-SCCmecII-agrI (254 patients, 66.6%) was the most common MRSA strain, followed by ST72-SCCmecIV-agrII (87 patients, 22.6%) and ST239-SCCmecII-agrII (16 patients, 4.2%). The ST72-SCCmecIV-agrII strain was less often seen in the late mortality group than in the early mortality and survival groups, although this difference
| Variable | Early mortality | Late mortality | Survival | p value<sup>a</sup> | p value<sup>b</sup> | p value<sup>c</sup> |
|----------|----------------|----------------|----------|----------------------|----------------------|----------------------|
| Demographic |                |                |          |                      |                      |                      |
| Age ≥ 65 year-old | 15 (60.0) | 27 (54.0) | 157 (50.6) | 0.81 | 0.41 | 0.76 |
| Male | 15 (60.0) | 34 (68.0) | 199 (64.2) | 0.61 | 0.67 | 0.64 |
| Site of MRSA acquisition |    |                |          |                      |                      |                      |
| Hospital-acquired | 17 (68.0) | 42 (84.0) | 228 (73.5) | 0.14 | 0.64 | 0.16 |
| Healthcare-associated | 7 (28.0) | 7 (14.0) | 68 (21.9) | 0.21 | 0.46 | 0.26 |
| Community-acquired | 1 (4.0) | 1 (2.0) | 14 (4.5) | 1.00 | 1.00 | 0.70 |
| Length of hospital stay before MRSA detection |    |                |          |                      |                      |                      |
| < 72 hours | 9 (36.0) | 9 (18.0) | 92 (29.7) | 0.10 | 0.50 | 0.09 |
| 3–7 days | 2 (8.0) | 4 (8.0) | 27 (8.7) | 1.00 | 1.00 | 1.00 |
| 8–28 days | 10 (40.0) | 25 (50.0) | 122 (39.4) | 0.47 | 1.00 | 0.17 |
| > 28 days | 4 (16.0) | 12 (24.0) | 69 (22.3) | 0.56 | 0.62 | 0.86 |
| Underlying disease |    |                |          |                      |                      |                      |
| Solid tumor | 14 (56.0) | 25 (50.0) | 115 (37.1) | 0.81 | 0.09 | 0.09 |
| Hematologic malignancy | 1 (4.0) | 7 (14.0) | 19 (6.1) | 0.26 | 1.00 | 0.07 |
| ESRD | 0 | 3 (6.0) | 39 (12.6) | 0.55 | 0.10 | 0.24 |
| Liver cirrhosis | 8 (32.0) | 8 (16.0) | 34 (11.0) | 0.14 | 0.01 | 0.34 |
| Cardiovascular disease | 5 (20.0) | 10 (20.0) | 55 (17.7) | 1.00 | 0.79 | 0.69 |
| Severity of comorbidity |    |                |          |                      |                      |                      |
| Charlson comorbidity score ≥ 5 | 12 (48.0) | 22 (44.0) | 68 (21.9) | 0.81 | 0.01 | <0.001 |
| McCabe and Jackson classification |    |                |          |                      |                      |                      |
| Rapidly or ultimately fatal | 20 (80.0) | 35 (70.0) | 97 (31.3) | 0.42 | <0.001 | <0.001 |
| Site of infection |    |                |          |                      |                      |                      |
| Catheter-related blood stream infection | 9 (36.0) | 24 (48.0) | 141 (45.5) | 0.46 | 0.41 | 0.76 |
| Arteriovenous fistula infection | 0 | 0 | 6 (1.9) | NA | 1.00 | 1.00 |
| Pneumonia | 5 (20.0) | 5 (10.0) | 30 (9.7) | 0.29 | 0.16 | 1.00 |
| Skin and soft tissue infection | 0 | 3 (6.0) | 12 (3.9) | 0.35 | 0.61 | 0.45 |
| Surgical site infection | 2 (8.0) | 2 (4.0) | 32 (10.3) | 0.60 | 1.00 | 0.20 |
| Bone and joint infection | 0 | 1 (2.0) | 18 (5.8) | 1.00 | 0.38 | 0.49 |
| Urinary tract infection | 0 | 0 | 3 (1.0) | NA | 1.00 | 1.00 |
| Infective endocarditis | 1 (4.0) | 3 (6.0) | 5 (1.6) | 1.00 | 0.37 | 0.09 |
| Unknown | 8 (32.0) | 24 (48.0) | 141 (45.5) | 0.46 | 0.41 | 0.05 |
| Severity of illness |    |                |          |                      |                      |                      |
| Severe sepsis or septic shock | 20 (80.0) | 27 (54.0) | 77 (24.8) | 0.04 | <0.001 | <0.001 |
| Pitt bacteremia score ≥ 3 | 17 (68.0) | 27 (54.0) | 73 (23.5) | 0.004 | <0.001 | <0.001 |
| Eradicable foci | 10 (43.6) | 28 (59.6) | 194 (64.9) | 0.31 | 0.046 | 0.51 |
| Early removal | 2 (16.7) | 24 (75.0) | 175 (78.1) | 0.001 | <0.001 | 0.66 |
| Anti-MRSA therapy |    |                |          |                      |                      |                      |
| On day 0 | 12 (48.0) | 24 (48.0) | 79 (25.5) | 1.00 | 0.02 | 0.002 |
| On day 0 or 1 | 16 (64.0) | 50 (100) | 308 (99.4) | <0.001 | <0.001 | 1.00 |
| Microbiologic factors |    |                |          |                      |                      |                      |
was not statistically significant in the multivariate analysis. The distribution of vancomycin MICs was as follows: in 121 cases (31.4%) it was ≤ 1.0 μg/mL, in 177 (45.9%) it was ≤ 1.5 μg/mL, in 82 (21.3%) it was ≤ 2.0 μg/mL, and in 5 (1.8%) it was > 2 μg/mL. The following virulent genes were not found in any isolates: seb, sed, seC, seh, sej, eta, etb, lukM, hlg, and edin. Regardless of survival, the following genetic factors were very rare: Panton-Valentine leukocidin, map/epa, sea, sek, sep, and seq. Virulent genes such as fnbA, clfA, clfB, can, and icaA were found in all isolates, and fnbB, bhp, ebps, sdrD, sdrE, seq, sci, sem, sen, seq, lukDE, lukE, hla, hld, and hlg2 were found in most isolates. The frequencies of virulent genes such as sdrC, sec, sel, and TSST-1 are given in Table 1. Among the virulent genes, sel was less frequent in patients with early mortality than in those with late mortality.

To compare the clinical and microbiologic factors seen in patients with early mortality versus those with late mortality, occurrence of severe sepsis or septic shock, presence of the ST272-SCCmecIV-agrI strain, and sel as a virulent gene were included in the multivariate analysis (Table 2). Compared with patients with late mortality, severe sepsis or septic shock (adjusted odds ratio [aOR], 4.49; 95% confidence interval [CI], 1.28 to 15.75) was the only statistically significant independent risk factor in patients with early mortality. To compare the clinical and microbiologic factors of patients with early mortality and those who survived, the following variables were included in the multivariate analysis: liver cirrhosis, severe sepsis or septic shock, and anti-MRSA therapy on day of blood culture (Table 2). Compared with patients who survived, liver cirrhosis (aOR, 3.79; 95% CI, 1.38 to 3.86) and severe sepsis or septic shock (aOR, 23.86) and severe sepsis or septic shock (aOR, 10.98; 95% CI, 5.23 to 27.45) were statistically significant independent risk factors in patients with early mortality. When rapidly or ultimately fatal McCabe and Jackson classification was added to the multivariate analysis and severe sepsis or septic shock was replaced with Pitt bacteremia score ≥ 3, both were also statistically significant (data not shown). Compared with patients who survived, rapidly or ultimately fatal McCabe and Jackson classification (aOR, 4.61; 95% CI, 2.37 to 9.00) and severe sepsis or septic shock (aOR, 2.95; 95% CI, 1.54 to 5.63) were statistically significant independent risk factors in patients with late mortality.

### Risk factors associated with severe sepsis or septic shock

The clinical and microbiologic characteristics of patients in the severe sepsis or septic shock and non-severe sepsis or septic shock groups are shown in Table 3. In the multivariate analysis, rapidly or ultimately fatal mortality was the only statistically significant independent risk factor in patients with late mortality. To compare the clinical and microbiologic factors of patients with early mortality and those who survived, the following variables were included in the multivariate analysis: liver cirrhosis, severe sepsis or septic shock, and anti-MRSA therapy on day of blood culture (Table 2). Compared with patients who survived, liver cirrhosis (aOR, 3.79; 95% CI, 1.38 to 3.86) and severe sepsis or septic shock (aOR, 23.86) and severe sepsis or septic shock (aOR, 10.98; 95% CI, 5.23 to 27.45) were statistically significant independent risk factors in patients with early mortality. When rapidly or ultimately fatal McCabe and Jackson classification was added to the multivariate analysis and severe sepsis or septic shock was replaced with Pitt bacteremia score ≥ 3, both were also statistically significant (data not shown). Compared with patients who survived, rapidly or ultimately fatal McCabe and Jackson classification (aOR, 4.61; 95% CI, 2.37 to 9.00) and severe sepsis or septic shock (aOR, 2.95; 95% CI, 1.54 to 5.63) were statistically significant independent risk factors in patients with late mortality.

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McCabe and Jackson classification as severity of comorbidity (aOR, 1.94; 95% CI, 1.25 to 3.02) and pneumonia as site of infection (aOR, 2.04; 95% CI, 1.03 to 4.02) were significantly associated with severe sepsis or septic shock. Fewer patients with isolates with vancomycin MICs ≥ 1.5 μg/mL experienced severe sepsis or septic shock (aOR, 0.53; 95% CI, 0.33 to 0.84).

**DISCUSSION**

The main aim of the current study was to identify clinical factors associated with early death in patients with MRSAB. Identifying key factors could help to identify those patients who require urgent and aggressive management. Liver cirrhosis and severe sepsis or septic shock were independent risk factors associated with early mortality. The secondary aim of our study was to investigate the microbiological factors associated with early mortality. Paradoxically, low vancomycin MIC was associated with severe sepsis or septic shock, although vancomycin susceptibility was not associated with early mortality. To our knowledge, this is the first study to extensively investigate the microbiological factors associated with early mortality in MRSAB patients.

Indices of the severity of comorbidities and illness are known to be associated with death of patients with S. aureus bacteremia (SAB) [11-13,30,31], and most previous studies investigated the factors associated with late mortality, such as 30-day mortality [11-13,30,31]. The exception is a recent study by Gasch et al. [6], which looked at early mortality, defined as death within 2 days of the onset of MRSAB, as in the current study. According to Gasch and colleagues [6], rapidly fatal McCabe and Jackson classification (aOR, 3.67; 95% CI, 1.32 to 10.24) and Pitt bacteremia score > 3 (aOR, 4.52; 95% CI, 1.72 to 9.24) were independent factors associated with early mortality. Our current findings also suggest that the severities of comorbidities and illness are important prognostic factors that influence early death as well as late death in patients with MRSAB.

Underlying liver cirrhosis was significantly associated

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**Table 2. Risk factors associated with early mortality in patients with MRSA bacteremia according to survival**

| Variable                        | Early mortality vs. late mortality | Early mortality vs. survival | Late mortality vs. survival |
|---------------------------------|-----------------------------------|------------------------------|----------------------------|
|                                 | Univariate analysis, OR (95% CI) | Univariate analysis, OR (95% CI) | Univariate analysis, OR (95% CI) |
| Liver cirrhosis                 | -                                 | 2.92 (1.52–5.61)             | 3.79 (1.38–10.37)          |
| McCabe and Jackson classification | Rapidly or ultimately fatal       | -                            | 2.24 (1.75–2.86)           |
|                                 |                                    |                              | 4.61 (2.37–9.60)           |
| Severe sepsis or septic shock   | 1.48 (1.07–2.05)                   | 4.49 (1.28–15.75)            | 3.22 (2.45–4.24)           |
|                                 |                                    |                              | 10.98 (3.82–31.52)         |
|                                 |                                    |                              | 2.17 (1.58–3.00)           |
|                                 |                                    |                              | 2.95 (1.54–5.63)           |
| Treatment                       | Anti-MRSA therapy on D0            | 1.88 (1.20–2.96)             | 1.41 (0.57–3.50)           |
| Microbiologic factors           | ST72-SCCmeCIV-agrI strain          | 3.20 (1.17–8.78)             | 3.14 (0.41–23.86)          |
|                                 | sel                                | 0.73 (0.53–0.99)             | 0.43 (0.07–2.77)           |

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; MRSA, methicillin-resistant Staphylococcus aureus; ST, sequence type; SCC, staphylococcal cassette chromosome.

*p < 0.05.*
Table 3. Risk factors associated with severe sepsis or septic shock in patients with MRSA bacteremia

| Variable                                      | Severe sepsis or septic shock (n = 124) | Non-severe sepsis or septic shock (n = 261) | p value | Univariate analysis, OR (95% CI) | Multivariate analysis, aOR (95% CI) |
|-----------------------------------------------|----------------------------------------|---------------------------------------------|---------|---------------------------------|-----------------------------------|
| **Demographic**                               |                                        |                                             |         |                                 |                                   |
| Age ≥ 65 year-old                             | 68 (54.8)                              | 131 (50.2)                                 | 0.45    | 1.21 (0.79–1.85)                |                                   |
| Male sex                                      | 83 (66.9)                              | 165 (63.2)                                 | 0.50    | 1.18 (0.75–1.85)                |                                   |
| **Site of MRSA acquisition**                  |                                        |                                             |         |                                 |                                   |
| Hospital-acquired                             | 92 (74.2)                              | 195 (74.7)                                 | 0.90    | 0.97 (0.60–1.59)                |                                   |
| Healthcare-associated                         | 27 (21.8)                              | 55 (21.1)                                  | 0.89    | 1.04 (0.62–1.75)                |                                   |
| Community-acquired                            | 5 (4.0)                                | 11 (4.2)                                   | 1.00    | 0.96 (0.32–2.81)                |                                   |
| **Length of hospital stay before MRSA detection** |                                        |                                             |         |                                 |                                   |
| < 72 hours                                    | 37 (29.8)                              | 73 (28.0)                                  | 0.72    | 1.10 (0.68–1.75)                |                                   |
| 3–7 days                                      | 10 (8.1)                               | 23 (8.0)                                   | 1.00    | 0.91 (0.42–1.97)                |                                   |
| 8–28 days                                     | 47 (37.9)                              | 110 (42.1)                                 | 0.44    | 0.84 (0.54–1.36)                |                                   |
| > 28 days                                     | 30 (24.2)                              | 55 (21.1)                                  | 0.51    | 1.20 (0.72–1.99)                |                                   |
| **Underlying disease**                        |                                        |                                             |         |                                 |                                   |
| Solid tumor                                   | 48 (38.7)                              | 106 (40.6)                                 | 0.74    | 0.92 (0.60–1.43)                |                                   |
| Hematologic malignancy                       | 11 (8.9)                               | 16 (6.1)                                   | 0.39    | 1.49 (0.67–9.32)                |                                   |
| ESRD                                          | 14 (11.3)                              | 28 (10.7)                                  | 0.86    | 1.06 (0.54–2.09)                |                                   |
| Liver cirrhosis                               | 17 (13.7)                              | 33 (12.6)                                  | 0.75    | 1.10 (0.59–2.06)                |                                   |
| Cardiovascular disease                       | 26 (21.0)                              | 44 (16.9)                                  | 0.33    | 1.11 (0.70–2.25)                |                                   |
| **Severity of comorbidity**                   |                                        |                                             |         |                                 |                                   |
| Charlson comorbidity score ≥ 5               | 36 (29.0)                              | 66 (25.3)                                  | 0.46    | 1.21 (0.75–1.99)                |                                   |
| McCabe and Jackson classification            |                                        |                                             |         |                                 |                                   |
| Rapidly or ultimately fatal                  | 63 (50.8)                              | 89 (34.1)                                  | 0.003   | 2.00 (1.29–3.08)                | 1.94 (1.25–3.02)                  |
| **Site of infection**                         |                                        |                                             |         |                                 |                                   |
| Catheter-related blood stream infection       | 60 (48.4)                              | 114 (43.7)                                 | 0.44    | 1.21 (0.79–1.86)                |                                   |
| Arteriovenous fistula infection               | 1 (0.8)                                | 5 (1.9)                                    | 0.67    | 0.42 (0.05–3.60)                |                                   |
| Pneumonia                                     | 19 (15.3)                              | 21 (8.0)                                   | 0.03    | 2.07 (1.07–4.01)                | 2.04 (1.03–4.02)                  |
| Skin and soft tissue infection                | 0                                      | 15 (5.7)                                   | 0.004   | NA                              |                                   |
| Surgical site infection                       | 9 (7.3)                                | 27 (10.3)                                  | 0.45    | 0.68 (0.31–1.49)                |                                   |
| Bone and joint infection                      | 5 (4.0)                                | 14 (5.4)                                   | 0.80    | 0.74 (0.26–2.11)                |                                   |
| Urinary tract infection                       | 1 (0.8)                                | 2 (0.8)                                    | 1.00    | 1.05 (0.10–11.72)               |                                   |
| Infective endocarditis                        | 3 (2.4)                                | 6 (2.3)                                    | 1.00    | 1.05 (0.26–4.20)                |                                   |
| Unknown                                       | 20 (16.1)                              | 29 (11.1)                                  | 0.19    | 1.54 (0.83–2.85)                |                                   |
| Early mortality                               | 20 (16.1)                              | 5 (1.9)                                    | < 0.001 | 9.85 (3.60–26.93)               |                                   |
| **Microbiologic factors**                     |                                        |                                             |         |                                 |                                   |
| Vancomycin MIC by E-test ≥ 1.5 μg/mL          | 73 (58.9)                              | 191 (73.2)                                 | 0.01    | 0.53 (0.33–0.82)                | 0.53 (0.34–0.84)                  |
| hVISA phenotype                               | 37 (32.5)                              | 76 (29.2)                                  | 1.00    | 0.99 (0.62–1.60)                |                                   |
| ST5-SCC mecI-agrHI strain                     | 80 (71.0)                              | 165 (63.2)                                 | 0.17    | 1.42 (0.90–2.26)                |                                   |
| ST72-SCC mecIV-agrI strain                    | 23 (18.5)                              | 63 (24.1)                                  | 0.24    | 0.72 (0.42–1.22)                |                                   |
| agr dysfunction                               | 89 (74.2)                              | 177 (71.1)                                 | 0.62    | 1.17 (0.71–1.91)                |                                   |

Values are presented as number (%).
MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; ESRD, end-stage renal disease; NA, not applicable; MIC, microbacterial inhibitory concentration; hVISA, heterogeneous vancomycin-intermediate *Staphylococcus aureus*; ST, sequence type; SCC, staphylococcal cassette chromosome.
with early mortality in the present analysis. A previously published report identified liver cirrhosis as an independent predictor of SAB-related mortality [21]. The association can be explained by weakened host defense in patients with liver cirrhosis, including impaired functioning of leukocytes [32] and Kupffer cells [33]. This association implies that patients with liver cirrhosis may require more careful and intensive management beginning in the early phase of infection.

Another important issue is whether treatment with empirical antibiotics can prevent early death from MRSA. If this is the case, such antibiotics should be administered without hesitation to patients with any risk factors associated with MRSA infection immediately after blood culture. Gasch et al. [6] reported that inappropriate antibiotic usage within 48 hours of MRSAB onset was independently associated with early mortality. The association of high vancomycin MIC with early mortality would imply that use of higher doses of appropriate empiric glycopeptide therapies are important for patient survival. In our study, in contrast, low vancomycin susceptibility was associated with a lower risk of severe sepsis or septic shock. In a prospective cohort study of MRSAB, Soriano et al. [9] also showed that episodes caused by strains with a vancomycin MIC of 2 mg/L were independently associated with a lower risk of shock (OR, 0.33; 95% CI, 1.68 to 24.3), as seen in this study. Using the non-mammalian model system *Galleria mellonella* (the wax moth), Peleg et al. [34] showed that killing was significantly attenuated after infection with a vancomycin-non-susceptible *S. aureus* strain in contrast with an isogenic, vancomycin-susceptible progenitor strain. This would mean that higher doses or loading doses of glycopeptides may have only a limited role in reducing the severity of MRSA bacteraemia.

These discordant results on the relationship of vancomycin MIC may be attributable to the fact that severe sepsis or septic shock has different properties from early mortality as an outcome indicator. Patients with early mortality were often classified as rapidly or fatal McCabe classification as an indicator of comorbidity, and it can be assumed that these patients were more likely to be exposed to antibiotics prior to MRSA infection. It is already known that exposure to glycopeptides increases MIC as the cell wall becomes thicker. Cui et al. [35] found that cells with thin cell walls displayed reduced growth in the presence of vancomycin compared to cells with thick cell walls. Therefore, the positive correlation between early mortality and vancomycin MIC values seen in a previous study can be interpreted as the result of a comorbidity rather than a risk factor affecting early mortality. On the other hand, severe sepsis or severe septic shock as an indicator of outcome is the result of host immune activation. It can be inferred that vancomycin MIC is inversely correlated because a strain with

**Figure 1.** Algorithm of enrollment and analysis. MRSAB, methicillin-resistant *Staphylococcus aureus* bacteremia.
a high vancomycin MIC induces less host immune activation, as it is a ‘fitness cost.’ A thickened cell wall can prevent teichoic acids and lipoteichoic acids from activating the immune system and consequently hinder the development of septic shock [9]. MRSA strains with high vancomycin MICs also tend to have slow growth rates [36]. Further well-designed studies that control bias due to non-microbiological factors should be undertaken to better understand the impact of reduced vancomycin susceptibility on early prognosis in MRSAB.

The ST72-SCCmeIV-agrI strain was more prevalent in the early mortality group than in the late mortality group in the univariate analysis. This is in agreement with the result of a previous study conducted by our colleagues in the same population, which showed that the community-associated MRSA strain ST72-SCCmeIV was independently associated with low crude mortality, compared to the ST5-SCCmeII strain (aOR, 0.26; 95% CI, 0.13 to 0.54) [37]. Also, sel, one of the staphylococcal superantigen genes that cause immune system dysregulation, was less frequent in the early mortality group. The patterns of strain type and virulent gene were similar in the early mortality group and survival groups, but different in the late mortality group. These unexpected results may be because host immune activation has a stronger influence on early mortality, and may offset the influence of microbiological factors as prognostic factors.

This study had several limitations. First, some variables that affect the outcomes of MRSAB patients may have been omitted from the analysis. Second, early death in some patients might not have been caused by MRSAB, but rather by alternative causes such as terminal cancer or impediments to care such as refusal of intensive care. A third limitation is the narrow range of ST types in our sample. Studies from different regions or countries that include various ST types of MRSA strains should be performed. Finally, the small size of the early mortality group is likely to have been insufficient to draw firm conclusions about whether any microbiological factors affect early mortality.

In conclusion, comorbidities such as liver cirrhosis and severity of illness such as severe sepsis or septic shock are important risk factors for early mortality in MRSAB, just as in late mortality. In the current situation, it seems that early intervention can play only a limited role in improving early prognosis in MRSA, and this conclusion emphasizes the importance of preventing MRSAB. The paradoxical relationship between vancomycin susceptibility and severe sepsis or septic shock suggests that these isolates may lose their virulence when acquiring vancomycin resistance. Further studies are required to explain the associations of these clinical and microbiological factors with early prognosis in patients with MRSAB.

**KEY MESSAGE**

1. About 7% of patients with methicillin-resistant *Staphylococcus aureus* bacteremia died within 2 days of blood culture.
2. Liver cirrhosis and severe sepsis or septic shock were independent clinical factors associated with early mortality.
3. Reduced vancomycin susceptibility appears to be linked to reduced disease severity.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

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